Is "Frank" DNA-Strand Breakage via the Guanine Radical Thermodynamically and Sterically Possible?

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Abstract: Using the reduction potential of one-electron oxidized guanosine in water and the pK_a values of the radical and of the parent, the N1–H bond energy of the 2′-deoxyguanosine moiety is determined to be (94.3 ± 0.5) kcal mol^{-1}. Using the DFT method, the energy of the N1-centered guanosine radical is calculated and compared with those of the C1′- and C4′-radicals formed by H-abstraction from the 2′-deoxyribose moiety of the molecule. The result is that these deoxyribose-centered radicals appear to be more stable than the N1-centered one by up to 3 kcal mol^{-1}. Therefore, H-abstraction from a 2′-deoxyribose C–H bond by an isolated guanosine radical should be *thermodynamically* feasible. However, if the stabilization of a guanine radical by intrastrand $\pi-\pi$ interaction with adjacent guanines and the likely lowering of the oxidation potential of guanine by interstrand proton transfer to the complementary cytosine base are taken into account, there is no more thermodynamic driving force for H-abstraction from a deoxyribose unit. As a further criterion for judging the probability of occurrence of such a reaction in DNA, the stereochemical situation that a DNA-guanosine radical faces was investigated utilizing X-ray data for relevant model oligonucleotides. The result is that the closest H-atoms from the neighboring 2′-deoxyribose units are at distances too large for efficient reaction. As a consequence, H-abstraction from 2′-deoxyribose by the DNA guanine radical leading subsequently to a "frank" DNA strand break is very unlikely. The competing reaction of the guanine radical cation with a water molecule which eventually yields 8-oxo-2′-deoxyguanosine (leading to "alkali-inducible" strand breaks) has thus a chance to proceed.

Keywords: bond energies · density functional calculations · DNA cleavage · electron transfer

Introduction

It is well known[1–5] that, among the DNA components, the nucleic acid bases are the most sensitive to modification by endo- or exogeneous (noxious) agents. With respect to oxidizing agents, guanine (G) is the most "labile" among the bases. It is thus typically the preferred site of attack of "reactive oxygen species" which are produced not only as intermediates and by-products of aerobic respiration but also through exposure of cells to ionizing radiation or photochemical (or "dark"[6]) reactions that generate free radicals. Free radical induced modifications of DNA bases and, specifically, G, are believed to be involved in physiologically deleterious processes such as cancer[7] and also in ageing.[8] However, for the living organism, the even more destructive process is *DNA-strand breakage*. This oxidation-induced reaction involves the deoxyribose-phosphate *backbone* of DNA and *not* (directly) a G moiety. The question is thus whether an apparently stable radical from a *more* easily oxidized component of DNA, that is G, is able to oxidize the much *less* easily oxidized deoxyribose(phosphate) moiety. Since this question is under debate,[9–11] we were interested in its thermodynamics and kinetic feasibility and we present data on this in the following.

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author: Table containing C–H bond angles in oligonucleotides; tables containing data (bond lengths and angles) obtained by the DFT calculations.

Results and Discussion

The first step in the approach we take is to determine the N1–H bond dissociation energy (BDE) of guanosine:

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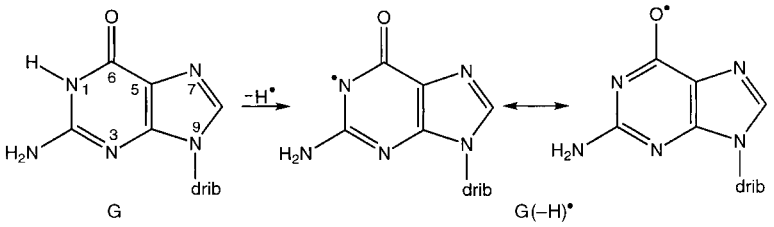
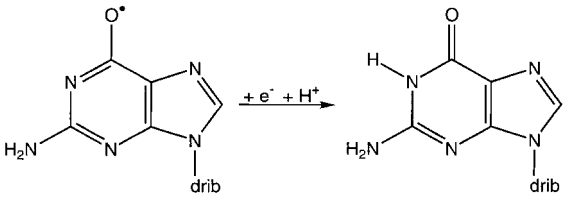


