Electron induced single strand break and cyclization: a DFT study on the radiosensitization mechanism of the nucleotide of 8-bromoguanine

Lidia Chomicz,[a] Al'ona Furmanchuk,[b,c] Jerzy Leszczynski[b] and Janusz Rak*[a]

*Corresponding author: e-mail: *janusz.rak@ug.edu.pl*, tel: +48 58 523 51 18

Abstract:

Cleavage of the O-P bond in 8-bromo-2'-deoxyguanosine-3',5'-diphosphate (BrdGDP), considered as a model of single strand break (SSB) in labelled double-stranded DNA (ds DNA), is investigated at the B3LYP/6-31++G(d,p) level. The thermodynamic and kinetic characteristics of the formation of SSB are compared to those related to the 5',8-cycloguanosine lesion. A first reaction step, common to both damage types, which is the formation of the reactive guanyl radical, proceeds with a barrier-free or low-barrier release of the bromide anion. The guanyl radical is then stabilized by hydrogen atom transfer from the C3' or C5' sites of the 2'-deoxyribose moiety to its C8 center. The C3' path, via the O-P bond cleavage, leads to a ketone derivative (the SSB model), while the C5' path is more likely to yield 5',8-cycloguanosine.

Keywords: DFT calculations, radiosensitizers, bromonucleotides, electron-induced DNA degradation, purine nucleoside cyclization

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[a] Department of Chemistry, University of Gdańsk, Wita Stwosza 63, 80-308 Gdańsk, Poland
[b] Interdisciplinary Nanotoxicity Center, Jackson State University, Jackson, Mississippi, 39217, USA
[c] A. Furmanchuk present address: Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208, USA

1. Introduction

While cancer is one of the most frequent reasons of death in human population, radiotherapy is one of the most common modality for cancer treatment. Indeed, more than fifty percent of cancer patients receive radiotherapy.[1] The most important target for ionizing radiation (IR), as concerns cell killing, is DNA. IR, absorbed by cytoplasm or membrane of eukaryotic cells causes only little lethal damage, while as soon as high energy photons reach the nucleus a spectacular increase of cellular death is noticed.[2] However, due to efficient DNA repair mechanisms[1] and hypoxia conditions in cancer cells,[3] an effective radiotherapy requires relatively high doses of IR which may lead to many side effects, including a secondary cancer.[4] This situation calls for applications of radiosensitizers – substances, which are able to increase DNA damage caused by a given dose of high energy radiation in cancer cells.

Surprisingly, the number of radiosensitizers currently employed in the clinical practice, is not very high,[5] which suggests a room for novel potential radiotherapy enhancers.[6] To rationally design them and predict their behavior as well as possible side effects, the radiosensitization mechanism of potential candidates has to be investigated.

IR causes cell death mainly through DNA damage induced by the products of water radiolysis: hydrogen radicals, hydroxyl radicals ($OH^\bullet$), and solvated electrons, which are the most numerous.[7,8] The indirect DNA damage is mostly a result of the highly reactive $OH^\bullet$ attack. Moreover, it seems that unlike presolvated electrons,[9,10] solvated electrons, the reducing counterparts of the $OH^\bullet$ radicals, are unable to induce DNA strand breaks.[11] The low reactivity of hydrated electrons with DNA may be related to the fact that in water solution the solvated electron is bound by ~3.4 eV[12] while the electron affinities of native nucleosides in DNA are around 2 eV only.[13,14] However, solvated electrons might be attached to DNA, if the biomolecule

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was modified with nucleosides of an increased electron affinity. Additionally, this type of radiosensitization requires that modified nucleosides are easily incorporated in DNA during its biosynthesis or repair, and are decomposed after electron attachment, yielding highly reactive radicals that could result in strand breaks or other types of cytotoxic DNA lesions in secondary steps.

Halogen substituted pyrimidines have been considered as potential sensitizers, likely to be used for clinical applications,[15-17] since the late nineteen fifties[18,19] when the photosensitizing properties of 5-bromo-2'-deoxyuridine (5BrdU) in *E. coli* cells were revealed. They were then studied as incorporated into cancer cells[20-22] and model DNA fragments[23-25]. Moreover, recently a revival interest of 5BrdU and its analogue 5IdU as radiosensitizing agents in the treatment of poorly radioresponsive human tumors can be seen.[26,27]

It is believed that sensitizing properties of halouracils incorporated in DNA are related to their interactions with solvated electrons, produced indirectly during radiotherapy.[28] Their increased electron affinity, in comparison to native uracil/thymine, makes them likely to bound solvated electrons that results in the primary anion radicals of the modified uracil. Then, these radicals undergo a rapid halide anion abstraction, producing almost quantitatively the reactive uridine-5-yl radical[29], that is able to lead to DNA damage, while stabilizing itself.

