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Chemistry and Structural Biology of DNA Damage and Biological Consequences

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Abstract

The formation of adducts by the reaction of chemicals with DNA is a critical step for the initiation of carcinogenesis. The structural analysis of various DNA adducts reveals that conformational and chemical rearrangements and interconversions are a common theme. Conformational changes are modulated both by the nature of adduct and the base sequences neighboring the lesion sites. Equilibria between conformational states may modulate both DNA repair and error-prone replication past these adducts. Likewise, chemical rearrangements of initially formed DNA adducts are also modulated both by the nature of adducts and the base sequences neighboring the lesion sites. In this review, we focus on DNA damage caused by a number of environmental and endogenous agents, and biological consequences.

Introduction

DNA Damage, arising from both endogenous and exogenous chemical insults, is believed to represent an initiating step in chemical carcinogenesis. Considerable data exist with regard how specific DNA adducts perturb its structure, and how these structural perturbations interfere with the biological processing of DNA [1]. A major goal is to understand the basis whereby chemical modification of DNA triggers specific mutations. The field has advanced rapidly over the past several decades. One reason has been the development of automated DNA synthesis methodologies [2], and progress in regioselectively and stereospecifically incorporating specific types of damage into duplex DNA [1]. Collectively, these approaches enable the construction of site-specifically damaged DNA templates for structural and biological studies. Additionally, advances in applications of NMR spectroscopy [3] and X-ray crystallography [4] to the study of DNA enable high-resolution structures of damaged DNA to be obtained. In this review, we will focus on the conformational and configurational rearrangements of DNA adducts, derived from a number of environmental and endogenous DNA damaging agents, and in the context of biological consequences.

Conformational Interconversions of DNA Adducts

Conformational interconversions involve rotation about one or more chemical bonds, but do not require bond breakage. The conformational interconversions of interest here have sufficiently large activation barriers that, under physiologically relevant conditions, interconversion occurs slowly at ms or slower time scales, and it is anticipated that different conformers may elicit differential biological responses. In DNA, a major site of conformational interconversion for deoxynucleosides involves the *N*-glycosyl bond connecting the deoxyribose sugar to the heteroaromatic nucleobase. In B-form DNA, the *N*-

glycosyl bond is maintained in the *anti*-conformation, thus orienting the sterically bulky nucleobase away from the deoxyribose sugar. In duplex DNA, this orients complementary nucleobases to form the canonical *Watson–Crick* base pairing interactions. Often, however, the introduction of sterically bulky substituents to DNA disrupts this conformational equilibrium, and shifts the *N*-glycosyl bond into the *syn*-conformation, in which the nucleobase is oriented toward the deoxyribose. In duplex DNA, this shifts the *Watson–Crick* H-bonding edge of the base toward the major groove, and hinders canonical *Watson–Crick* H-bonding. Characteristic examples of bulky adducts that undergo such conformational interconversions include those arising from C8-dG alkylation by aromatic amines, C8-dG oxidative-damage products 8-oxo-dG and 8-oxo-dA, 1,*N*²-etheno and -propano annelation products of dA and dG, and 4-hydroxy-equilenin.

Aromatic Amines

Early evidence that conformational heterogeneity modulated the structures of DNA adducts came from studies of arylamine adducts. The subject has been reviewed by *Cho* [5] and *Patel et al.* [6]. Arylamines are environmental carcinogens; human exposures are associated with the etiology of bladder cancer [7]. The most studied example is *N*-acetyl-2-aminofluorene. 2-Aminofluorene (AF) is acetylated *in vivo*; the acetylated species then reacts with DNA [8–10] to give 2-amino-*N*-(deoxyguanosin-8-yl)fluorene (C8-dG AF) (Fig. 1). This has been detected in mammalian cells [11]. When the C8-dG AF adduct is placed opposite dC in the 5′-AXG-3′ sequence, it exists in two conformations, referred to as the external-AF and inserted-AF conformations [12]. The external-AF conformation features the *anti*-conformation, while the inserted-AF conformation features the *syn* conformation about the glycosyl bond (Fig. 2). In the external-AF conformation, the AF moiety is in the major groove. The X(*anti*)-C(*anti*) base pair exhibits *Watson–Crick* H-bonding [12] (Fig. 2). In the inserted-AF conformation, the *syn* glycosyl bond places the AF moiety into the DNA helix and displaces the damaged guanine base and the complementary cytosine [12], resulting in the disruption of *Watson–Crick* H-bonding at the X(*syn*)-C(*anti*) base pair (Fig. 2). A similar equilibrium is observed between external- and inserted-AF in the 5′-CXC-3′ sequence [13]. When the C8-dG AF adduct is placed opposite dA in the 5′-CXC-3′ sequence, modeling the intermediate associated with G→T mutations observed for AF [14], the damaged nucleotide also adopts the *syn* conformation about the glycosyl bond, but the AF moiety orients in the minor groove [15]. The AF-dG adduct has also been examined in sequences derived from *c-Ha-ras*-protooncogenes with modification at codon 61, a site of G→T mutations, by *Cho et al.* [16], and *Eckel* and *Krugh* [12][17]. The amount of the major conformation of the AF-dG adduct is *ca.* 60% [16]; the aminofluorene moiety rotates toward the major groove. The major conformer adopted by the corresponding 4-aminobiphenyl-modified base [18] is similar.

Base substitutions are associated with these adducts, especially G→T mutations [14], although the correct incorporation of dCTP predominates during translesion bypass [19]. Frameshift mutations induced by AF adducts are associated with the *E. coli* *NarI* hot spot sequence (C-G¹-G²-C-G³-C-C), in which –2 base deletions occur at G³ [20–25]. The *NarI* frameshift pathway is SOS-dependent but umuDC-independent, and DNA Pol II is responsible for the frameshifts [25]. When the AF-dG adduct is placed into the *E. coli* *NarI* sequence (C-G¹-G²-C-G³-C-C), associated with –2 base deletions at G³ [20–25], its conformation is sequence-dependent [26]. The adduct favors the external-AF conformation when placed at G¹ and G², respectively, while an equal mixture of both conformers exists when AF is placed at G³. The conformational equilibrium is also affected by the next nearest neighbors [6]. Structures of the C8-dG adduct placed opposite to 3′-terminal primer cytosine have been obtained in a ternary complex with the Dpo4 polymerase [27]. The C8-dG AF adduct remained in the *anti*-conformation about the glycosyl bond with the AF

moiety positioned in the major groove [27]. Overall, the conformational equilibrium of the C8-dG AF adduct, and the concomitant distortion of DNA structure, may contribute to both base substitution and frameshift mutations during DNA replication, in a sequence-dependent manner [12].