(1)

Based on the known pK_a values of the parent,[12] and of the guanosine radical,[13] and of the reduction potential of the latter,[14] that is, the potential for the process:



(2)

and using an established formalism,[15–18] the following Equations can be written, for which data is also available:

Case A: Use of pK(guanosine *radical*) ≡ pK_r

$G \rightleftharpoons G(-H)^{\bullet} + H^{\bullet}$ BDE(G–H)

$G^{\bullet+} \rightleftharpoons G(-H)^{\bullet} + H^{+}$ p$K_r = 3.90$[13]

$G^{\bullet+} + e^{-} \rightleftharpoons G$ $E^0(G^{\bullet+}/G) = 1.58$ V[14]

$H^{+} + e^{-} \rightleftharpoons H^{\bullet}$ $E^0(H^{+}/H^{\bullet}) = -2.29$ V[18]

$BDE(G{-}H) = 1.37\,pK_r - 23.06\,E^0(H^{+}/H^{\bullet}) + 23.06\,E^0(G^{\bullet+}/G)$

from which BDE(G–H) results as 94.6 kcal mol^{-1}.

Case B: Use of pK(guanosine) ≡ pK_a

$G(-H)^{-} \rightleftharpoons G(-2H)^{2-} + H^{+}$ p$K_{a2} = 12.33$[12]

$G(-2H)^{\bullet-} + e^{-} \rightleftharpoons G(-2H)^{2-}$ $E^0(G(-2H)^{\bullet-}/G(-2H)^{2-}) = 1.05$ V[14]

$H^{+} + e^{-} \rightleftharpoons H^{\bullet}$ $E^0(H^{+}/H^{\bullet}) = -2.29$ V

$BDE(G{-}H) = 1.37\,pK_{a2} - 23.06\,E^0(H^{+}/H^{\bullet}) + 23.06\,E^0(G(-H)^{\bullet-}/G(-2H)^{2-})$ from which BDE(G–H) results as 93.9 kcal mol^{-1}.

Since the BDEs obtained with the two different sets of values (cases A/B) are very similar, it is legitimate to take the average of the two as the N–H bond energy [Eq. (1)] of guanosine, that is BDE(G–H) = 94.3 ± 0.5 kcal mol^{-1}. This value is reasonable in comparison with analogous ones[19, 20] from simpler compounds, for example, BDE(H_2N–H) = 108, BDE(*para*-NCC_6H_4NH–H) = 91.6, BDE(glutarimide, *cycl*-(O=C)$CH_2CH_2CH_2$(C=O)N–H) = 116, BDE(HC(O)NH–H)[21] = 116 kcal mol^{-1}.

The BDE(G–H) = 94.3 ± 0.5 kcal mol^{-1} is larger than that of *C*–H bonds, such as 88 kcal mol^{-1} for $HOCH(CH_3)$-H,[22] or 92 kcal mol^{-1} for tetrahydrofuryl–2*H*.[23] Concerning radicals formed by H-abstraction from the 2′-deoxyribose unit, *relative* stabilities have recently been calculated using density functional theory.[24] According to these authors the C4′-radical is the most stable, followed by the C1′ and C3′ radicals which are ≈2 kcal higher in energy. If these energy values for the 2′-deoxyribose radicals are converted into C–H bond energies, the value for the C4′-site is 83.62 kcal mol^{-1}.[25] On this basis, the (hypothetical) H-abstraction from C4′ by the guanosine radical would be exothermic by 94.3 – 83.6 = 10.7 kcal mol^{-1}.