Not only 5BrdU, but also other brominated nucleosides: 8-bromo-2'-deoxyadenosine, 5-bromo-2'-deoxycytidine and 8-bromo-2'-deoxyguanosine, isolated or as a fragment of DNA chain have been considered[30-37] in the context of their radiosensitivity. Our recent computational studies on electron capturing by the four bromonucleobases (BrNBs) show that their radical anions behave similarly, i.e. they release the bromide anion and produce a base-localized,

potentially reactive, radical.[38] Encouraged by those results, we compared electron stimulated desorption (ESD) from thin layers of native or brominated single stranded oligonucleotide trimmers anions. We concluded that abstraction of the bromide anion is one of the primary degradation paths typical for brominated trimmers, giving the explanation to their radiosensitivity. Moreover, in the HPLC analysis of the brominated oligonucleotides, bombarded with 10 eV electrons, we proved that they are 2-4 times more radiosensitive than the native ones.[39,40]

In the present computational report we describe electron attachment to a model nucleotide of bromoguanine, i.e. to 8-bromo-2'-deoxyguanosine 3',5'-diphosphate (BrdGDP) and propose the mechanism of subsequent radical reactions that finally lead to sugar-phosphate chain break or 5',8-cycloguanosine mutation – a helix-distorting lesion and DNA replication and transcription blocker.[41,42] We reveal that an electron attached to BrdGDP primarily activates a low- or barrier-free abstraction of the bromide anion, producing thereby the reactive 8-guanosyl radical. The aforementioned might stabilize itself by hydrogen atom shift between the own deoxyribose fragment and the nucleobase. At the very end it leads to the O-P bond break (which mimics SSB in the labelled DNA) or to the formation of 5',8-cycloguanosine. Thus, we compare two competitive degradation mechanisms, which might be effective in the irradiated aqueous solutions of DNA labelled with 8-bromoguanine.

2. Methods

All calculations were performed with the use of B3LYP functional[43] in the 6-31++G(d,p) basis set[44] , both in the gas phase and in water solution. The B3LYP method was reviewed and proved to be useful for predictions of electron binding energies for valence-bound molecular

anions.[45] To account for the aqueous environment effect, Polarizable Continuum Model (PCM)[46] was employed. Unconstrained geometry optimizations were carried out separately in the gas phase and in solution. Previously, we have used the same methodology to model electron-induced degradation of brominated adenosine diphosphate.[47]

The energy changes calculated for particular reaction steps (ΔEs) are the differences between the electronic energies of products and substrates. Analogically, the corresponding Gibbs free energies changes (ΔGs) are ΔEs including zero-point energies, thermal corrections as well as the pV and entropy terms, computed in the rigid rotor-harmonic oscillator approximation at T=298 K and p=1 atm.[48] ΔGs in aqueous solutions are corrected in the same manner as the changes in gas-phase Gibbs free energies.[49]

The adiabatic electron affinity (AEA_E) is the difference between electronic energies of the neutral molecule and its corresponding anion radical, both at their fully optimized geometries. Similarly, a difference between the Gibbs free energies of the fully relaxed neutral and anion radical is marked as AEA_G. Electron vertical detachment energy (VDE) is the change in electronic energy of the neutral and the corresponding anion radical at the anion radical fully relaxed geometry, while the vertical electron affinity (VEA) is also defined as the difference in electronic energy of neutral and anion, but at the fully relaxed neutral geometry.

The Gaussian09[50] code was used for all computations, while the molecules structures were visualized with the GaussView package.[51]

3. Results and discussion

In the following sections we will discuss the thermodynamics and kinetics of several possible degradation pathways induced by electron attachment to the diphosphate of 8-

bromogunosine. First, the electron attachment process coupled with the subsequent bromide anion release and formation of the guanine radical will be characterized. Then three degradation paths of the radical will be considered: i) the first, leading through intranucleotide hydrogen atom transfer and phosphodiester bond break at the 3'-site to a ketone derivative, ii) the second, leading analogically to SSB at the 5'-site, with an aldehyde derivative formation, iii) the third, leading to the 5',8-cycloguanosine product (cycloG), with no strand breakage (see Figure 1.)

3.1. Model

The electron induced degradation of DNA, substituted with brominated purines, was analysed with the use of a model bromoguanine: 8-bromo-2'-deoxyguanosine diphosphate (BrdGDP). The starting geometry of this potential radiosensitizer was built with the use of experimental X-ray data for 2'-deoxyguanosine nucleotide in the B type helical DNA fragment (PDB accession code: 3BSE).[52] More precisely, the BrdGDP structure was cut out from the aforementioned B-DNA helix cutting the O-P bonds between guanosine and its 5' and 3' neighbors. Then, such created unsaturated bonds were filled with methyl groups and the negatively charged phosphate moieties were neutralized by protons. Finally, the C8 position hydrogen atom was replaced with bromine, with the 1.9 Å C8-Br bond distance, which had been previously optimized for 9-methyl-8-bromoguanine at the B3LYP/6-31++G(d,p) level.[38] This neutral initial geometry converged, within the B3LYP optimization, to a structure that hardly differs from the starting one. This suggests that the chosen model maintains correctly the B-DNA constraints.