The heterocyclic amines 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) [28–31] and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) are produced, when protein-rich foods are cooked. IQ is activated to an *N*-hydroxy oxidation product [32–35] and reacts with DNA to produce C8-dG adducts that are observed in rodents and primates, as measured by ³²P post-labeling [36]. A minor adduct forms at *N*²-dG [37]. In nucleosides, the C8-dG IQ adduct (Fig. 1) exists in the *syn*-conformation about the glycosyl bond [38], while the *N*²-dG IQ adduct adopts the *anti* conformation. When placed opposite cytosine in a duplex containing the *E. coli* *NarI* sequence, the C8-dG IQ adduct also adopts the *syn*-conformation (Fig. 3) [40], as does the C8-dG PhIP adduct (Fig. 4) [41]. This places the *Watson–Crick* edge of the modified dG into the major groove. The IQ moiety intercalates between the flanking C·G base pairs. These studies corroborated molecular-mechanics analysis of the C8-dG IQ-modified duplex [42]. As for the C8-dG AF adduct, the *syn* conformation of the C8-dG IQ adduct may contribute to error-prone replication, in a sequence-dependent manner. The structure of the *N*²-dG IQ adduct has not yet been examined in an oligodeoxynucleotide duplex. It has been proposed that differences in the accumulation and rates of removal of C8-dG IQ vs. *N*²-dG IQ adducts in rodents and non-human primates may be attributable to differences in conformation about the glycosyl bond in these two adducts. Adducts in the *syn*-conformation may be more easily recognized and excised as they induce greater distortion in the DNA [43]. *Turesky et al.* [43] showed that C8-dG IQ adduct was removed, whereas the *N*²-dG IQ adduct was persistent. In bacteria, mutations occur primarily at G·C base pairs [44][45], and IQ gives frameshift mutations in (CG)_{*n*} repeats. Similar levels of mutations are observed in mammalian hprt [46] and ef-2 [47] gene assays.

8-Oxo-dG and 8-Oxo-dA

Deoxyadenosine and deoxyguanosine are hydroxylated at C(8) to form 7,8-dihydro-8-oxoadenine (8-oxo-dA) and 7,8-dihydro-8-oxoguanine (8-oxo-dG) (Fig. 5) [48][49]. These lesions tautomerize [50][51]; the 6-amino-8-oxo and 6,8-dioxo [50–52] species predominate for 8-oxo-dA and 8-oxo-dG, respectively, in oligodeoxynucleotides [53][54]. DNA Synthesis proceeds past both lesions. High-fidelity polymerases insert dCTP or dATP opposite 8-oxo-dG in varying proportions dependent upon the polymerase, with extension preferentially occurring from 8-oxo-dG·A base pairs [55–58]. Consistent with this observation, 8-oxo-dG induces primarily G→T transversions in human cells [59]. The Y-family polymerases Dpo4 [60–62] and Pol η [63][64] preferentially insert dCTP over dATP opposite 8-oxo-dG, but favor extension from the 8-oxo-dG·C pair, thus allowing error-free bypass.

The 8-oxo-dG lesion perturbs base interactions and backbone conformations in single-stranded DNA [65]. *In vitro*, 8-oxo-dG pairs with all four dNTPs [66], but preferentially with A and C [58]. Studies of 8-oxo-dG and different complementary bases indicate that one base generally adopts the *syn*-conformation in the purine·purine pairs [67–69]. Thus, 8-oxo-dG mismatched with A adopts the *syn*-conformation, and the complementary A adopts the *anti*-conformation about the glycosyl bond [70][71], similar to G·A mispairs [69][72] (Fig. 6). This could explain the mis-insertion of dATP opposite 8-oxo-dG, yielding G→T transversions. In contrast, when 8-oxo-dG pairs with C, both 8-oxo-dG and C adopt the *anti*-conformation about the glycosyl bond, and the 8-oxo-dG·C pair forms *Watson–Crick* H-bonds [53][73]. Template distortion associated with 8-oxo-dG (*anti*) complementary to primer terminus dC has been observed for T7 [74] and for the *Bacillus* Pol I fragment BF [75]. In contrast, neither the template nor the polymerases were affected by 8-oxo-dG (*syn*)

opposite primer terminus dA, possibly enabling the 8-oxo-dG·A base pair to evade proofreading by T7 [74] or Bacillus Pol I fragment BF [75]. This may also provide an explanation for extension by these polymerases from the 8-oxo-dG·A base pair [55–58]. Structures of 8-oxo-dG opposite A, C, T, or G, and the next nascent base pair in ternary complexes with the Dpo4 polymerase show that neither the template backbone nor the structure of the active site are perturbed by the 8-oxo-dG·C or 8-oxo-dG·A pairs [76]. However, the 8-oxo-dG·A pair adopts both the 8-oxo-dG (*syn*)·A (*anti*) and 8-oxo-dG (*anti*)·A (*syn*) alignments. This may explain the poor primer extension from the 3'-terminal primer base A by the Dpo4 polymerase. In the case of the 8-oxo-dG·C pair, the unperturbed Dpo4-active site explains the efficient primer extension. The OGG-2 glycosylase repairs 8-oxo-dG paired with G or A [77]. The *E. coli* glycosylase MutY repairs 8-oxo-dG·G mispairs [78]. A duplex containing the 8-oxo-dG·G mispair has been examined. The 8-oxo-dG lesion adopts the *syn*-conformation about the glycosyl bond. The damaged base is inserted into the helix (Fig. 7) [79]. With 8-oxo-dA, dTTP is predominantly incorporated by Y-family polymerases, yielding error-free bypass [80]. In COS-7 cells, the mutagenicity of 8-oxo-dA is four times lower than that of 8-oxo-dG [81]; it induces mainly A→C transversions. The mutation frequency and spectrum associated with 8-oxo-dA depends on the sequence context of the lesion. In the 5'-TXG-3' sequence, the mutation frequency was 1.2%. In the 8-oxo-dA·G mispair 8-oxo-dA adopts the *syn*-conformation, while the complementary G adopts the *anti*-conformation [82] (Fig. 8).

Etheno Adducts

These arise from the reaction of vinyl chloride with DNA. The 3,*N*⁴-*ed*C adduct (Fig. 9) is mutagenic. *In vitro* studies showed that the mammalian polymerases α and δ predominantly incorporate dATP or dTTP opposite 3,*N*⁴-*ed*C, while polymerase β incorporates primarily dCTP [83]. *In vitro* replication studies with a DNA template containing 3,*N*⁴-*ed*C using the *Klenow exo*⁻ fragment of DNA polymerase I showed primarily dATP and dTTP incorporation opposite the lesion [84–86]. The structures of 3,*N*⁴-*ed*C opposite dA, dT, dG, or dC have been determined [87–90]. When placed opposite dT in duplex DNA, 3,*N*⁴-*ed*C adopts the *syn*-conformation about the glycosyl bond, while the complementary dT adopts the *anti*-conformation [88] (Fig. 10, *a*). The 3,*N*⁴-*ed*C (*syn*)·T (*anti*) alignment is stabilized by a H-bond between T N(3)H and 3,*N*⁴-*ed*C C(4)–N. This base pair stacks with the flanking base pairs. The conformational change of 3,*N*⁴-*ed*C from the *anti*- to *syn*-orientation and maintaining coplanar alignment may explain the facilitation of misincorporation of dTTP opposite 3,*N*⁴-*ed*C by DNA polymerases.