In order to check this result which partly contains experimentally determined (BDE(G–H) = 94.3 kcal mol^{-1}) and partly calculated[26] (the BDE(C′–H)) energies, theoretical calculations were performed with the GAUSSIAN 98 program package[27] utilizing the density functional theory (DFT) employing an unrestricted wave function.[28] The functional was the Lee, Yang and Parr for the correlation part[29] and the Becke's three parameter functional for the exchange part (B3LYP).[30, 31] The basic split valence standard 6-31G basis set[32] was used for the geometry optimization and frequency analysis. The zero-point energy was scaled according to Wong (0.9804).[33] Subsequent single-point energy calculations were performed with the 6-31+G(d,p) basis set with diffuse and polarisation functions.[34, 35]

The idea is to get the energy change in the loss of an H$^{\bullet}$ from the N1 of the *guanine* moiety of 2′-dGuo, a reaction which gives rise to the same radical (G(–H)$^{\bullet}$) as that from the N1-deprotonation of the radical cation of the guanine moiety,[13] and, using exactly the same method and parameters, to get and to compare this with the energy change in the loss of an H$^{\bullet}$ from one of the carbons of the *2′-deoxyribose* part of the same molecule. The energy of the 2′-*d*Guo(N1(–H)$^{\bullet}$) radical is used as the basis for comparison, that is its energy is arbitrarily set to zero. From the comparison with the relative energy of the parent compound (calculated to be –404.7 kcal mol^{-1}) and taking into account the energy of H$^{\bullet}$ (–313.9 kcal mol^{-1}) the N1–H bond energy results in 90.8 kcal mol^{-1} which is not far off the experimentally determined number of 94.3 ± 0.5 kcal mol^{-1} which relates to aqueous phase, in contrast to the vacuum environment relevant for the calculated value.

Compared with the base-derived radical N1$^{\bullet}$, the energies of the deoxyribose-derived radicals turned out to be partly lower and partly higher, depending on the position on the deoxyribose moiety (which is in agreement with the analogous DFT results of ref. [24]), as shown in Table 1:

The conclusion is thus that the C4′- and, particularly, the C1′-radical is more stable than the N1-radical.[36] On this basis, formation of C4′- or C1′-yl from N1-yl is a possibility. Concerning, however, the situation in DNA, there are two factors that can be predicted to change the thermodynamics: a) *Intra*strand π – π interactions in "clusters" of purine bases

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Table 1. Relative energies of 2′-deoxyguanosine radicals [kcal mol^{-1}].

Site of radical	Relative energy
N1	≡0.0[a]
C1′	−3.1
C2′	4.7
C3′	1.6
C4′	−0.4
C5′	1.6

[a] The N1–H bond energy is 90.8 kcal mol^{-1}.

(e.g., AG, GG, GGG, G$_n$) lead to a decrease of the ionization potential of this moiety which has been calculated[37, 38] to correspond to 0.47 eV (10.8 kcal mol^{-1}) for $n=2$, and 0.68 eV (15.7 kcal mol^{-1}) for $n=3$. Even if these values are overestimated, the oxidation potential of G *in DNA* can still be assumed to be lowered due to *inter*strand proton transfer *within* the base pair,[2, 39] that is from G$^{\bullet+}$ to C. At present, the latter effect can only be quantified crudely, based on the greater basicity of C (pK_a(CH$^+$) = 4.3) as compared to H_2O (pK_a(H_3O^+) = −1.7),[40] to lead to a decrease of the reduction potential of G$^{\bullet+}$ by 8 kcal mol^{-1}[41] and thus, as the consequence, to a decrease of the G–H bond energy (making H-abstraction by the G-radical from a ribose unit even less likely if not impossible).[42]

We consider next the *steric* situation which a guanine radical faces in DNA. Since the guanine radical can be assumed to have high spin density on N1, N3, and O^6,[43] (see also ref. [44]), H-abstraction by these atoms has to be considered, as shown below[45, 46] in Scheme 1:

Concerning the situation of the guanine radical in DNA, structures of an increasing number of oligonucleotides are available via the Nucleic Acid Database (NDB[47]).[48] The case first presented relates to 5′-d(GCCCGGGC)-3′ (NDB ID: ADH008), a synthetic nucleotide which assumes the A conformation.[49, 50] X-ray diffraction data do not provide information on the position of hydrogen atoms. To overcome this difficulty, we have inserted H-atoms in the oligonucleotides at the positions of minimum energy according to the MM3 force field,[51–53] using the program Web Lab Viewer. An illustrative example is shown in Figure 1.[54]

Furthermore, in a GGG triplet, the first (5′ side) guanine has been shown to have the lowest energy.[37, 38] Therefore, the distances between the N1, N3, and O^6 atoms of *this* base and the hydrogens on the deoxyribose carbon atoms were measured, whereby the hydrogens on the neighboring 5′ side (C, $n-1$), the same (G, n), and the neighboring 3′ side (G, n+1) nucleotides were considered. The results are shown in Table 2.