3.2. Electron attachment and the bromide anion release

An electron, when attached to the neutral BrdGDP (*neu* – see Figures 1 and 2) in the gas phase, forms a weakly bound dipole bound (DB) anion radical, *anrad*, in which the C-Br bond breaks to produce an anionic complex (*complex*, see Figure 2) which represents the vertically and adiabatically stable valence anion (see Table 1). *Anrad* formed immediately after electron attachment, possesses a typical diffuse SOMO orbital localized on the positive pole of the molecular dipole . The formation of the DB state remains in accordance with the fact that in the gas phase 8-bromo-1-methylguanine supports the same type of anion.[47]

A stable DB type *anrad* anion radical is observed in the gas phase only. Indeed, in a condense phase a DB state is strongly destabilized and, therefore, a dipole bound anion of a nucleobase does not occur in a biological system.[53] In an aqueous solution, electron attachment to BrdGDP immediately induces a barrier free C-Br bond breakage that yields the *complex* anion (indeed, within the PCM model of water the B3LYP geometry optimization of the BrdGDP anion starting from the geometry of the neutral converges smoothly – without any kinetic barrier – to the anionic complex). But even in the gas phase, the C-Br bond breakage is thermodynamically a highly favourable (ΔG=-21.5 kcal/mol), low-barrier process (ΔG*=0.4 kcal/mol, see Table 2). The electron affinity value computed for *complex* demonstrates its high adiabatic stability, especially in the aqueous solution (see Table 1). Comparing the electron affinity of BrdGDP (3.0 eV) with the analogical non-brominated nucleotide dGDP (0.95 eV)[13], one can see once again, how the bromine substituent increases nucleotide sensitivity to an excess electron. Notably, only the AEA value of the nucleotide of brominated guanine falls in the range of energies characteristics for the fully equilibrated solvated electron (ca. 3.4 eV)[12] . It is not surprising that the non-modified DNA is resistant to the electron-induced damage.

To enable a further damage, complete release of the bromide anion is necessary, as it produces a highly reactive guanine nucleotide radical (*rad*). Although the *complex* anion has bromide detached already, a complete separation of the bromide anion and the *rad* radical is rather unlikely in the gas phase due to thermodynamic reasons (ΔG=27.5 kcal/mol, see Table 2). This suggests that although C-Br bond is sensitive to electron-induced cleavage in the gas phase, the formed bromide anion stays in close vicinity to the produced *rad*, which might hinder further reaction steps. On the other hand, in the water solution, the complete separation of *rad* and Br$^-$ interacting in *complex* is more likely (ΔG=3.4 kcal/mol, see Table 2). This suggests that even in the very first step the aqueous solution strongly enhances the electron-induced damage of BrdGDP. Such a barrier-free bromide anion release has been recently described for the 9-methyl-8-bromoadenine anion[38] and 8-bromo-2'-deoxyadenosine-3',5'-diphosphate anion.[47] The above results indicate, thus, that the presence of DNA strand does not bring in any additional activation barrier for the electron-induced C8-Br bond dissociation in brominated purines.

3.3. Intranucleotide hydrogen atom transfer

Once the open-shell *rad* with electron density localized on the purine ring is produced, it might be stabilized by hydrogen abstraction from its own sugar at the C3' or C5' positions, forming *rad3* or *rad5*, respectively (see Figures 1 and 3 and Table 2 for energetic characteristics).

The H5' shift, with the kinetic barrier of only 2.7 (gas phase) and 3.2 kcal/mol (solution) in the free enthalpy scale, is more likely than the H3' shift (see Table 2). However, one should notice that these barriers are underestimated due to the deformation of sugar-phosphate backbone while producing the *ts-base-5* structure (compare it with *ts-base-3* in Figure 3). Similar, bending

of DNA chain is not likely in ds DNA, hence the *ts-base-5* structure cannot occur in the native biopolymer. However, the hydrogen bond created between the phosphates (see *ts-base-5* in Figure 3), impossible in ds DNA, causes an increase of the *ts-base-5* stability. This finally leads to underestimation of the considered barrier. In order to quantify this hydrogen bond effect we recomputed the path leading to *rad5*, with the use of the IRC procedure,[54] starting from the non-physiological, hydrogen bonded *ts-base-5* (in its most stable geometry depicted in Figure 3). The reactants *rad* and *rad5,* obtained in this manner, also have the backbone bonded in the same way as the transition state *ts-base-5* structure. Such a treatment enabled us to obtain a lower value of the discussed barrier, which is then equal to 6.2 and 6.7 kcal/mol in the free enthalpy scale, for the gas phase and aqueous solution, respectively (see Table 2). Nevertheless, one should note that the corrected values of the activation barrier of the O-P bond break on the C5' path are still substantially lower than 13.6 and 12.4 kcal/mol calculated for the C3' path (see Table 2). However, having in mind an amount of the energy released due to electron attachment to BrdGDP (3.0 eV, see Table 1), it can be concluded that both the *rad → rad5* and *rad → rad3* elemental reactions might be competitive.

