



Energetics of hole transfer in DNA

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Dedicated to the memory of Professor Micheal C. Zerner who left his mark on theoretical chemistry.

Abstract

Using the semi-empirical scheme NDDO-G, we estimated energies for hole transfer in DNA duplexes on the basis of calculated ionization potentials (IP) of nucleobases in triplets of regular structure. All possible triad 5'-XBY-3' duplexes (X,B,Y = A,G,C,T) were considered. We find that the stabilization of B⁺ is considerably influenced by the *subsequent* base Y while the effect of the *preceding* base X is rather small. We test the application of triplet models by comparison with a decamer duplex. The present semi-empirical results have also been compared with data from ab initio calculations and experiment. © 2000 Elsevier Science B.V. All rights reserved.

1. Introduction

Electron transfer mediated by nucleotide stacks of DNA duplexes has recently received considerable attention, primarily due to its connection to oxidative damage of DNA [1,2], and DNA-based nano technologies [3,4]. Guanine (G) is known to be the most easily oxidized nucleobase and, therefore, the corresponding cation radical is a key intermediate formed by one-electron oxidation of DNA [1,2,5]. In fact, the oxidation potential of guanine is about 0.4 eV lower than that of adenine (A) and significantly lower than the oxidation potentials of cytosine (C) and thymine (T) [5–8]. It has been shown experimentally, that a guanine radical cation radical (G⁺)

can be generated in DNA far away from an oxidant because of hole transfer [1,5,9,10]. the transport of positive charge. GGG triplets were found to act as the most effective traps in hole transfer [11–14]. Fundamental mechanisms of charge migration in DNA have recently been discussed in terms of long-range hole hopping involving exclusively guanine intermediates [15–17]. To understanding details of these processes. data on energetics of the migration of positive charges in DNA are needed.

The energy for hole transfer between two bases B and B' can be estimated as difference in ionization energies of these bases. Since holes are trapped at sites of minimum oxidation potentials, calculations of ionization energies may be useful for predicting the reactivity of different sites in DNA toward one-electron oxidation. Recently, Saito and co-workers reported ionization potentials (IP) for XGY triplets obtained with the help of the Hartree–Fock (HF)

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SCF calculations with a 6-31G* basis set using the Koopmans approximation [13,14]. They showed that the calculated IPs are in good agreement with experimentally observed relative reactivities of duplexes toward photo-induced one-electron oxidation. However, note that the Koopmans approximation within ab initio methods is rather rough; calculated IPs of organic molecules typically deviate from experimental values by 1–2 eV [18]. While relative ionization energies of G in various duplexes seem to be reproduced rather accurately, the energetics of hole transfer between different nucleobases in DNA provided by such calculations does not seem reliable enough. In this connection, a semi-empirical method that is specially designed for calculating spectroscopic properties appears to be more reliable.

The purpose of the present work is to estimate the energetics of positive charge transfer between nucleobases in DNA. The semi-empirical method, NDDO-G, recently elaborated [19] to simulate absorption spectra and ionization energies of large organic and biological molecules should be a very suitable tool for this aim.

2. Computational details

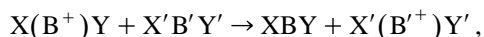
Geometries of B-DNA fragments were constructed using the program SCHNArP [20]. The relative positions of nucleobases in duplexes correspond to the regular structure of DNA. The distance between the planes of the nucleobases (rise) and the twist between consecutive bases along the oligomer chain were assumed to be 3.38 Å and 36°, respectively. The structures of the four bases A, C, G, and T were generated with the help of averaged experimental atomic coordinates taken from high-resolution X-ray and neutron crystal structure [21]. Each model consists of Watson–Crick pairs. Thus, the structural parameters of our models should be very similar to those used in recent ab initio calculations [13].

