



# Magnetic interactions in dehydrogenated Guanine–Cytosine base pair

Prasenjit Seal<sup>a</sup>, Prakash Chandra Jha<sup>b</sup>, Hans Ågren<sup>b</sup>, Swapan Chakrabarti<sup>a,\*</sup>

<sup>a</sup> Department of Chemistry, University of Calcutta, 92, A.P.C. Ray Road, Kolkata – 700 009, West Bengal, India

<sup>b</sup> Department of Theoretical Chemistry, School of Biotechnology, Royal Institute of Technology, S-106 91 Stockholm, Sweden

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## ABSTRACT

Spin flip broken symmetry density functional theory is employed to determine the magnetic interactions in dehydrogenated Guanine–Cytosine (G–C) base pair. An antiferromagnetic (AFM) interaction between the electronic spins is suggested which gradually decreases at larger separation distances between the DNA bases. Beyond a certain separation distance, this AFM interaction becomes very weak and saturation in the values of magnetic coupling constant,  $J$  is observed. The variation in  $J$  values is in very good agreement with  $r^{-6}$  potential curve and also with the singlet–triplet energy gap. The overall investigation emphasizes the importance of H-bonding in determining the magnetic interactions in G–C diradicals.

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## 1. Introduction

The formation of radicals and anions among the DNA base pairs significantly alter their structure and may lead to DNA damage or formation of lesions within DNA strands [1–3]. As a consequence, strand breaking in DNA double helix structures, cellular inactivation, loss of genetic information and mutation is observed [4–6]. Lesions in DNA also result in the formation of cancer cells [7,8]. The DNA damage primarily occurs via harmful effects of radiation and also through oxidative bond cleavage [5,9–12]. There have been many novel investigations in this context explaining the mechanism of various possible channels that lead to DNA damage. Boudaiffa et al. [13] reported early the breakage of DNA strands by low energy electrons. Later on, several theoretical as well as experimental works have demonstrated that electrons with even near-zero eV energies are sufficient to form lesions in DNA [14–21].

Due to the effect of direct radiation, hydrogen atoms can be abstracted from the DNA base pairs and result in the formation of stable neutral, cationic and anionic radicals. Several studies have been carried out in this respect in order to characterize different possible stable radicals that could be derived from the DNA base pairs and also from individual bases [22–26]. Recently, Schaefer III and co-workers [7,27], have reported the possibility of formation of several open-shell deprotonated Guanine–Cytosine (G–C) radicals. They also investigated the structural changes that occur in the DNA base pairs due to the formation of these radicals. The group of Schaefer III also investigated the structures, energetics and properties of various deprotonated adenine–uracil (A–U) base pairs within density functional theory [8]. Apart from these works, there are numerous theoretical investigations based on the study of struc-

tures and energetics of closed shell adenine–thymine (A–T) and G–C base pairs [25,28] as well as of individual DNA bases [29–31].

Just like the formation of monoradicals in different DNA base pairs, in the present investigation we would intend to see what happen if diradical is formed? In these systems, two hydrogen atoms are abstracted simultaneously from the neutral DNA base pairs. At this point it is highly instructive to mention that earlier it has been observed that diradicals in DNA may be formed as an intermediate [32]. In the present work, we reported the results of one such diradical system, the G–C diradical. The two free radical centers on the G–C diradical may have ferromagnetic (FM) or antiferromagnetic (AFM) interaction. In order to evaluate the strength of magnetic interactions in this system, we have chosen the broken symmetry density functional theory (BS–DFT) as the prime investigating tool. We also intend to explore how the H-bonding influences the strength of magnetic interactions in the G–C diradical.

## 2. Computational details

The geometry optimization of the most stable diradical has been carried out at the spin-polarized Møller–Plesset perturbation (MP2) level of theory using Pople's 6-31+G(d,p) basis set within the GAUSSIAN 03 suite of programs [33].

The magnetic interactions for this diradical were determined by evaluating the Heisenberg coupling constant,  $J$ . Other parameters which include the diradical character and overlap integral have also been calculated within the broken symmetry (BS) formalism using the spin flip (SF) technique to generate an initial wave function. This SF approach [34,35] is a very useful tool for generating the broken symmetry solution in systems having unpaired electrons. Very recently, Seal and Chakrabarti [36] reported results for the magnetic interactions in alkyl-substituted cyclohexane diradical systems, using the spin flip broken symmetry density functional theory (SF–BS–DFT) scheme, which corroborate well

\* Corresponding author. Fax: +91 33 23519755.