3.4. O-P bond breakage or cyclization?

While the electron-induced 5',8-cyclopurines formation has been already proposed by Chatgilialoglu,[31-37,41] the O-P bond break seems to be also a possible competitive mechanism for the brominated purine nucleotides damage.[47] Analysing the energetic characteristics gathered for the considered degradation paths (Table 2), one can conclude that only two of the proposed paths (A and C) are possible to occur. Path A (see Figure 3) that leads through the 3'-site SSB to the *ketone* derivative and path C, leading through *rad5* intermediate to the 5',8-cycloguanosine

(*cycloG*) derivative. Path B, where the *aldehyde* is produced after 5'-site O-P bond break, is not competitive to cyclization. Not only the last activation barrier, leading to 5'-site O-P bond break, is higher than that leading to cyclization (compare ΔG^*=19.3 vs. 15.5 kcal/mol in aqueous solution), but also thermodynamically 5'-site O-P bond break is not very likely (compare ΔG=5.6 vs. -5.1 kcal/mol in an aqueous solution), which makes path B uncompetitive.

Comparing the 3'-site O-P SSB (Figure 3, path A) with the 5'-site cyclization (Figure 3, path C) one can further conclude that although the first stage of path C is favourable kinetically, the first step of path A is also achievable. Looking at the thermodynamic characteristics of the next steps (degradation of *rad3* or *rad5*, see Table 2), it is apparent that the O-P bond break may occur only in water solution, while cyclization is exergonic also in the gas phase. The kinetic barriers are comparable for both paths, A and C. Taking all these facts into consideration, one can conclude, that electron attachment to BrdGDP should lead to two kinds of products: the 5',8-cycloguanosine mutation and the ketone derivative related to SSB.

4. Conclusions

In the current project we predicted at the B3LYP/6-31++G(d,p) level and analyzed the electron induced degradation of model brominated purine nucleotide – 8-bromo-2'-deoxyguanosine-3',5'-diphosphate. One of two main paths, leading to phosphodiester bond breakage, mimics single strand break in ds DNA labeled with 8-bromoguanine as radiosensitizer. The feasibility of SSB process is compared to the path involving electron-induced purine cyclization. Our results show that BrdGDP has much larger electron affinity than native guanine nucleotide, which in water solution is close to the stabilization energies of solvated electron. This feature could explain the radiosensitizing properties of the considered brominated purine.

The first and crucial step of degradation mechanism involves the electron-induced low-barrier (or barrier-free) abstraction of the bromide anion from BrdGDP. Guanyl radical, being the reactive product of this step can then undergo a sequence of step-wise reactions, resulting finally in the phosphodiester bond break (an equivalent of single strand break in DNA), or 5',8-cycloguanidine mutation. Although the breakage of O-P bond might occur at the 3'- or 5'-side, leading respectively to cyclic ketone or aldehyde, we suggest, that only the 3'-site O-P bond break is possible due to thermodynamic and kinetic reasons. The only process leading to the stabilization of the 5'-site radical is its cyclization, with the 5',8-cycloguanosine derivative as a product.

Radiolytic experiments demonstrating the formation of the ketone and the cyclic derivatives could confirm the suggested here mechanism of the electron induced BrG labeled dsDNA degradation.

Acknowledgments

References

(1) M. Joiner, A. van der Kogel in *Basic Clinical Radiobiology,* ed. Hodder Arnold, London U.K., 4th edn., 2009.

(2) R. L. Warters, K. G. Hofer, C. R. Harris, J. M. Smith, *Curr. Top. Radiat. Res.,* 1978, **12**, 389.

(3) A. Daşu, J. Denekamp, *Radiother. Oncol.,* 1998, **46**, 269.

(4) E. J. Hall, C.-S. Wuu, *Int. J. Radiat. Oncol., Biol., Phys.,* 2003, **56**, 83.

(5) H. Choy in *Chemoradiation in Cancer Therapy*, Humana Press Inc., Totowa, NJ, 2011.

(6) P. J. Tofilon, K. Camphausen, *Chem. Rev.,* 2009, **109***, 2974.

(7) C. von Sonntag in *The Chemical Basis Of Radiation Biology*, Taylor and Francis, London U.K., 1987.

(8) B. G. Ershov, A. V. Gordeev, *Radiat. Phys. Chem.,* 2008, **77**, 928.

(9) C.-R. Wang, J. Nguyen, Q.-B. Lu, *J. Am. Chem. Soc.*, 2009, **131**, 11320.

(10) J. Nguyen, Y. Ma, T. Luo, R. G. Bristow, D. A. Jaffray, Q.-B. Lu, *Proc. Natl. Acad. Sci. U.S.A.*, 2011, **108**, 11778.