Semi-empirical NDDO-G calculations [19] of IPs were carried out using the Koopmans theorem. This approximation seems to be reliable since the NDDO-G parameters were determined by comparing (among other criteria) experimental and calculated IP values

based on the Koopmans approximation. Employing 123 comparisons, this method was shown to reproduce IPs of organic molecules with a mean absolute error of 0.24 eV [19]. While absolute ionization energies of nucleobases within DNA cannot be obtained accurately due to the considerable electrostatic interaction of nucleobases with charged sugar-phosphate fragments and the polar environment (water, cations H₃O⁺ and Na⁺), one may assume that *relative* IP values should provide a rather reasonable platform for estimating the energetics of hole transfer in DNA. This assumption relies on the fact that different nucleic bases in DNA exhibit a very similar environment.

3. Results and discussion

The energy of the hole transfer reaction between two bases, B and B', in DNA,



may be estimated as the difference of the vertical IPs of B and B'. Here X, Y and X', Y' represent the nearest-neighbor nucleobases of B and B', respectively.

We start by comparing absolute experimental gas-phase [22] and calculated vertical IPs (Table 1). With an absolute error of 0.1 eV, calculated and observed values agree very well. For comparison, we mention other predictions for the IP of guanine. With the RHF/6-31G* method (applying the Koopmans approximation) one obtains 7.72 eV; the hybrid density functional method B3LYP/6-31G* (applying a Δ SCF procedure) yields a value of 7.31 eV [23]. The

Table 1
Comparison of calculated ^a and experimental vertical ionization energies (in eV) of DNA bases

	NDDO-G	Exp. ^b
G	8.098	8.24
A	8.528	8.44
T	9.148	9.14
C	9.097	8.94

^a At regular geometries; see Ref. [21].

^b Ref. [22].

experimental value is 8.24 eV [22] and the present NDDO-G model predicts the IP of bare guanine to 8.10 eV (Table 1). Thus, one may expect reaction energies for hole migration between nucleotide cation radicals in DNA as calculated by the NDDO-G model to be reliable even when the neighboring bases to B and B' are different.

According to the NDDO-G model, formation of H-bonded complexes G...C and A...T lowers the ionization energies of G and A, by about 0.3 eV. The lowest IPs of GC and AT are found to be 7.76 and 8.22 eV, respectively. The role of G as the base with the lowest IP is invariant to H-bonding in the Watson–Crick pairs.

3.1. $X(G^+)Y$ triplets

As already mentioned, it was found experimentally [1–3,5] that guanine is the most effective trap for cation radical states in DNA. Therefore, information about the relative IPs of G-containing triplets is of special interest. Our previous calculations (see also the results for a model oligonucleotide presented below) show that relative ionization energies of nucleobases may be considerably effected by the neighboring bases. However, the influence of more distant bases is relatively small and may be neglected. Thus, to estimate the energy of hole migration in DNA, nucleobase triplets seem to be a suitable type of model.

Table 2 shows calculated reaction energies of hole transfer from GG^+G to other $5'-XG^+Y-3'$ triplets. Because all values are positive, GGG is most easily oxidized among the 16 triplets, in line with experimental findings and previous calculations [5,13,14]. Inspection of Table 2 reveals that the stabilization of G^+ is considerably influenced by the *subsequent* base 3'-Y, while the *preceding* base 5'-X has rather a small effect on the hole transfer energy. The most stable base sequences are the XG^+G . The sequences XG^+A are less stable by about 0.15 eV, followed by XG^+T (with energies higher by about 0.27 eV) and XG^+C (energies about 0.32 eV larger). The influence of the preceding base 5'-X is smaller by an order of magnitude (0.03 eV). The stabilizing effect of 3'-Y neighbors decreases in the order $G > A > T > C$.