Figure 1. Structure of the first (5′ side) G nucleotide of the GGG triplet in the oligonucleotide 5′-d(GCCCGGGC)-3′ including the inserted deoxyribose hydrogen atoms. Details of the position of the hydrogen atoms are given in Table 2.

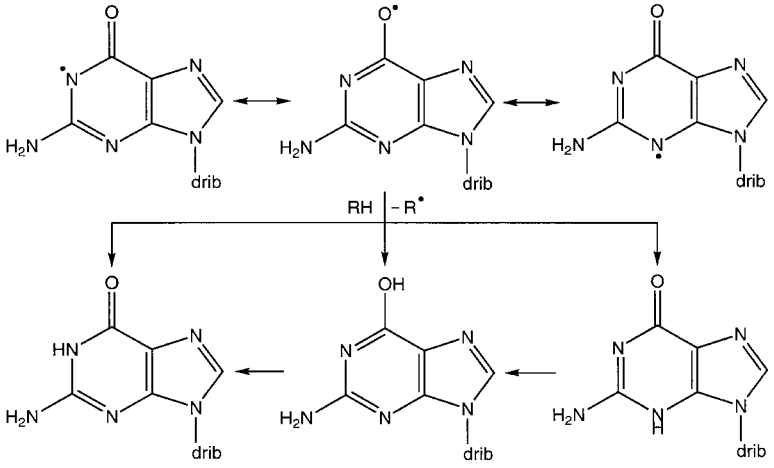
From the values in Table 2 it is evident that the C1′ and C2′ hydrogens, which point towards the base-stack, are in general closer to the guanine than those on C3′, C4′, and C5′. Moreover, the hydrogens of the 3′-side neighboring nucleotide are closer than those on the 5′ side.

Table 2. Bond lengths [Å] between atoms of the first (5′ side) G of the GGG triplet and the H-atoms of close deoxyribose groups in the oligonucleotide 5′-d(GCCCGGGC)-3′.

		N1	N3	O^6
	C1′	8.4	7.1	8.4
	C2′	7.4, 8.6	6.1, 7.0	7.2, 8.7
C ($n-1$)	C3′	9.2	8.2	8.6
	C4′	11.0	9.7	10.7
	C5′	12.0, 12.1	10.9, 11.1	11.3, 11.4
	C1′	5.1	2.9	6.2
	C2′	4.7, 6.0	2.7, 3.7	6.0, 7.3
G (n)	C3′	6.1	4.4	6.6
	C4′	7.9	5.7	8.6
	C5′	8.0, 9.1	6.4, 7.2	8.1, 9.4
	C1′	4.6	3.7	6.6
	C2′	6.1, 6.7	5.7, 5.9	7.6, 8.4
G (n+1)	C3′	7.0	6.0	8.2
	C4′	7.5	5.9	9.3
	C5′	7.7, 8.6	5.7, 6.8	9.1, 9.9

In order to judge the situation in *B*-DNA, the same procedure was applied to the oligonucleotide 5′-d(CAAAGAAAAG)-3′ (NDB ID: BDJ081).[55] The distances between atoms on the central G and vicinal deoxyribose hydrogens on the same and on the complementary strand (Figure 2) were measured and are shown in Table 3.

From Table 3 it is evident that, as in the case of *A*-DNA, the C1′ and C2′ hydrogens are the closest to the guanine. It can also be seen that some C1′ and C2′ hydrogen atoms on the complementary strand are at distances slightly shorter than 6 Å. Nonetheless, the overall reaction distances are too large for the H-abstraction reaction



Scheme 1.