When placed opposite dA, 3,*N*⁴-*ed*C and the complementary dA remain in the *anti*-conformation about the glycosyl bond [87]. The 3,*N*⁴-*ed*C (*anti*)·dA (*anti*) pair adopts a staggered conformation in which each nucleotide displaces 5'-side and intercalates between the bases on the complementary strand (Fig. 10, *b*). The partial intercalation of 3,*N*⁴-*ed*C (*anti*) and dA (*anti*) bases produces stacking between the aromatic rings of 3,*N*⁴-*ed*C and dA, and with flanking base pairs. Steric factors preclude a coplanar alignment between 3,*N*⁴-*ed*C and dA. Nevertheless, dATP is preferentially incorporated opposite 3,*N*⁴-*ed*C *in vitro* [86], and both dATP and dGTP are incorporated opposite this lesion in cells [91]. The structural data suggest that the partially intercalated structure may promote translesion synthesis past this lesion.

When placed opposite dG, both 3,*N*⁴-*ed*C and dG adopt the *anti* conformations [89]. The 3,*N*⁴-*ed*C is displaced and shifts towards major groove, while the complementary dG remains stacked (Fig. 10, *c*). The 3,*N*⁴-*ed*C (*anti*)·G (*anti*) alignment is stabilized by H-bonds involving dG. The structural studies corroborate the low mutagenicity of 3,*N*⁴-*ed*C in *E. coli*, suggesting that 3,*N*⁴-*ed*C (*anti*)·G (*anti*) pairing occurs during replication.

The 1, N^6 - ϵ dA adduct (Fig. 9) induces A \rightarrow C transversion. When placed opposite dG, 1, N^6 - ϵ dA adopts the *syn*-conformation about the glycosyl bond, positioning the exocyclic ring toward the major groove, while dG adopts the *anti*-conformation [92]. The 1, N^6 - ϵ dA (*syn*)-G (*anti*) alignment is stabilized by two H-bonds from the N(1)H imino H-atom and one H-atom from NH₂ of dG to N(9) and N(1) of 1, N^6 - ϵ dA, respectively (Fig. 11). The *syn* conformation of 1, N^6 - ϵ dA is accommodated without disruption of flanking base pairs and may account for the incorporation of dGTP opposite 1, N^6 - ϵ dA during replication. In mammalian cells, the alkylpurine-DNA-*N*-glycosylase recognize and repair 1, N^6 - ϵ dA by a similar mechanism as proposed for 1, N^2 - ϵ dG adduct (for a review, see [93]).

The 1, N^2 - ϵ dG lesion (Fig. 9) is released from DNA by both the *E. Coli* mismatch-specific uracil DNA glycosylase and the human alkylpurine-DNA-*N*-glycosylase [94]. The flipping of damaged nucleotides out of the helix and into the glycosylase-active site provides a mechanism by which the DNA glycosylases interact with damaged DNA [93]. At neutral pH, 1, N^2 - ϵ dG equilibrates between the *syn*- and *anti*-conformations about the glycosyl bond. At acidic pH, it adopts the *syn*-conformation, and the complementary dC adopts the *anti* conformation (Fig. 12, a) [95]. This 1, N^2 - ϵ dG (*syn*)-dC (*anti*) pair is stabilized by *Hoogsteen* H-bonds. 1, N^2 - ϵ dG introduces a localized perturbation involving the modified base pair and its 3'- and 5'-neighbor base pairs. The 3'-neighbor dG-dC base pair also equilibrates between *Watson-Crick* and *Hoogsteen* pairs (Fig. 12, b). At basic pH, both 1, N^2 - ϵ dG and the complementary dC adopt the *anti*-conformation about the glycosyl bond (Fig. 12, c) [96]. The etheno moiety is inserted into the duplex, and dC is displaced. No H-bonding is observed between the base pairs. A similar conformational transition is observed for 1, N^2 - ϵ dG opposite dC in the 5'-CXC-3' sequence [97]. The decreased melting temperature of the DNA containing the 1, N^2 - ϵ dG adduct [95][96] and its conformational exchange in duplex DNA, at neutral pH, may facilitate damage recognition [94].

Product analysis from the primer extension studies suggests that the Dpo4 polymerase uses several mechanisms, including dATP incorporation and also a variation of dNTP-stabilized misalignment to bypass 1, N^2 - ϵ dG lesions [98]. Insertion of the correct nucleotide might be facilitated by the *syn*-conformation of 1, N^2 - ϵ dG, which would allow *Hoogsteen* pairing with incoming dCTP. However, in structures of 1, N^2 - ϵ dG inserted into a template containing the 5'-TXG-3' sequence, and the formation of either binary or ternary complexes with the *S. solfataricus* DNA polymerase Dpo4, 1, N^2 - ϵ dG adopted the *anti*-conformation about the glycosyl bond [98], as does the structurally similar 1, N^2 -propanodeoxyguanosine (PdG) adduct [99].

1, N^2 -Propanodeoxyguanosine

When incorporated into the 5'-(CpG)₄-3' frameshift hot-spot of the *hisD3052* gene carried on an M13 vector, PdG (Fig. 13) induces frameshift mutations [100]. In both *E. coli* and simian kidney COS-7 cells, G \rightarrow T transversions are observed; in SOS-induced *E. coli*, G \rightarrow A transitions are also observed. The mutation frequency for single-stranded DNA that contains PdG is 100% in non-SOS-induced *E. coli*, 68% in SOS-induced cells, but only 8% in COS-7 cells [91]. The structure of PdG adduct has been studied in a variety of sequence contexts [101–110]. Its characterization paired to dC has been performed in two sequences, within a d(CG)₃-iterated repeat and in the 5'-TXT-3' sequence. In both, it adopts the *syn* conformation about the glycosyl bond, forming a PdG(*syn*)-C⁺(*anti*) *Hoogsteen*-like pair (Fig. 14). In the 5'-(CG)₃-3' iterated repeat, the 3'-neighbor dG also interconverts between *syn*- and *anti*-conformations, generating multiple structures. A correlation between the formation of tandem *Hoogsteen* base pairs and the two-base deletion mutations observed in the d(CG)₃ context has been proposed. PdG also displays conformational exchange about the glycosyl bond when placed opposite dA. The *syn*-conformer forms two H-bonds with protonated dA; the *anti*-conformer partially intercalates between its partner dA and the 5'-

neighbor nucleotide (Fig. 15). The PdG·G pair is similar to the PdG·A pair in that PdG adopts the *syn*-conformation about the glycosyl bond and forms two H-bonds with the complementary dG.

4-Hydroxyequilenin

A metabolic product of equilin and equilenin, formulated in the hormone replacement therapy drug *Premarin* [111][112], 4-hydroxyequilenin (4-OHEN), auto-oxidizes to form cytotoxic quinoids [111]. These alkylate DNA [113–118] to form cyclic dC, dA, and dG adducts [112][115][119][120]; structures of four stereoisomeric adducts have been identified [119][120] for each modified base [121]. The 4-OHEN-dC (Fig. 16) adduct predominates. Two stereoisomeric dA and three dG 4-OHEN adducts have been found in the mammary fat pads of rats upon 4-OHEN injection [115], and dA, dG, and dC adducts have been detected in breast tissues of patients [122]. The *Watson-Crick* edge of 4-OHEN-derived adducts is obstructed by the formation of the cyclic ring (Fig. 16).