E-mail address: [swapanchem@yahoo.co.in](mailto:swapanchem@yahoo.co.in) (S. Chakrabarti).

with experiments. In the SF approach, the spin up ( $\alpha$ ) and spin down ( $\beta$ ) densities of a converged high-spin (HS) state are combined to get total density and spin density matrices. The obtained spin density matrix is then modified by changing the sign of the matrix elements of any one of the radical centers. Using this modified spin density matrix and the total density matrix obtained earlier, initial guesses for both  $\alpha$  and  $\beta$  densities for the BS state is generated. In this context, it is to be noted that Krylov and co-workers developed another spin flip approach (SF-TDDFT) [37,38], which can efficiently handle multi-configurational situations without invoking BS solutions. In the present study, we employed the SF-BS methodology adopted by Neese [34] which is quite similar to that adopted by Rudberg et al. [35]. The BS method via the exchange of  $\alpha$  and  $\beta$  spins is well implemented in the ORCA [34] suite of programs. All the magnetic property calculations using the SF-BS technique were performed using the hybrid functional B3LYP [39,40] (20% HF exchange) and Pople's 6-311++G(d,p) basis set [41]. The magnetic property calculations employing the unrestricted BS-DFT method through orbital mixing (BS-UDFT) has also been performed within the GAUSSIAN 03 suite of programs [33].

### 3. Results and discussion

#### 3.1. Structures of dehydrogenated Guanine–Cytosine (G–C) base pair, i.e., G–C diradical

In this section, we describe the possible structures of the G–C diradical and its most stable form. There can be eight possible structural arrangements for the G–C diradical keeping the three H-bonds intact. In order to demonstrate all these eight structures, we provided a schematic representation in Fig. 1. The figure shows G–C base pair with numbers I–VIII written twice. To obtain the structure of one G–C diradical, we removed two hydrogen atoms bearing the same number at a time. In this way, one can easily obtain all the eight G–C diradicals by abstracting the H-atoms having the same number. Geometries for all these eight G–C diradicals are given in the Supplementary material. It is to be noted that the numbering in this figure is done in order of decreasing stability, i.e., arrangement I has got the highest stability, which gradually decreases as arrangement VIII is approached. In the present study we have taken only the most stable G–C diradical, i.e., diradical I for further calculation. At this point it is instructive to mention that the positions in the neutral G–C base pair from where the two

hydrogen (H) atoms are abstracted to form neutral G–C diradical I are attached with the sugar groups in nucleosides or nucleotides. However, in the present investigation, we performed our calculations on isolated G–C base pair and these two positions were found to be the most favorable one for the removal of H atoms [27].

A controversy is there in the literature regarding the removal of H atoms from the DNA bases. Jena and Mishra [31] in their work reported the interactions of guanine and its anions and radicals with lysine in different charge states. Their results suggest that in neutral guanine, removal of amino group H atom involved in H-bonding with cytosine occurs first than the H atom that we abstracted in the present investigation. However, Bera and Schaefer [27] earlier reported that the radical obtained by the removal of amino group H atom in guanine is about 15.5 kcal/mol less stable than that obtained by the removal of the H atom from the position used for sugar phosphate linkage in DNA, i.e., from where we abstracted the H atom of guanine to form diradical I. The reason behind this discrepancy in the removal of H atoms is mainly attributed to the different molecular environment. While Bera and Schaefer [27] have taken the DNA base pair and removed the H atoms from any one of the DNA bases, Jena and Mishra [31], on the other hand reported the results based on the calculation of single DNA base. In the present investigation, we have taken the DNA base pair and observed the sequential removal of H atoms and our results concur well with that of Bera and Schaefer [27].