(11) B. D. Michael, P. O'Neill, *Science,* 2000, **287**, 1603.

(12) B. Abel, U. Buck, A. L. Sobolewski, W. Domcke, *Phys. Chem. Chem. Phys.,* 2012, **14**, 22.

(13) J. Gu, Y. Xie, H. F. Schaefer III *Nucleic Acids Res.,* 2007, **35**, 5165.

(14) J. Gu, J. Leszczynski, H. F. Schaefer III, *Chem. Rev.,* 2012, **112**, 5603.

(15) B. Djordjevic, W. Szybalski, *J. Exp Med.*, 1960, **112**, 509.

(16) R. L. Erikson, W. Szybalski, *Radiat. Res.,* 1963, **20**, 252.

(17) J. W. Cramer, W. H. Prusoff, A. D. Welch, A. C. Sartorelli, I. W. Delamore, C. F. von Essen, P. K. Chang, *Biochem. Pharmacol. (Amsterdam, Neth.),* 1962, **11**, 761.

(18) S. Greer, S. Zamenhof, Am. Chem. Soc., Miami Beach, FL, 1957, p:3C (Abstr).

(19) S. Greer, *J. Gen. Micro.,* 1960, **22**, 618.

(20) D. Brust, J. Feden, J. Farnsworth, C. Amir, W. C. Broaddus, K. Valerie, *Cancer Gene Ther.,* 2000, **7**, 778.

(21) B. S. Dabaja, P. McLaughlin, C. S. Ha, B. Pro, C. A. Meyers, L. F. Seabrooke, R. B. Wilder, A. P. Kyritsis, H. A. Preti, W. K. Yung, V. Levin, F. Cabanillas, J. D. Cox *Cancer,* 2003, **98**, 1021.

(22) M. D. Prados, W. Seiferheld, H. M. Sandler, J. C. Buckner, T. Phillips, C. Schultz, R. Urtasun, R. Davis, P. Gutin, T. L. Cascino, H. S. Greenberg, W. J. Curran Jr., *Int. J. Radiat. Oncol. Biol. Phys.,* 2004, **58**, 1147.

(23) S. Cecchini, S. Girouard, M. A. Huels, L. Sanche, D. J. Hunting, *Radiat. Res.,* 2004, **162**, 604.

(24) S. Cecchini, S. Girouard, M. A. Huels, L. Sanche, D. J. Hunting, *Biochemistry,* 2005, **44**, 1932.

(25) M.-E. Dextraze, J. R. Wagner, D. J. Hunting, *Biochemistry,* 2007, **46**, 9089.

(26) T. J. Kinsella, *Cancer Biol. Ther.,* 2008, **7**, 1567 and references therein.

(27) S. Kummar, L. Anderson, K. Hill, E. Majerova, D. Allen, Y. Horneffer, S. P. Ivy, L. Rubinstein, P. Harris, J. H. Doroshow, J. M. Collins, *Clin. Cancer Res.,* 2013, **19**, 1852.

(28) P. J. Godefridus in *Deoxynucleoside Analogs in Cancer Therapy*, Humana Press Inc., New Jersey, USA, 2006.

(29) X. Li, L. Sanche, M. D. Sevilla, *J. Phys. Chem., A* 2002, **106**, 11248.

(30) Y. Razskazovskii, S. G. Swarts, J. M. Falcone, C. Taylor, M. D. Sevilla, *J. Phys. Chem. B,* 1997, **101**, 1460.

(31) R. Flyunt, R. Bazzanini, C. Chatgilialoglu, Q. G. Mulazzani, *J. Am. Chem. Soc.,* 2000, **122**, 4225.

(32) C. Chatgilialoglu, M. Guerra, Q. G. Mulazzani, *J. Am. Chem. Soc.,* 2003, **125**, 3839.

(33) F. Boussicault, P. Kaloudis, C. Caminal, Q. G. Mulazzani, C. Chatgilialoglu, *J. Am. Chem. Soc.,* 2008, **130**, 8377.

(34) C. Chatgilialoglu, C. Caminal, M. Guerra, Q. G. Mulazzani, *Angew. Chem. Int. Ed.,* 2005, **44**, 6030.

(35) C. Chatgilialoglu, C. Caminal, A. Altieri, C. C. Vougioukalakis, Q. G. Mulazzani, T. Gimisis, M. Guerra, *J. Am. Chem. Soc.,* 2006, **128**, 13796.

(36) A. Manetto, S. Breeger, C. Chatgilialoglu, T. Carell, *Angew. Chem. Int. Ed.,* 2006, **45**, 318.

(37) D. Fazio, C. Trindler, K. Heil, C. Chatgilialoglu, T. Carell, *Chem. Eur. J.,* 2011, **17**, 206.

(38) L. Chomicz, J. Rak, P. Storoniak, *J. Phys. Chem. B,* 2012, **116**, 5612.