The conformations of the four 4-OHEN-C stereoisomers have been examined in the 5′-GXT-3′ sequence by computational approaches [123][124]. The calculations suggest that the lesions are located in the major or minor groove with the modified cytosines adopting the *syn*- or *anti*-conformations, respectively. The configuration of the 4-OHEN-dC adducts orients the equilenin rings with respect to the 5′→3′ direction of the modified strand, and positions the equilenin CH₃ and OH groups. Calculations have also been performed on stereoisomeric 4-OHEN-dA adducts [124][125]. The 4-OHEN-dC adducts differ structurally as compared to 4-OHEN-dA adducts in terms of H-bonding, stacking, bending, groove dimensions, solvent exposure, and hydrophobic interactions.

The 4-OHEN-dC adduct induces C→G and C→A transversions when a supF shuttle vector plasmid system is propagated in human cells [126]. Polymerases bypass the 4-OHEN-dC and dA lesions with efficiencies depending upon configuration and the identity of the damaged base [127–129]. Primer extension conducted with the polymerases Dpo4, Pol η , and Pol κ indicate that 4-OHEN-dC is bypassed with insertion of an incorrect dNTP or by strand slippage [128][130]. With Pol κ , both dCTP and dATP are inserted opposite stereoisomeric 4-OHEN-dC adducts, and primer extension with complementary dC is greater than that with complementary dA [128]. The insertion of dGTP is inefficient. With Pol η , the bypass frequencies of 4-OHEN-dC stereoisomers [128] differ by two orders of magnitude. With Pol η , both insertion of dATP and extension are greater than those for dGTP, the correct nucleotide. For 4-OHEN-dA, the bypass frequency also depends upon configuration [129]. However, both pols η and κ insert the correct nucleotide dTTP opposite 4-OHEN-dA [129]. Mismatched dATP and dCTP products are also observed for Pol κ and Pol η , respectively.

Polycyclic Aromatic Hydrocarbons

DNA Adducts arising from polycyclic aromatic hydrocarbons (PAHs) undergo more extensive conformational rearrangements, allowing the large planar aromatic moiety to intercalate into the DNA helix, or orient in the minor or major groove of the DNA. The complex subject of PAH structure–activity relationships has been reviewed by *Geacintov et al.* [131][132], and *Broyde et al.* [133]. Exposures to PAH are associated with cancer etiology [134–137]. Benzo[*a*]pyrene (B[*a*]P) is one of the most common PAHs [138]. It is metabolized to 9,10-epoxy-7,8-diol stereoisomers, principally the (+)-(7*R*,8*S*,9*S*,10*R*)-enantiomer (B[*a*]PED), although minor amounts of the (–)-(7*S*,8*R*,9*R*,10*S*)-enantiomer also form [139]. These diols alkylate the N²-dG position by *trans*-addition to C(10) of B[*a*]PED, but minor amounts of *cis*-addition are observed [140][141]. The lesions form efficiently in the presence of m⁵dC in 5′-CpG-3′ sequences that are recognized by DNA

methyltransferases [142–144]. With respect to structure–activity relationships, the most studied adducts are (+)-*trans*-B[a]P- N^2 -dG, (+)-*cis*-B[a]P- N^2 -dG, (–)-*trans*-B[a]P- N^2 -dG, and (–)-*cis*-B[a]P- N^2 -dG [131]. For the (+)-*trans*- and (–)-*trans*-B[a]P- N^2 -dG adducts, the pyrenyl moieties orient in the minor groove, pointing either into the 5′- or the 3′-directions of the modified strand, respectively, relative to the modified guanine [145][146]. The (+)-*cis*-B[a]P- N^2 -dG adduct differs, having a base-displaced intercalative conformation with the modified guanine and the complementary cytosine displaced into the minor and major grooves, respectively [147]. Sequence-dependent and stereospecific conformational differences play an important role in the structural biology of PAH adducts [148].

If not repaired, the B[a]P- N^2 -dG adducts (Fig. 17) induce mutations [149–152]. In cell-free extracts, removal of the (+)-*trans*-B[a]P- N^2 -dG lesion by the NER apparatus depends on the base sequence in which it is embedded. The rate of incision of the lesion by the prokaryotic UvrABC system is two-fold greater in the 5′-TXT-3′ than in the 5′-CXC-3′ sequence. The former sequence exhibits a lower thermal stability [153]. In the 5′-CXC-3′ sequence, the pyrenyl moiety of (+)-*trans*-B[a]P- N^2 -dG resides in the minor groove in the 5′-direction along the modified strand [145]. In the 5′-TXT-3′ sequence, a similar motif is accompanied by increased conformational heterogeneity [154]. Furthermore, the 5′-CXC-3′ sequence is characterized by a rigid bend, whereas the 5′-TXT-3′ sequence is characterized by a more flexible bend [155]. The two sequences have also been investigated using molecular dynamics (MD) calculations [156][157]. The MD results highlight the importance of local dynamics in the vicinity of the lesion and show that the 5′-TXT-3′ sequence is more flexible, and exhibits weaker *Watson–Crick* H-bonding adjacent to the lesion, poorer stacking interactions, local roll/bending dynamics, and minor groove flexibility. In the 5′-TXC-3′ sequence, a similar minor groove conformation is observed, but a minor conformation involving insertion of the BP moiety into the duplex with disruption of *Watson–Crick* H-bonding at the lesion site is proposed [158]. Sequence effects on the minor groove conformations of this adduct in the 5′-CXG-3′ and 5′-GXC-3′ sequences have also been reported [159] in the 5′-GG-3′ mutation hotspot context. *Cai et al.* [157] have proposed that the amino groups in tandem 5′-GG-3′ sequences modulate the efficiency of NER.

Structures of DNA template-primers containing the (+)-*trans*-B[a]P N^2 -dG adduct, complexed with the *S. sulfataricus* Dpo4 polymerase, have been examined [160]. In one, the adducted base mispairs with adenine at the template-primer junction, and an incoming dATP is opposite template dT 5′ to the lesion. This corresponds to efficient incorporation of dATP; moreover, the X·A mispair is efficiently extended by the polymerase. Significantly, the B[a]P intercalates, occupying space corresponding to one base pair between the last two bases at the primer strand terminus [160]. The damaged base is in the *syn*-conformation about the glycosyl bond and shifts into the minor groove. Base pairing is disrupted both at the X·A mispair and the T·dATP insertion complex 5′ to the lesion. The 3′ orientation of B[a]P relative to the modified base allows B[a]P to stack with the neighboring bases with its long axis at an angle of 40° with respect to the DNA.