#### 3.2. Magnetic interactions in the most stable dehydrogenated Guanine–Cytosine (G–C) base pair, i.e., G–C diradical

It is well known that the magnetic coupling constant,  $J$  can be explained by the Heisenberg–Dirac–van Vleck Hamiltonian. Earlier, Noodleman and co-workers [42,43] estimated this coupling constant after getting the unrestricted solutions for the high spin (HS) and BS state determinants as

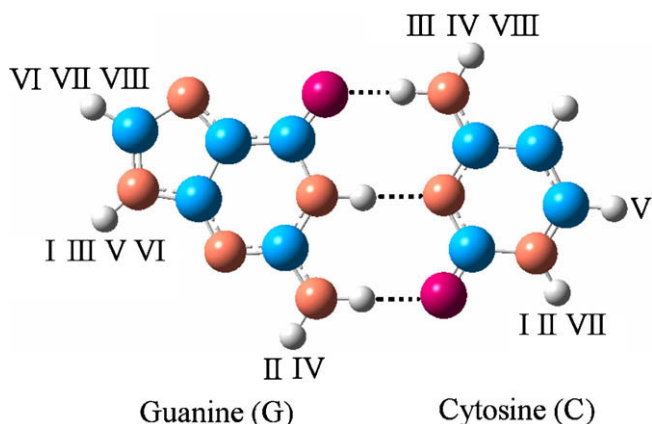
$$J_{\text{NOODLEMAN}} = -\frac{E_{\text{HS}} - E_{\text{BS}}}{S_{\text{max}}^2} \quad (1)$$

where  $E_{\text{HS}}$  and  $E_{\text{BS}}$  are the energies for the HS and BS states, respectively and  $S_{\text{max}}$  is the spin multiplicity of the HS state. However, Eq. (1) is valid only in the weak coupling region. Later on, Yamaguchi and co-workers [44,45] generalized Noodleman's equation over the entire coupling regime and obtained the following expression for  $J$ .

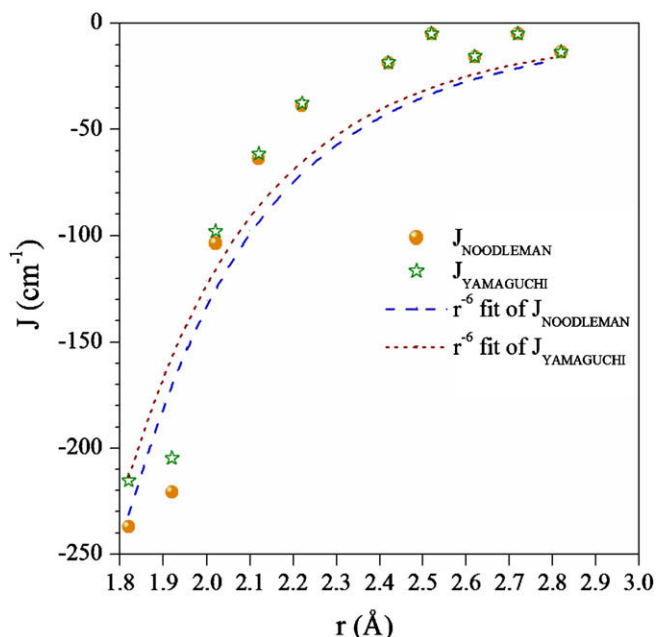
$$J_{\text{YAMAGUCHI}} = -\frac{E_{\text{HS}} - E_{\text{BS}}}{\langle \hat{S}^2 \rangle_{\text{HS}} - \langle \hat{S}^2 \rangle_{\text{BS}}} \quad (2)$$

where the denominator contains the spin expectation values for the HS and BS state determinants. This Yamaguchi equation (Eq. (2)) reduces to Noodleman's equation (Eq. (1)) in the weak coupling region.

Fig. 2 presents the variation of the magnetic coupling constant,  $J$  in both the Noodleman and Yamaguchi formalisms with increasing the distance of separation,  $r$  between the dehydrogenated DNA bases in the G–C diradical. The separation distance,  $r$  is the distance between the >NH of dehydrogenated guanine and the nitrogen atom of dehydrogenated cytosine (the middle H-bond in Fig. 1). An antiferromagnetic (AFM) interaction is observed between the electronic spins in the G–C diradical. Interestingly, it is observed that this AFM interaction reduces by 2–6 times at  $r = 2.02$ – $2.22$  Å relative to that at the equilibrium geometry ( $r = 1.82$  Å) and at  $r = 1.92$  Å. Beyond  $r = 2.32$  Å, i.e., from  $r = 2.42$  to  $2.82$  Å, an even-odd oscillation is observed in the  $J$  values. At higher distances of separation, the interaction between the spins is very weak. Another interesting observation is that as we approach a larger separation distance, the differences in the  $J$  values in Noodleman and Yamaguchi formalisms are reduced, and at  $r = 2.42$ – $2.82$  Å the