Table 2

Relative energies ^a of duplexes XB^+Y (in eV) calculated with the NDDO-G model at regular geometries ^b

Y	G	A	T	C
GG ⁺ Y	0.000	0.132	0.265	0.303
AG ⁺ Y	0.001	0.134	0.266	0.304
TG ⁺ Y	0.026	0.157	0.288	0.326
CG ⁺ Y	0.036	0.168	0.299	0.336
GA ⁺ Y	0.442	0.575	0.697	0.717
AA ⁺ Y	0.459	0.502	0.718	0.736
TA ⁺ Y	0.486	0.617	0.747	0.765
CA ⁺ Y	0.496	0.629	0.749	0.769
GT ⁺ Y	1.283	1.454	1.592	1.697
AT ⁺ Y	1.319	1.489	1.615	1.730
TT ⁺ Y	1.391	1.545	1.648	1.831
CT ⁺ Y	1.406	1.576	1.762	1.812
GC ⁺ Y	1.545	1.714	1.892	1.959
AC ⁺ Y	1.561	1.730	1.906	1.971
TC ⁺ Y	1.612	1.770	1.957	2.021
CC ⁺ Y	1.628	1.796	1.968	2.031

^a Absolute values of ionization energies may be obtained by adding 7.304 eV.

^b Ref. [20].

Thus, we conclude that 5'-G in GG stacks is most reactive for oxidation. This result is consistent with the experimental finding that the 3'-side G of doublets GG or triplets GGG is far less reactive than the adjacent guanines [5]. In general, there is good agreement between our energetic results and the relative reactivity of G sites in DNA fragments. In particular, the XGG triplets have the largest susceptibility to one-electron oxidation, while pyrimidine–G–pyrimidine triplets (TGT, TGC, CGT and CGC) are almost unreactive [13]. It should be noted that the results of previous RHF/6-31G* calculations [13] are in several cases at variance with the present NDDO-G results. For instance, the IPs of AGG and GGA were found to be very similar in ab initio calculations (the difference between them is less than 0.01 eV) while they differ by 0.13 eV according to the NDDO-G method. Thus, ab initio calculations [13] predict GG and GA stacks to be equivalent. However, it is known from experiment that GG is more reactive than GA [13,14]. Furthermore, within the RHF/6-31G* approach the ionization energies of GGT and GGC are calculated to be lower than

those of AGA and TGA. The NDDO-G model predicts the reverse order.

3.2. $X(A^+)Y$ triplets

Estimates for energies of hole migration between cation radicals from $G(G^+)G$ to $X(A^+)Y$ are also shown in Table 2. The trends of various relative energies of XA^+Y triplets are very similar to those found for XG^+Y triplets. Inspection of Table 2 shows that there is no overlap between the energy ranges of these two types of triplets. The highest ionization energy computed for CG^+C , 0.336 eV, is still smaller than the lowest value of 0.442 eV found for GA^+G (Table 2). Note that the difference between ionization energies of analogous A and G triplets, e.g. 0.44 eV for GAG and GGG (Table 2), is close to the corresponding difference of IPs, 0.43 eV, calculated for bare nucleobases (Table 1).

3.3. $X(T^+)Y$ and $X(C^+)Y$ triplets

The ionization energies (relative to the energy of GG^+G) of the systems $X(T^+)Y$ and $X(C^+)Y$ as calculated by the NDDO-G model are also listed in Table 2. Because of the rather high-energy values, 1.3–2.0 eV, transfer of a hole from G^+ to the bases T and C is unlikely. According to the present calculations, the ranges of IP values of T and C triplets overlap. For instance, while $G(T^+)G$ is calculated to be most stable among the 32 T^+ and C^+ triplets (1.283 eV, see Table 2), $G(C^+)G$ is found

to be more stable than all $X(T^+)T$ and $X(T^+)C$ species. These data may be used for estimating the energy gain which accompanies the transfer of a hole state generated by oxidation of T or C to the bases G and A.