The B[a]P epoxy diols also react with DNA to form N^6 -dA adducts (Fig. 17) [161][162]. Repair studies of N^6 -dA adducts formed by fjord-region B[a]P epoxy diols *vs.* bay region epoxy-diol metabolites of benzo[*c*]phenanthrene (B[*c*]P) show that the bay region adducts are removed, while fjord region adducts are refractory to repair [163]. If not repaired, these N^6 -dA adducts are mutagenic, correlating with reports on B[a]P-induced mutagenesis at adenines [164–166]. The mutagenic spectra of N^6 -dA B[a]P adducts depend upon configuration at C(10) position, configurations of the OH groups at C(7), C(8), and C(9), and depend upon DNA sequence [167–169]. For N^6 -dA B[a]P adducts, C(10) (C(10) is the site of DNA alkylation) (*R*)-stereoisomers intercalate in the 5′-direction [170–173], whereas

C(10) (*S*)-stereoisomers intercalate in the 3' direction [174]. The structure of the (+)-*cis*-B[a]P-*N*⁶-dA adduct in a primer extension complex with the Dpo4 polymerase has been obtained, in which the adduct is paired with primer terminus dT, and the incoming dATP pairs with the next undamaged templating base, dT. Two conformations of the (+)-*cis*-B[a]P-*N*⁶-dA adduct are observed. In the first, the B[a]P is intercalated. In the other, it orients in the major groove perpendicular to the DNA base pairs. The (+)-*trans*-B[a]P-*N*⁶-dA adduct, mismatched opposite dG, adopts the *syn* conformation about the glycosyl bond [175] (Fig. 18). This could explain A→C transversions induced by the (+)-*trans*-B[a]P-*N*⁶-dA adduct.

Other *N*⁶-dA PAH adducts follow a similar pattern with respect to the configuration at the adducted C-atoms. For benz[a]anthracene, this is the C(1)-atom. The (1*R*)-adduct intercalates to the 5'-side of the damaged base [176], while the (1*S*)-adduct intercalates to the 3'-side [177]. Likewise, for *trans*-B[c]P, configuration at C(1) is crucial [178][179]. The (1*S*)-adduct permits the B[c]P ring to intercalate 3' to lesion site without disrupting *Watson-Crick* H-bonding. The (1*R*)-adduct intercalates to the 5'-side of the modified base pair [178][179]. The greater thermal stabilities of duplexes containing fjord region *N*⁶-dA lesions correlate with lower susceptibilities of excision by NER [163]. Computational studies of a template-primer containing the (-)-(1*S*)-*trans*-B[c]P-*N*⁶-dA adduct in a complex with the Dpo4 polymerase suggest that B[c]P intercalation likely impedes replication [180]. The (+)-*trans*-benzo[*g*]chrysene-dA adduct also follows the pattern whereby (*R*)-configuration at C(14) correlates with 5'-intercalation [181].

Configurational Rearrangements of DNA Adducts

Increasingly, the importance of interconversions of DNA adducts involving bond breakage and rearrangement has become recognized. Such rearrangements can be either chemically reversible, *i.e.*, existing at equilibrium, or irreversible. Examples of specific adducts include abasic sites, the epimerization of thymine glycol lesions, deamination and the *Dimroth* rearrangement of N1-dA lesions, the rearrangement of 1,*N*²-dG lesions arising from malondialdehyde and α,β -unsaturated enals, and α/β anomerization of formamidopyrimidine (FAPY) lesions.

Deamination of Butadiene-Derived N1-dA Adducts

Buta-1,3-diene (BD) is extensively used in the polymer industry, *e.g.*, in the manufacture of styrene-butadiene rubber [182][183]. The metabolism of BD is depicted in Scheme 1. Reaction of butadiene epoxides with dA results in the formation of N1-dA adducts. These may undergo hydrolysis of the 6-NH₂ group to give the analogous inosine derivatives [184] (Fig. 19). Deamination of dA represents a promutagenic event, because, during DNA replication, the resulting dI nucleotide is recognized as dG and preferentially pairs with incoming dCTP. When ligated into the single-stranded vector M13mp7L2 and transfected into repair-deficient *E. coli*, the 2'-deoxy-*N*¹-[(2*S*)-1-hydroxybut-3-en-2-yl]inosine adduct codes for incorporation of dCTP [185]. Similar results are observed with COS-7 cells [186]. Structural analyses reveal that, following deamination of the N1-dA lesion, the glycosyl bond of the (*S*)-N1-BDO-dI adduct rotates into the *syn*-conformation, placing the BD moiety into the major groove. The complementary dT (*anti*) remains intrahelical at the adduct site. The results suggest that the tendency of the (*S*)-N1-BDO-dI adduct to code for incorporation of dCTP may be attributed to the propensity of this adduct to form a protonated *Hoogsteen*-pairing interaction with dCTP during replication [186].

Dimroth Rearrangement of N1-dA Adducts. Alternatively, N1-dA adducts of BD undergo chemical rearrangement to isomeric *N*⁶-dA adducts *via* a *Dimroth* rearrangement [187], in which ring cleavage between the N(1)- and C(2)-atoms of dA is followed by 180° internal

rotation [188]. The consequence is that the initially formed N1-dA lesion, which is anticipated to be highly mutagenic due to the fact that it precludes *Watson–Crick* bonding during DNA replication, is converted to an N^6 -dA lesion (Fig. 19), which is projected to orient into the major groove of DNA, resulting in minimal structural perturbation and be less mutagenic. Structural studies of a series of N^6 -dA adducts of styrene oxide and butadiene epoxides suggests that, indeed, they induce minimal structural perturbation of DNA and are contained within the major groove [189–194]. Likewise, site-specific mutagenesis conducted in *E. coli* revealed that these adducts are only weakly mutagenic [195][196].

Malondialdehyde

Malondialdehyde (MDA), produced by lipid peroxidation and prostaglandin biosynthesis [197][198], is mutagenic in bacterial and mammalian cells [199–201] and is carcinogenic in rats [202]. In *Salmonella typhimurium*, MDA induces insertions and deletions as well as base substitutions [200][203][204]. Replication of MDA-modified single-stranded M13 genomes in *E. coli* causes G→T, A→G, and C→T mutations [199]. Adduction of MDA to deoxyguanosine produces 3-(2'-deoxy- β - δ -erythro-pentofuranosyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (M₁dG; Fig. 13) [205][206]. Like PdG, discussed above, M₁dG is a 1,2-dG annelation product, but chemically and biologically, it behaves much differently in DNA. Reddy and Marnett [207] incorporated M₁dG into an oligodeoxynucleotide. The spectrum of mutations induced by M₁dG using M13 vectors replicated in *E. coli* showed M₁dG →A and M₁dG →T mutations, and low levels of M₁dG →C mutations; however, the mutation frequency was *ca.* 1%, when cytosine was placed opposite the lesion [208]. M₁dG also induced –1 and –2 base deletions when positioned in an iterated 5'-(CpG)₄-3' sequence, but not when positioned in a non-iterated sequence in both *E. coli* and in COS-7 cells [209].