**Fig. 1.** A schematic representation of the G–C base pair with numbering I–VIII. The carbon, nitrogen, oxygen and hydrogen atoms are represented by sky blue, orange, pink and white colored balls, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 2.** Variation of the magnetic coupling constant,  $J$  in both the Noodleman (solid balls) and Yamaguchi (hollow stars) formalisms with the distance of separation between dehydrogenated Guanine and Cytosine bases in G-C diradical,  $r$  in SF-BS-DFT method. The minimum distance in the X-axis corresponds to the equilibrium geometry of the G-C diradical. The dashed and dotted lines are the  $r^{-6}$  fits of the  $J$  values in the Noodleman and Yamaguchi formalisms, respectively. In the web version, the solid balls are orange colored whereas the hollow stars are olive colored.

two values are almost equal. This is clear from Fig. 2, where the solid balls ( $J_{\text{NOODLEMAN}}$ ) and hollow stars ( $J_{\text{YAMAGUCHI}}$ ) almost get smeared at higher  $r$  values. At this point it is highly instructive to mention that at the geometry corresponding to  $r = 2.32$  Å and its near vicinity, the magnetic strength calculation does not converge and for this reason we are unable to provide any results related to that distance of separation. Interestingly, it has been observed that the variation in the  $J$  values obtained from both the formalisms adopted bear close resemblance with  $r^{-6}$  potential curve. In general, systems with weak interactions quite often follow the trend of  $r^{-6}$  potential in some of their properties. In the G-C diradical, this resemblance of  $J$  values with  $r^{-6}$  potential curve might be attributed to the presence of weak H-bonding interactions. We provided here the  $r^{-6}$  fits of  $J$  values in order to see how far the trend observed in the coupling constant values corroborate with this curve. In Fig. 2, the fittings are shown by dashed (Noodleman formalism) and dotted (Yamaguchi formalism) lines. At lower separation distance (except at  $r = 1.92$  Å), the  $J$  values are in well agreement with the  $r^{-6}$  curve, however, at some of the higher values of  $r$ , deviation from the fitted curve is observed.

It is to be noted that we also performed the magnetic interaction calculation via the usual BS-UDFT method through orbital mixing and obtained almost the same trend in the  $J$  values as that shown in Fig. 2. The relevant plot along with the  $r^{-6}$  fits is provided in the Supplementary material. In case of the BS-UDFT calculation, the  $J$  values at lower  $r$  concur well with the potential fit. On the other hand, at some of the higher  $r$  values, deviations in the  $J$  values are observed. The overall trend, however, is well in accordance with the  $r^{-6}$  potential fit.

### 3.3. Other parameters of interest including the overlap integral and diradical character

In order to provide an explanation of the trends observed in the  $J$  value, several other parameters of interest, including that of the

**Table 1**

Different parameters of interest calculated for the most stable Guanine-Cytosine (G-C) diradical using the SF-BS-DFT method.

$r$ (Å)	$S_{\text{var}}$	$c_{\text{ion}}^2$ (%)	$c_{\text{T}}^2$ (%)	$R_{\text{BS}}$ (%)
1.82 (Equilibrium geometry)	0.31093	4.83	45.17	90.33
1.92	0.27114	3.67	46.33	92.65
2.02	0.23187	2.69	47.31	94.62
2.12	0.19379	1.88	48.12	96.24
2.22	0.15572	1.21	48.79	97.57
2.32	–	–	–	–
2.42	0.12351	0.76	49.24	98.47
2.52	0.09991	0.50	49.50	99.00
2.62	0.05038	0.13	49.87	99.75
2.72	0.04042	0.08	49.92	99.84
2.82	0.03011	0.04	49.96	99.91

overlap integral,  $S_{\text{var}} (= \langle \phi_A | \phi_B \rangle)$ , and diradical character,  $R_{\text{BS}}$ , have also been determined using the SF-BS-DFT method. The wave function corresponding to the BS state can be written via the following expression [46].