3.4. A model oligonucleotide

Our calculations for the model triplet oligonucleotides show that GG and GGG are the most easily oxidized sequences. The 5'-G base in a GG stack has the lowest IP. We present NDDO-G calculations on a decamer model duplex to assess the transferability of the model triplet energies ΔE_{tr} (Table 2) for the migration of a cation radical state from $G(G^+)G$ to an arbitrary triplet $X(B^+)Y$. Of considerable interest is the energetics of hole transfer from a single G^+ to GGG. From these calculations we also infer on the relative energies of the G bases in the GGG hole trap. Relative IPs ΔE were calculated for the decamer model duplex 5'-C₁A₂T₃T₄C₅G₆G₇G₈C₉T₁₀-3'/5'-A₁₁G₁₂C₁₃C₁₄C₁₅G₁₆A₁₇A₁₈T₁₉G₂₀-3' which contains 10 Watson-Crick base pairs (see Table 3). Of course, no comparison can be provided for the terminal nucleobases numbers 1, 10, 11, and 20. Inspection of Table 3 confirms that, instead of carrying out the corresponding calculation on the full system, the energies of model triplets listed in Table 2 may be used for predicting reaction energies of hole transfer in polynucleotides (within an accuracy of 1 kcal/mol) in a semi-quantitative fashion. The mean deviation $\Delta\Delta = \Delta E - \Delta E_{tr}$ between the rela-

Table 3

Relative ionization energies^a ΔE for nucleobases in the decamer duplex 5'-CATTCTGGGCT-3' calculated with the NDDO-G model at regular geometry^b. Also given are the results for triplets ΔE_{tr} (see Table 2) and the differences $\Delta\Delta = \Delta E - \Delta E_{tr}$. All energies in eV

Nucleobase	C ₁ ^c	A ₂	T ₃	T ₄	C ₅	G ₆	G ₇	G ₈	C ₉	T ₁₀ ^c
ΔE	1.968	0.831	1.654	1.757	1.516	-0.042	0.0	0.312	1.946	1.809
ΔE_{tr}		0.749	1.615	1.831	1.612	0.036	0.0	0.303	1.892	
$\Delta\Delta$		0.082	0.039	-0.074	-0.096	-0.078	-	0.009	0.054	
Nucleobase	G ₂₀ ^c	T ₁₉	A ₁₈	A ₁₇	G ₁₆	C ₁₅	C ₁₄	C ₁₃	G ₁₂	A ₁₁ ^c
ΔE	0.375	1.349	0.644	0.530	0.122	1.607	1.982	1.953	0.397	0.696
ΔE_{tr}		1.319	0.718	0.575	0.168	1.628	2.031	1.959	0.304	
$\Delta\Delta$		0.030	-0.074	-0.045	-0.046	-0.021	-0.049	-0.006	0.093	

^a Absolute values of ionization energies may be obtained by adding 7.083 eV to ΔE and 7.304 eV to ΔE_{tr} .

^c Ref. [20].

^c No comparison may be given for terminal bases.

tive ionization energies in the decamer and the corresponding triplets are summarized in Table 3. For 16 such comparisons the mean value of $\Delta\Delta$ is 0.042 eV (0.97 kcal/mol), which is on the verge of the accuracy of the present calculations. More data are necessary to analyze whether these small energy differences indeed exhibit systematic trends. In any case, the triplet data (Table 2) should be used with caution when predicting small effects. For the 5'-G₆G₇G₈-3' hole trap our results show that the IPs of G₆ and G₇ are the lowest, being about equal. This computational result is in agreement with the experimental data [14] for the oxidation of the two terminal G bases in GGG.

4. Summary

Using the semi-empirical method NDDO-G designed for studying spectroscopic properties of organic and biological molecules, we calculated the reaction energy for migration of cation radical states between different nucleotide triplets XBY in DNA (X,B,Y = A,G,C,T). We found that, independent of neighboring bases, the states X(G⁺)Y are most stable, followed by states X(A⁺)Y and then by the states corresponding to T⁺ and C⁺. A significant new finding is that the stabilization of B⁺ in X(B⁺)Y is considerably affected by the *subsequent* base Y-3' while the effect of the *preceding* base 5'-X is rather small. Sequences of guanines, e.g., GG and GGG provide the most effective hole traps. For GG the moiety 5'-G of fragments 5'-XGG-3' provides the most effective trap for holes where the nature of X seems to be not very important. For GGG the two guanines on the 5'-side are most easily oxidized.