An explanation as to why M₁dG is weakly mutagenic was elucidated when it was discovered that when M₁dG is placed opposite dC it rearranges to *N*²-(3-oxoprop-1-enyl)-dG (OPdG; Scheme 2) [210]. Riggins *et al.* [211][212] concluded that ring opening of M₁dG as a nucleoside or in oligodeoxynucleotides occurs *via* a reversible second-order reaction with hydroxide, catalyzed by the complementary dC. The closure of the resulting *N*²-(3-oxo-1-propenyl)-dG anion is pH-dependent and under neutral and acidic conditions ring-closure is biphasic, leading to the rapid formation of intermediates that slowly convert to M₁dG in a general-acid-catalyzed reaction, in the presence of dC in the complementary strand. Structural studies in the 5'-(CpG)₃-3' sequence show that the OPdG propenyl chain is located in the minor groove, facilitating *Watson–Crick* H-bonding with dC [213]. Structural studies with OPdG adduct located in the 5'-TXT-3' sequence lead to a similar conclusion [214].

Structural studies have also been conducted when M₁dG and OPdG adducts are placed opposite a 2-base deletion (2BD) complementary strand in the 5'-(CpG)₃ sequence [215–217]. M₁dG is stable in the 2BD duplex and remains ring-closed when it is the 5'-nucleotide of a two-nucleotide bulge [215]. Both bulged nucleotides are in the *anti* conformation about the glycosyl bond and appear inside the helix, but lack H-bonding interactions [216]. On the other hand, the OPdG-2BD duplex undergoes bulge migration from the 3'-neighbor base pairs to the adduct region [217]. The bulge migration transiently positions OPdG opposite dC in the complementary strand and, consequently, hinders the conversion of OPdG to M₁dG. Thus, in contrast to the rapid OPdG→M₁dG conversion during denaturation [210], the ring-closure of OPdG in this 2-base deletion 5'-(GpC)₃ sequence requires 140 days at room temperature. When the M₁dG-containing primer-template was crystallized with the polymerase Dpo4 and dNTP, M₁dG maintained the ring-closed form. It intercalated into the duplex and displaced the complementary dC to the minor groove [218].

Enal-Derived Adducts

Acrolein is mutagenic in bacterial and mammalian cells [204][219–221], and is carcinogenic in rats [222]. The binding pattern of acrolein-DNA adducts is similar to the *p53* mutational pattern in human lung cancer, implicating acrolein as a major cigarette-related lung cancer-inducing agent [223]. Acrolein causes tandem G→T transversions in the *supF* gene on the shuttle vector plasmid pMY189. Crotonaldehyde is genotoxic and mutagenic in human lymphoblasts [224] and induces liver tumors in rodents [225]. 4-Hydroxynonenal (HNE) is produced from the metabolism of membrane lipids [226] and is a major *in vivo* peroxidation product of ω -6 polyunsaturated fatty acids [197][227]. HNE induces a DNA damage response in *Salmonella typhimurium* [228][229]. It also causes mutations in V79 CHO cells, and DNAs from liver specimens from individuals suffering from *Wilson's* disease and hemochromatosis contain mutations attributed to HNE-dG adducts [230]. Acrolein and related α,β -unsaturated aldehydes undergo *Michael* addition to dG, also yielding 1, N^2 -dG ring-annulation products. Like the M₁dG lesion, these also undergo further downstream chemistry in DNA, in a sequence-dependent manner. Enal-derived adducts have been detected in human and rodent DNA [231–235]. *Harris, Rizzo*, and co-workers site-specifically incorporated acrolein, crotonaldehyde, and HNE derived γ -OH-PdG adducts into oligodeoxynucleotides [236–238].

i) Acrolein—Acrolein reacts with dG to produce γ -OH-PdG and α -OH-PdG (Fig. 13). Correct replication across γ -OH-PdG is efficient in both mammalian and bacterial cells [239–241]. In DNA, γ -OH-PdG undergoes ring opening when placed opposite dC, forming N^2 -(3-oxopropyl)-dG (Scheme 2) [242]. This facilitates *Watson-Crick* H-bonding with the complementary dC and could explain the weak mutagenicity of γ -OH-PdG. *Nair et al.* [243] showed that yeast Rev1 DNA polymerase incorporates the correct nucleotide dC opposite PdG, a model for γ -OH-PdG, with nearly the same efficiency as opposite an undamaged dG. But it cannot extend the primer. However, Pol ζ can carry out the subsequent extension reaction. The crystal structure, in complex with Rev1, showed that PdG rotated to the *syn* conformation about the glycosyl bond, and the incoming dCTP did not pair with PdG, but instead paired with Arg324 from yeast Rev1 polymerase.

Unlike γ -OH-PdG, α -OH-PdG (Fig. 13) blocks DNA replication in human cells, and it codes for dCTP incorporation, with minor G→A and G→T base substitution mutations when bypassed by Y-family polymerases [241]. The α -OH-PdG lesion is stable in DNA when placed opposite dC [244]. It adopts the *syn*-conformation around the glycosyl bond, forming a *Hoogsteen*-like pair to its complementary cytosine (Fig. 20). *In vitro* replication using Y-family DNA polymerases showed that Pol η and Pol κ catalyze mutagenic replication across α -OH-PdG, while Rev1 and Pol τ mediate accurate replication, with the later incorporating dATP and dTTP at low frequencies [245]. As for γ -OH-PdG, the ternary complex containing Rev1, PdG-modified DNA, and dCTP showed that PdG rotates to the *syn* conformation about the glycosyl bond, which positions PdG into a small hydrophobic cavity, while the incoming dCTP interacts with an Arg residue by forming two H-bonds [243]. Thus, the structure of α -OH-PdG reported by *Zaliznyak et al.* [244] identified the bonds that would keep the α -OH-PdG in the *syn*-conformation at the replication fork of Pol τ . This supports the formation of a non-mutagenic α -OH-PdG (*syn*)-C (*anti*) replication intermediate.

ii) Crotonaldehyde—Similar methodology has been used to study the crotonaldehyde-derived γ -OH-PdG adduct, in which the α -CH₃ group creates a new stereogenic center at C(6) [246]. Four stereoisomers are possible for the crotonaldehyde-derived γ -OH-PdG adducts; those with *trans*-configuration of γ -OH and α -CH₃ predominate. In single-strand DNA, the major and minor epimers at C(8) interconvert. The ring-opened intermediate is

undetectable in single-strand DNA. The diastereoisomeric adducts have been placed opposite dC and dT in DNA. The crotonaldehyde-derived γ -OH-PdG adducts exhibit higher stability than does the acrolein-derived adduct. When placed opposite dT, the ring-opened species is undetectable. On the other hand, both (*R*)- and (*S*)- α -CH₃- γ -OH-PdG adducts undergo ring-opening to the *N*²-dG aldehydes and corresponding *N*²-dG aldehydols when placed opposite dC (Scheme 2). However, the ring-opening is incomplete. Higher pH and temperatures favor the *N*²-dG aldehyde adducts. The structure of the (*S*)- α -CH₃- γ -OH-PdG adduct shows the ring-opened (*S*)- α -CH₃-*N*²-dG aldehyde adduct forms *Watson-Crick* pairing with the complementary dC, leaving the aldehyde moiety within the minor groove. The aldehyde of the *N*²-dG aldehyde adduct orients in the 3'-direction, while the (*S*)- α -CH₃ group orients in the 5'-direction [247].