(39) K. Polska, J. Rak, A. D. Bass, P. Cloutier, L. Sanche, *J. Chem. Phys.,* 2012, **136**, 075101.

(40) Y. Park, K. Polska, J. Rak, J. R. Wagner L. Sanche *J. Phys. Chem. B,* 2012, **116**, 9676.

(41) C. Chatgilialoglu, C. Ferreri, M. A. Terzidis, *Chem. Soc. Rev.,* 2011, **40**, 1368.

(42) A. Mazouzi, A. Vigouroux, B. Aikeshev, P. J. Brooks, M. K. Saparbaev, S. Morerab, A. A. Ishchenko, *Proc. Natl. Acad. Sci. USA,* 2013, **110**, E3071.

(43) A. D. Becke, *Phys. Rev. A* 1988, **38**, 3098. A. D. Becke, *J. Chem. Phys.,* 1993, **98**, 5648; C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B,* 1988, **37**, 785.

(44) R. Ditchfield, W. J. Hehre, J. A. Pople *J. Chem. Phys.,* 1971, **54**, 724; W. J. Hehre, R. Ditchfield, J. A. Pople *J. Chem. Phys.,* 1972, **56**, 2257.

(45) J. C. Rienstra-Kiracofe, G. S. Tschumper, H. F. Schaefer III, *Chem. Rev.,* 2002, **102**, 231.

(46) S. Miertuš, E. Scrocco, J. Tomasi, *Chem. Phys.,* 1981, **55**, 117; S. Miertuš, J. Tomasi, *Chem. Phys*., 1982, **65**, 239; M. Cossi, V. Barone, R. Cammi, J. Tomasi, *Chem. Phys. Lett.,* 1996, **255**, 327.

(47) L. Chomicz, J. Leszczynski, J. Rak, *J. Phys. Chem. B,* 2013, **117**, 8681.

(48) D. A. McQuarrie, J. D. Simon in *Molecular Thermodynamics,* University Science Books, Sausalito, CA, 1999.

(49) M. H. Wong, K. B. Wiberg, M. Frisch, *J. Chem. Phys.,* 1991, **95**, 8991.

(50) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. Montgomery, J. A., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O̎. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Rev. C.01, Wallingford, CT, 2009.

(51) GaussView, Version 5, R. Dennington, T. Keith, J. Millam, *Semichem Inc*., Shawnee Mission KS, 2009.

(52) N. Narayana, M. A. Weiss, *J. Mol. Biol.,* 2009, **385**, 469.

(53) M. D. Sevilla, B. Besler, A. O. Colson, *J. Phys. Chem.,* 1994, **98,** 2215.

(54) K. Fukui, *Acc. Chem. Res.*, 1981, **14**, 363.

Table 1. Adiabatic Electron Affinities (AEA), Vertical Detachment Energies (VDE) and Vertical Attachment Energies (VAE) calculated for *anrad* and *complex* anion radicals. All values in eV.

	Gas phase	Aqueous solution
AEA_E	0.3[a]	[c]
	1.2[b]	2.8[b]
AEA_G	0.4[a]	[c]
	1.3[b]	3.0[b]
VDE	0.4[a]	[c]
	3.8[b]	5.2[b]
VAE	0.3	1.2

[a] With respect to *anrad.* [b] With respect to *complex.*
[c] No *anrad* available in aqueous solution.

Table 2. Thermodynamic (ΔE and ΔG) and kinetic (ΔE* and ΔG*) characteristics of particular reaction steps for the BrdGDP degradation mechanism (see Figure 1). All values in kcal/mol.

Mechanism step	Gas phase				Aqueous solution			
	ΔE*	ΔE	ΔG*	ΔG	ΔE*	ΔE	ΔG*	ΔG
C-Br bond break								
anrad → complex	3.3	-20.7	0.4	-21.5	*barrier free C-Br bond break. no anrad*			
complex → rad + Br⁻		38.9		27.5		13.1		3.4
Radical rad deactivation								
rad → rad3	15.6	-31.1	13.6	-26.5	14.4	-19.3	12.4	-20.3
rad → rad5	2.7	-21.7	2.7	-20.2	4.1	-21.9	3.2	-20.8
	8.3[b]	-16.1[b]	6.2[b]	-16.8[b]	9.2[b]	-16.9[b]	6.7[b]	-17.2[b]
O-P bond break								
rad3 → ketone-rad	21.6	11.0	18.8	5.7	12.6	0.6	15.0	0.2
ketone-rad → ketone + phos. rad		15.4		1.8		10.2		-2.6
rad5 → aldehyde-rad	22.6	1.1	19.0	-3.1	22.5	12.0	19.3	5.6
aldehyde-rad → aldehyde + phos. rad		23.3		11.5		8.1		-0.4
Cyclization								
rad5 → cycloG	13.4	-7.6	14.9	-4.7	14.8	-7.6	15.5	-5.1
Total rad transformation								
rad → ketone + phos. rad		-4.7		-19.0		-8.5		-22.7
rad → aldehyde + phos. rad		2.6		-11.8		-1.8		-15.5
rad → cycloG		-29.3		-25.0		-29.6		-25.9

[b] Corrected with the use of hydrogen-bonding for all the reagents (see text).