$$|\phi^{\text{BS}}\rangle = |\phi_A \bar{\phi}_B\rangle = c_{\text{ion}} |^1\phi^{\text{ion}}\rangle + c_{\text{n}} |^1\phi^{\text{n}}\rangle + c_{\text{T}} |^3\phi^{\text{T}}\rangle \quad (3)$$

where the coefficients can be written as

$$c_{\text{ion}} = \frac{S_{\text{var}}}{\sqrt{2}}, \quad c_{\text{n}} = \frac{1}{\sqrt{2}}, \quad \text{and} \quad c_{\text{T}} = \sqrt{1 - c_{\text{ion}}^2 - c_{\text{n}}^2} \quad (4)$$

Eq. (3) clearly reveals the fact that the BS wave function have three components, i.e.,  $|^1\phi^{\text{ion}}\rangle$ ,  $|^1\phi^{\text{n}}\rangle$  and  $|^3\phi^{\text{T}}\rangle$ . The first component,  $|^1\phi^{\text{ion}}\rangle$  which accounts for the ionic nature, is a superposition of two orbitals where both unpaired electrons are centered only on one radical site (negatively charged) whereas the other site is electron deficient in nature and may be considered as positively charged. The second ( $|^1\phi^{\text{n}}\rangle$ ) and third ( $|^3\phi^{\text{T}}\rangle$ ) components are the neutral singlet and triplet respectively. These two terms are of pure diradical nature with the two unpaired electrons located on two different sites, one having opposite spin with respect to the other. However, the neutral component is antisymmetric whereas the triplet component is symmetric with respect to the exchange of electrons.

Another important parameter is the diradical character,  $R_{\text{BS}}$  which is written as

$$R_{\text{BS}} = 100(1 + |S_{\text{var}}|)(1 - |S_{\text{var}}|) \quad (5)$$

It is quite clear from the above equation (Eq. (5)) that diradical character contains only one parameter, i.e., the overlap integral,  $S_{\text{var}}$  and hence its role is of great significance in determining the nature of BS state, which in turn is related with magnetic interactions. In the weak coupling region, i.e., when  $S_{\text{var}}$  approaches zero, the BS state is an equal mixture of the singlet and triplet states while in the strong coupling region ( $S_{\text{var}}$  tends to unity), the BS state is a pure close shell state. In an intermediate situation, the BS state is a variationally determined mixture of ionic and neutral contributions and the percentage contributions are reflected in the value of  $S_{\text{var}}$ . The variation of all these parameters with increasing separation distance,  $r$ , is tabulated in Table 1. The plotting of each of these parameters is given in the Supplementary material. From the table and also from the figures (see Supplementary material), it is quite clear that as we increase the separation distance between the dehydrogenated DNA bases, the diradical character  $R_{\text{BS}}$  approaches 100% and the triplet state gets stability. On the other hand, at smaller  $r$  values,  $R_{\text{BS}}$  is much less than 100% and the BS state gets stability. A reverse trend is observed for the overlap integral,  $S_{\text{var}}$ , i.e., it approaches zero at higher  $r$  values.

### 3.4. The singlet–triplet energy gap

Apart from the calculation of magnetic coupling constant,  $J$ , singlet–triplet (S–T) gaps for the G-C diradical are also calculated. The

**Table 2**

Calculated singlet–triplet energy gaps for the G–C diradical (diradical I) using the SF–BS–DFT method.

$r$ (Å)	$E_{S-T}^{G-C}$ (kcal/mol)
1.82 (Equilibrium geometry)	–0.6780
1.92	–0.6319
2.02	–0.2952
2.12	–0.1822
2.22	–0.1107
2.32	–
2.42	–0.0530
2.52	–0.0138
2.62	–0.0438
2.72	–0.0138
2.82	–0.0392

S–T gaps are determined by taking the energy difference between the broken symmetry (BS) and high spin (HS) states, i.e.,  $E_{S-T} = E_{BS} - E_{HS}$ . A variation of the same is tabulated in Table 2 with increasing the separation distance,  $r$ . The table justifies the stability of the BS state compared to the HS state at all the separation distances in the G–C diradical. However, on approaching larger  $r$ , the relative stability of the HS state is much larger than that of the BS state and hence the singlet–triplet gap decreases. This gradual decrease in the energy gap is also reflected in the variation observed for the  $J$  value where the AFM interaction decreases appreciably as the relative stability of the triplet state increases at higher  $r$  values.