iii) 4-Hydroxynonenal—HNE reacts with the *N*²-amino group of dG to give four diastereomeric 1,*N*²-dG adducts (Fig. 21) [248–250], and all of them are detected in cellular DNA [231][251–256]. HNE is mutagenic [227] and carcinogenic in rodent cells [257]. HNE induces primarily G→T transversions, accompanied by lower levels of G→A transitions, in the *supF* gene of shuttle vector pSP189 replicated in human cells [258]. The site-specific mutagenesis studies showed that the (6*S*,8*R*,11*S*)- and (6*R*,8*S*,11*R*)-1,*N*²-HNE-dG adducts are mutagenic, inducing low levels of G→T transversions and G→T transitions. The initial studies revealed that, when 1,*N*²-HNE-dG adducts are placed opposite dC in duplex DNA, the exocyclic ring opens, leaving intact *Watson-Crick* base pairing for the coding face of the adducted dG (Scheme 2) [259]. This accounts for the low levels of mutations associated with these adducts. When mismatched with dA in DNA, (6*S*,8*R*,11*S*)-1,*N*²-HNE-dG maintains its exocyclic structure [260]. This duplex mimics the situation following incorrect incorporation of dATP opposite the (6*S*,8*R*,11*S*)-1,*N*²-HNE-dG adduct (G→T transversion). The adduct undergoes a conformational equilibrium between the *syn*- and *anti*-conformations about the glycosyl bond. At basic pH, the equilibrium shifts toward the *anti*-conformation where 1,*N*²-HNE-dG intercalates and displaces the complementary dA in the 5'-direction (Fig. 22). The HNE aliphatic chain is oriented toward the minor groove of the DNA. At acidic pH, the equilibrium shifts toward the *syn*-conformation in which the HNE moiety is located in the major groove (Fig. 22). The complementary adenine is protonated, and the (6*S*,8*R*,11*S*)-1,*N*²-HNE-dG (*syn*)-dA⁺ (*anti*) base pair is stabilized by *Hoogsteen* type H-bonding. Thus, at neutral pH, both the *syn*- and *anti*-conformations are present. *Xing et al.* [248] attributed the low levels of G→T transversions to the reorientation of the (6*S*,8*R*,11*S*)-1,*N*²-HNE-dG adduct into the *syn* conformation around the glycosyl bond, which might allow misincorporation of dATP opposite the lesion. The results confirm that such reorientation happens, when (6*S*,8*R*,11*S*)-1,*N*²-HNE-dG is mismatched with dA in DNA.

Abasic Sites

Hydrolytic cleavage of the nucleobase from the 2'-deoxyribose creates the abasic site, or apurinic and apyrimidinic sites (AP; Scheme 3). There probably is a constant level of *ca.* 10,000 abasic sites in typical human cells [261]. Most AP sites result from spontaneous depurination [261], but deamination of cytosine to uracil, which is then eliminated by uracil glycosylases, also occurs [262]. The abasic site is also an intermediate in the base excision repair process [263]. AP Sites are mutagenic [264] and cause mis-incorporation in bacterial and mammalian cells [265–271]. DNA Polymerases preferentially incorporate dATP opposite AP sites (sometimes referred to as the 3A-rule3) [272–274]. During translesion DNA synthesis by Y-family DNA polymerases, AP sites also cause frameshifts [275–278].

The AP site exists in three configurations, the cyclic hemiacetal **1** (a and b), the aldehyde **2**, and the hydrated aldehyde **3** (Scheme 3). The equilibria of these species in different

sequences, when AP sites are placed opposite all four 2'-deoxynucleotides [279][280], show that cyclic hemiacetal **1** predominates and constitutes over 99% of the population. Less than 1% of aldehyde **2** is also observed, whereas **3** is undetectable.

The equilibrium of AP species leads to the anomeric configuration interconversion of the deoxyribose. Stereoisomers **1a** and **1b** exist in equilibrium, when the AP site is placed opposite dA, dC, dG, or dT [279]. *Beger* and *Bolton* [281] reported that the β -anomer exists predominantly, when the AP site is placed opposite dC in the 5'-AXA-3' sequence (X = AP site), whereas both α - and β -anomers exist, when AP is placed opposite dA. They proposed that a H₂O-bridged H-bond with the complementary dC might contribute to the stereoselectivity. Based on the structure of the human ApeI endonuclease/THF-containing duplex, from which it was concluded that the β -anomer could not be accommodated in the active site of the enzyme, *Mol et al.* [282] proposed that the endonuclease only incises the α -anomer. However, other binding studies of AP surrogates with this enzyme show no differences for the two anomers and lead to the opposite conclusion that the configuration at C(1') of deoxyribose is not important for enzymatic recognition [283].

AP Sites decrease the stability of DNA, depending especially on the identities of the flanking base pairs but only mildly on the orphan base [284][285]. The structures of α - and β -anomer of the AP site have been compared. Structural and dynamic studies have been performed, when AP or AP surrogates are placed opposite dA, dC, dG, or dT in different sequences [286]. The conformation around the AP site is more perturbed, when the base opposite to the AP is a pyrimidine than a purine [287][288]. The deoxyribose position depends on the type of orphan base, the configuration at C(1') of the deoxyribose, and the flanking base pairs. *Goljer et al.* [289] reported that, when dA is the orphan base, the α -anomer of the natural AP site adopts an extrahelical conformation, whereas the β -anomer adopts an intrahelical conformation. Further studies by the same group, however, showed that both AP anomers stack interhelically in different sequences [281]. When AP is placed opposite dA, a H₂O-mediated H-bond has been proposed [281]. This forms between the orphan dA and the hemiacetal OH group of the β -anomer, and maintains the deoxyribose moiety inside the helix. Formation of a H₂O bridge is impossible for the α -anomer, which then adopts an extruded conformation [281]. When the AP site was placed opposite dC, the α -anomer was not present. Rather, two conformations of the β -anomer were observed, depending on the H₂O-mediated H-bond between the OH group and the orphan cytosine N(3) or C(2)=O. Both H-bonds keep the β -anomer inside the helix [281]. Recent structural and dynamic studies with AP and AP surrogates confirm that both AP anomers are inside the helix [283][287][288]. However, the OH group of both α -AP and β -AP is more likely to form H-bonds directly with opposite dA, dC, and dT [287][288]. The biological effects of the anomers of the AP lesion remain unclear.

Thymine Glycol

The oxidation of thymine and 5-methylcytosine produces 5,6-dihydro-5,6-dihydroxy-2'-thymine, thymine glycol (Tg) [290][291]. Tg has been detected in animal and human urine; human cells probably repair hundreds of these lesions per day [292][293]. Tg blocks DNA replication [294–296] and induces base-substitution mutations [297]. It inhibits DNA synthesis by many prokaryotic and eukaryotic DNA polymerases one nucleotide before and opposite the lesion site. Several DNA polymerases lacking 3',5' exonuclease activity can bypass the Tg lesion, albeit slowly [298–300].