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Figure Captions

Figure 1. Electron induced degradation paths for 8-bromo-2'-deoxyaguanosine diphosphate.

Figure 2. Electron induced C-Br bond break in BrdGDP. In an aqueous solution *anrad* converts to *complex* in a barrier-free process.

Figure 3. Radical *rad* deactivation paths, leading via the 3'-site O-P bond break to the ketone derivative (A), via the 5'-site O-P bond break to the aldehyde derivative (B) and via the 5'-site cyclization to the cycloguanosine derivative (C). Reagents stationary geometries along with kinetic (ΔG*) and thermodynamic (ΔG) barriers, calculated in aqueous solution, given in kcal/mol.
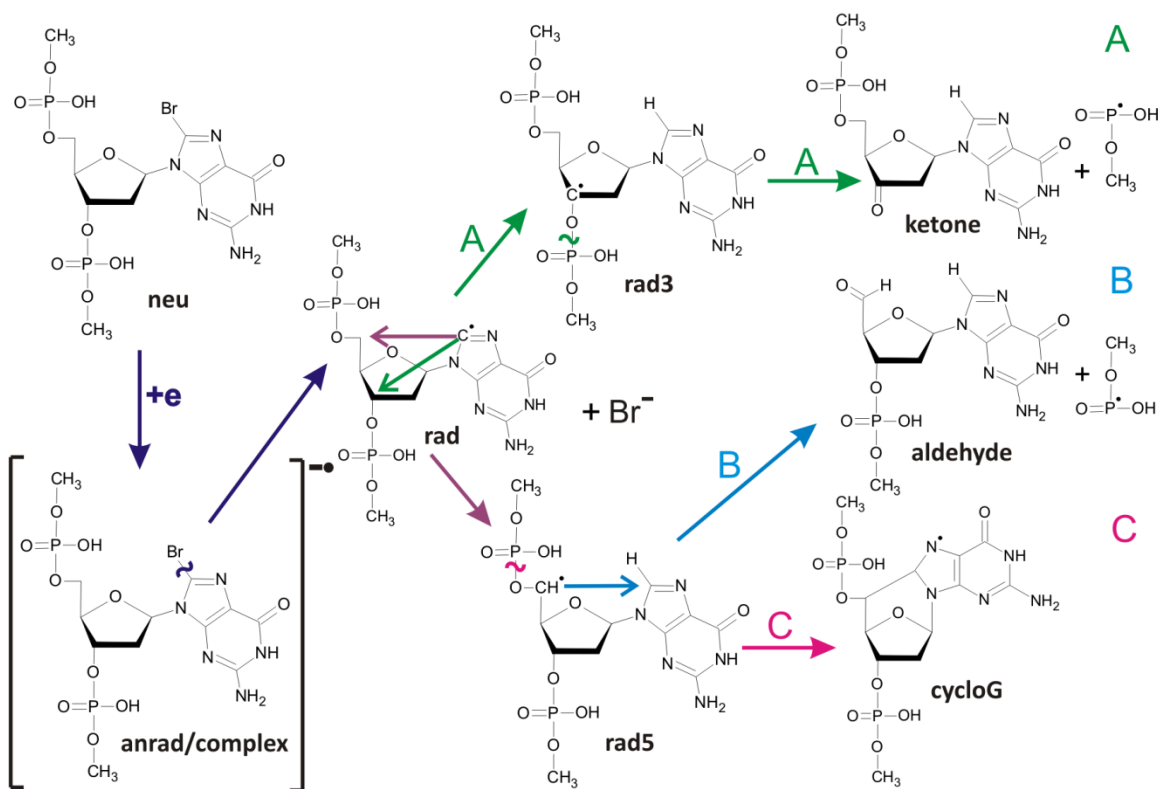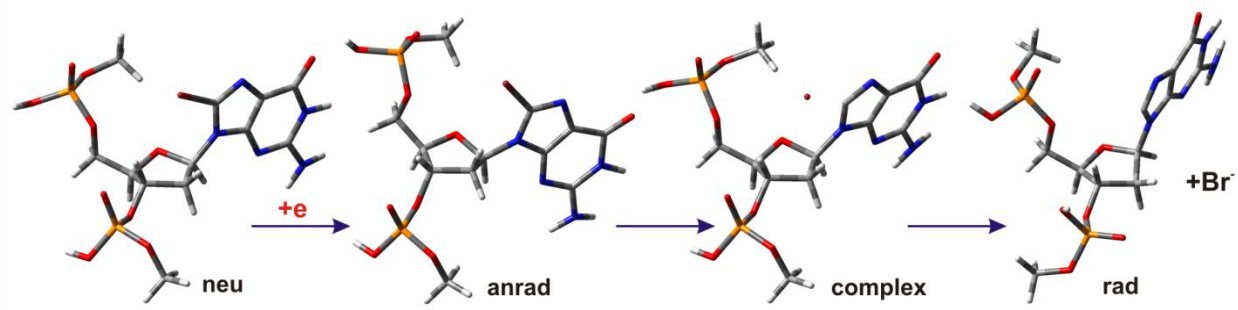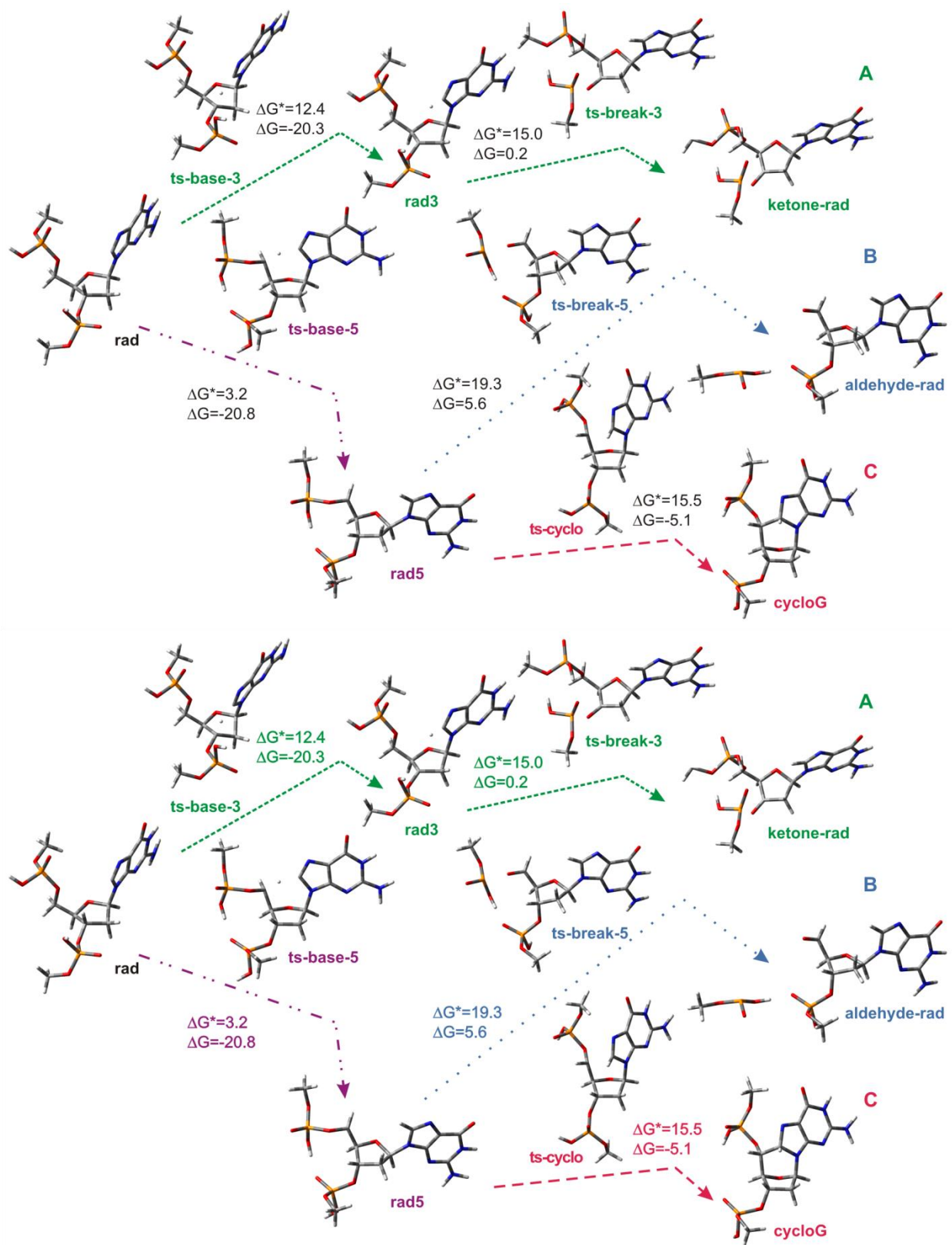
Figure 1

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Figure 2

Figure 3

GRAPHICAL ABSTRACT

AUTHOR NAMES

Lidia Chomicz, Al'ona Furmanchuk, Jerzy Leszczynski and Janusz Rak

TITLE

Electron Induced Single Strand Break or Cyclization. A DFT Study on the Radiosensitization Mechanism of the Nucleotide of 8-Bromoguanine.

TEXT

Radiosensitization mechanism of 8-bromoguanosine is studied on its 3',5'-diphosphate. Electron attachment to the nucleotide results in phosphodiester bond breakage or 5',8-cycloguanosine lesion.

GRAPHICAL ABSTRACT FIGURE