### 3.5. Role of H-bonding in the magnetic interactions of dehydrogenated Guanine–Cytosine (G–C) base pair, i.e., G–C diradical

As the G–C diradical (diradical I) contains three hydrogen bonds, they may have some role to play in interpreting the magnetic interactions in this system. To find out whether the H-bonding plays any crucial role in determining the nature of variation in the  $J$  values as given in Fig. 2, we performed SF–BS–DFT calculation taking the equilibrium geometry of the G–C diradical and replacing the two oxygen atoms (one from the dehydrogenated guanine and the other one from the dehydrogenated cytosine bases) with four hydrogen atoms, two on each site. This is done in order to remove the two (out of three) hydrogen bonds that are present in the G–C diradical (diradical I). The relevant geometry is given in the Supplementary material. The  $J$  values obtained ( $J_{\text{NOODLEMAN}} = -28.98 \text{ cm}^{-1}$  and  $J_{\text{YAMAGUCHI}} = -28.90 \text{ cm}^{-1}$ ) clearly indicates that the AFM interaction reduces appreciably (more than 8 times) when we removed the hydrogen bonds compared to that of the equilibrium geometry ( $J_{\text{NOODLEMAN}} = -237.17 \text{ cm}^{-1}$  and  $J_{\text{YAMAGUCHI}} = -215.28 \text{ cm}^{-1}$ ). Presence of strong H-bonding interactions at short distance of separation can also be checked if we place the dehydrogenated guanine and cytosine bases perpendicular to each other keeping the separation distance same as that of the equilibrium geometry. In this perpendicular arrangement of GC diradical where two out of three H-bonds is removed, the  $J$  values obtained are  $-40.69 \text{ cm}^{-1}$  and  $-38.70 \text{ cm}^{-1}$ , respectively in the Noodleman and Yamaguchi formalisms. It also clearly justifies the role of H-bonding in influencing the magnetic interactions in these GC diradicals. Moreover, it is also observed that if we go beyond a certain separation distance ( $r = 2.8 \text{ Å}$  from the equilibrium geometry, i.e., when  $r = 0.0 \text{ Å}$ ), then ground state may be ferromagnetic also ( $J_{\text{NOODLEMAN}} = 7020.97 \text{ cm}^{-1}$  and  $J_{\text{YAMAGUCHI}} = 6589.37 \text{ cm}^{-1}$ ), which in turn indicates the crucial role of H-bonding interaction ( $r^{-6}$ ) in determining the ground state for the GC diradical. In this context, it is instructive to mention that earlier, the H-bonding mediated AFM ground state has been observed for dinuclear Ni(II) complexes [47]. The trend observed in the  $J$  values in Fig. 2 also suggests that the

magnetic interaction in this G–C diradical is strongly influenced by the weak interactions present in this system. In principle, this work can further be improved by using Truhlar's potential [48] and dispersion corrected functionals of Grimme [49,50].

## 4. Conclusion

In the present investigation, spin flip broken symmetry density functional theory (SF–BS–DFT) has been employed in order to interpret the magnetic interaction in Guanine–Cytosine (G–C) diradicals. Our results suggest an antiferromagnetic interaction in these diradicals. This antiferromagnetic interaction reduces appreciably, by 2–6 times, as larger separation distances ( $r = 2.02$ – $2.22 \text{ Å}$ ) are approached between the dehydrogenated DNA bases relative to that at lower  $r$  values ( $r = 1.82$  and  $1.92 \text{ Å}$ ). Although an even–odd oscillation in the  $J$  values is observed at higher  $r$  values, the interaction between the electronic spins is very weak compared to that at lower separation distances. The trend observed in the magnetic coupling constant,  $J$ , corroborates with the  $r^{-6}$  potential. The calculated singlet–triplet gap also support the variation observed in the magnetic coupling constant values. The overall investigation highlights the crucial role of H-bonding in determining the magnetic interactions in G–C diradicals.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cplett.2008.09.069.

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