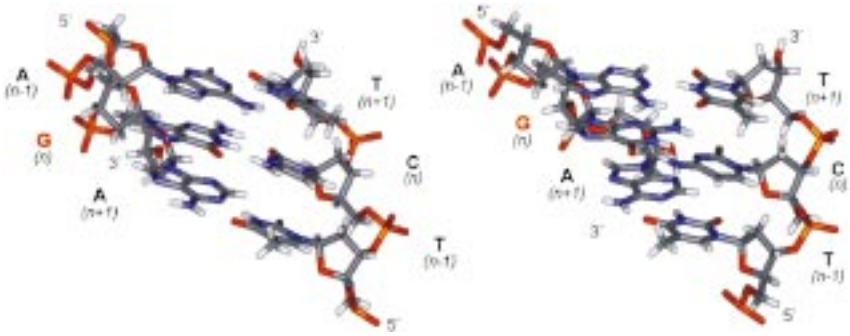


Figure 2. Structure of a segment of the oligonucleotide 5′-d(CAAAGAAAAG).

Table 3. Bond lengths [Å] between atoms of the central G and the hydrogens of close deoxyribose groups in the oligonucleotide 5′-d(CAAAGAAAAG)-3′.

			N1	N3	O^6
		C1′	6.4	5.4	6.4
		C2′	6.8, 7.0	5.6, 6.3	6.7, 6.4
	A ($n-1$)	C3′	9.2	8.3	8.6
		C4′	9.4	8.3	9.2
		C5′	10.6, 11.1	9.9, 10.2	10.0, 10.6
		C1′	4.6	2.3	5.9
		C2′	5.9, 6.1	3.9, 4.3	7.1, 6.7
same strand	G (n)	C3′	7.9	5.9	8.6
		C4′	7.5	5.3	8.6
		C5′	8.1, 9.0	6.3, 7.0	8.6, 9.7
		C1′	5.6	4.4	7.5
		C2′	7.3, 7.5	5.8, 6.3	8.8, 9.3
	A (n+1)	C3′	8.7	6.8	10.4
		C4′	7.6	5.6	9.6
		C5′	7.3, 8.6	5.0, 6.4	9.1, 10.3
		C1′	6.0	6.0	7.9
		C2′	7.9, 8.0	8.5, 8.1	9.5, 9.7
	T (n+1)	C3′	9.2	9.5	11.0
		C4′	7.8	7.8	9.9
		C5′	7.9, 9.2	8.3, 9.5	9.7, 11.1
		C1′	5.9	7.2	7.3
		C2′	7.3, 7.5	8.6, 9.2	8.6, 8.4
complementary strand	C (n)	C3′	9.4	10.9	10.4
		C4′	8.8	10.1	10.0
		C5′	9.3, 10.3	10.9, 11.8	10.0, 11.1
		C1′	7.7	9.5	8.0
		C2′	8.3, 8.4	10.4, 10.6	8.4, 8.1
	T ($n-1$)	C3′	10.5	12.7	10.3
		C4′	10.8	12.7	10.8
		C5′	11.4, 12.2	13.4, 14.2	11.1, 11.9

to be fast enough to be of importance (for the lifetime of the guanine radical in DNA in aqueous solution, see ref[56]). The conclusion is thus that such a reaction in DNA is not very likely. This gives the reaction of the guanine radical cation with a (nucleophilic) water molecule a chance to proceed. In double-stranded DNA, this reaction leads (see ref. [57]) to an 8-oxo-2′-deoxyguanosine moiety which, upon treatment of the DNA with piperidine, gives rise to a strand break. It should be kept in mind, however, that in *solution* DNA is not a stiff rod but undergoes dynamic structural changes (see ref. [58–60]) as a result of which the reaction distance for H-abstraction may be reduced to more favorable values. A possibility is that radical formation in DNA[2] leads to an increase in the flexibility of the strand with a corresponding enhancement of the degrees of motional freedom, allowing an even closer mutual approach of the reaction partners.[61] These possibilities are at present difficult to quantify.

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