Ionization energies calculated for the decamer duplex CATTGGGCT suggest that the reaction energies for hole transfer within oligonucleotides may be estimated in a semi-quantitative fashion from energies obtained for model triplets (Table 2). The present study focused on energy differences between various nucleotide cation radical states. To calculate oxidation potentials of nucleobases within oligonucleotides that may be directly compared to experiment, both environmental effects and structure dynamics have to be taken into account. Computational work in this direction has been initiated.

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References

- [1] K.E. Erkill, D.T. Oldom, J.K. Barton, Chem. Rev. 99 (1999) 2777.
- [2] E. Meggers, M.-E. Michel-Beyerle, B. Giese, J. Am. Chem. Soc. 120 (1998) 12950.
- [3] S.O. Kelley, N.M. Jackson, M.G. Hill, J.K. Barton, Angew. Chem. Int. Ed. Engl. 38 (1999) 941.
- [4] H.-W. Fink, C. Schynenberger, Nature (London) 398 (1999) 407.
- [5] H. Sugiyama, I. Saito, J. Am. Chem. Soc. 118 (1996) 7063.
- [6] C.A.M. Seidel, A. Schulz, M.H.M. Sauer, J. Phys. Chem. 100 (1996) 5541.
- [7] M. Faraggi, M.H. Klapper, J. Chem. Phys. 91 (1994) 1054.
- [8] S. Steenken, S.V. Jovanovic, J. Am. Chem. Soc. 119 (1997) 617.
- [9] E. Meggers, M.-E. Michel-Beyerle, J. Am. Chem. Soc. 120 (1998) 12950.
- [10] B. Giese, S. Wessely, M. Spormann, U. Lindemann, E. Meggers, M.-E. Michel-Beyerle, Angew. Chem. Int. Ed. 38 (1999) 996.
- [11] E.D.E. Stemp, M.R. Arkin, J.K. Barton, J. Am. Chem. Soc. 119 (1997) 2921.
- [12] I. Saito, M. Takayama, Sugiyama, H.K. Nakatani, A. Tsuchida, M. Yamamoto, J. Am. Chem. Soc. 117 (1995) 6406.
- [13] I. Saito, T. Nakamura, K. Nakatani, Y. Yoshioka, K. Yamaguchi, H. Sugiyama, J. Am. Chem. Soc. 120 (1998) 12686.
- [14] Y. Yoshioka, Y. Kitagawa, Y. Tukan, K. Yamaguchi, T. Nakamura, I. Saito, J. Am. Chem. Soc. 121 (1999) 8712.
- [15] M. Bixon, J. Jortner, Adv. Chem. Phys. 106 (1999) 35.
- [16] J. Jortner, M. Bixon, T. Langenbacher, M.-E. Michel-Beyerle, Proc. Natl. Acad. Sci. USA 95 (1998) 12759.
- [17] M. Bixon, B. Giese, S. Wessely, T. Langenbacher, M.-E. Michel-Beyerle, J. Jortner, Proc. Natl. Acad. Sci. USA 96 (1999) 11713.
- [18] G. Bieri, L. Asbrink, J. Electron Spectrosc. Relat. Phenom. 20 (1980) 149.
- [19] A.A. Voityuk, M.C. Zerner, N. Rösch, J. Phys. Chem. A 103 (1999) 4553.
- [20] X.J. Lu, M.A. El Hassan, C.A. Hunter, J. Mol. Biol. 273 (1997) 681.
- [21] L. Clowney, S.C. Jain, A.R. Srinivasan, J. Westbrook, W.K. Olson, H.W. Berman, J. Am. Chem. Soc. 118 (1996) 509.
- [22] N.S. Hush, A.S. Cheung, Chem. Phys. Lett. 34 (1975) 11.
- [23] F. Prat, K.N. Houk, C. Foot, J. Am. Chem. Soc. 120 (1998) 845.