Tg exists in DNA as two diastereoisomeric pairs of epimers, the (5*R*)-*cis,trans*-pair (5*R,6S*); (5*R,6R*) and the (5*S*)-*cis,trans*-pair (5*S,6R*);(5*S,6S*) (Scheme 4) [301–303]. The (5*R*) pair is more abundant and more stable [302]. For both the (5*R*)- and (5*S*)-pairs, the *cis*-epimers predominate at the nucleoside level [302]. The biological responses to Tg adducts are

modulated by configuration. For example, the Y-family polymerase Pol η bypasses the (5*R*)-epimers more efficiently [304], whereas Pol κ bypasses the (5*S*)-epimers more efficiently [305]. The human hNTH1 glycosylase shows a greater preference for excising the (5*R*)-epimers [306], whereas the hNEIL1 glycosylase shows a greater preference for excising the (5*R*)-epimers [307][308]. Similar observations have been made for prokaryotic, yeast, and murine glycosylases [309]. The base excision repair of Tg lesion by DNA N-glycosylases/AP lyases is modulated by the *cis/trans*-epimerization of these two sets of diastereoisomers [310].

The (5*R*) epimers have been studied, when Tg is placed opposite dA or dG in the 5'-GXG-3' (X=Tg) sequence [311]. For the duplex containing the X·A pair, the ratio *cis*-(5*R*,6*S*)/*trans*-(5*R*,6*R*) is 7 :3 at 30°. In contrast, for the duplex containing the X·G pair, the *cis*-(5*R*,6*S*)-epimer predominates; the *trans*-(5*R*,6*R*) epimer is undetectable. The introduction of (5*R*)-Tg in the 5'-AXA-3' and 5'-GXC-3' sequence contexts when paired opposite dA induces localized structural perturbations with the loss of H-bonding at the lesion sites [312] [313]. Tg is displaced toward the major groove, increasing its exposure to the solvent. In contrast, when paired opposite dA in the 5'-GXG-3' sequence, the *cis*-(5*R*,6*S*)-Tg lesion only minimally distorts the helical backbone [314]. Both Tg and the complementary dA insert into the helix and remain in a *Watson-Crick* alignment (Fig. 23,*a* and *b*). However, stacking between Tg and the 3'-neighbor G·C base pair is disrupted. Two conformations are obtained for the *cis*-(5*R*,6*S*)-Tg, depending on the axial or equatorial conformations of the Me group. The NMR-based MD simulations predict that the axial conformation of the *cis*-(5*R*,6*S*)-Tg is favored. An intrastrand H-bond observed between the Tg C(6)-OH and the N(7) position of a 3'-purine may account for the structural differences the *cis*-(5*R*,6*S*)-Tg in the 5'-GXG-3' and 5'-GXC-3' sequence contexts. Consistent with the structure in the 5'-GXG-3' sequence, when (5*R*)-Tg-containing binary primer-template complex is co-crystallized with the replicative RB69 DNA polymerase, the *cis*-(5*R*,6*S*)-Tg epimer is intrahelical and forms a *Watson-Crick* base pair with the dA at the primer 3'-terminus. The Tg Me group is in the axial conformation, hindering stacking of the adjacent 5'-template guanine. These results provide a rationale for the observation that extension past the (5*R*)-Tg lesion by the *Klenow* fragment of *E. coli* DNA polymerase I or T4 DNA polymerase is prohibited.

The base excision repair of Tg lesions also depends upon the identity of the opposing base. The hNth glycosylase repairs the *cis*-(5*R*,6*S*)-Tg more efficiently when it is placed opposite adenine than when placed opposite guanine [310]. Thus, the solution structure of *cis*-(5*R*,6*S*)-Tg-containing oligodeoxynucleotide has also been refined in the 5'-GXG-3' sequence when mismatched with dG (Fig. 23,*c* and *d*) [315]. Both Tg and the opposite dG remain stacked in the helix. The Tg·G base pair is in the wobble orientation. The Tg shifts toward the major groove and stacks below the 5'-neighbor base, its complement dG also stacks below the 5'-neighbor. Stacking between the Tg and the 3'-neighbor base pair is disrupted. In contrast to when placed opposite dA, the *cis*-(5*R*,6*S*)-Tg does not form strong intrastrand H-bonds with the imidazole N(7)-atom of the 3'-neighbor purine.

Alkaline hydrolysis of Tg produces urea adduct (Scheme 4), which exists as the minor species of thymine oxidation by exposure to the ionizing radiation [290][316]. Urea adducts constitute replicative blocks for DNA polymerases and subsequently inhibit chain elongation [295][317]. It also preferentially promotes misincorporation of dGTP [318]. To explain the biological effects, a structure of the nucleotide containing urea adduct has been studied, when dT or dG is placed opposite [319]. Whereas the conformation is undeterminable due to the broad NMR resonances when placed opposite dG, the urea deoxyribose exists as two conformations when placed opposite dT, depending on the *cis/trans*-orientation of the urea unit with respect to the deoxyribose. The *trans-anti*-isomer,

which exists as the major species, is expected to be placed intrahelically and form H-bonds with opposite thymine. The *cis*-isomer is unable to form these H-bonds and exists as the minor species.

The urea adduct has also been placed in a -1 frame shift sequence [320]. Again, at equilibrium, two species are found in slow exchange. The urea adduct is either intra- or extrahelical within the right-handed DNA duplex, determined by the H-bonds formed by the *cis/trans*-isomers. In the minor intrahelical species, the *cis*-isomer forms two H-bonds with the bases in the opposite strand, whereas the *trans*-isomer does not. For the major extrahelical species, the *trans*-isomer forms two H-bonds, one is intrastrand with the guanine in the modified strand, the other is interstrand with the adenine in the opposite strand, whereas the *cis*-isomer only forms one H-bond. In the major species, the urea residue lies in the minor groove, and the neighboring bases are stacked over each other in a way similar to a normal B-DNA structure.

Oxidation of 8-Oxo-dG to Guanidinohydantoin and Spiroiminodihydrantoin

The fact that initially formed 8-oxo-dG lesions, discussed above, can undergo further oxidation, has become appreciated in recent years. The 8-oxo-dG is more prone to oxidation than is guanine [321], its downstream oxidation products are guanidinohydantoin (Gh), and two stereoisomers of spiroiminodihydrantoin ((*R*)-Sp and (*S*)-Sp) (Fig. 24) [322–324]. Gh predominates in duplex DNA, while Sp predominates at the nucleoside level [325]. Sp has been detected in DNA from *E. coli* cells [326]. Gh-Containing DNA is bypassed by *E. coli* DNA pol I, which inserts dATP or dGTP opposite the lesion [327]. However, Gh and Sp are strong replication blocks to Pol α and human Pol β [327]. Gh is mutagenic with DNA polymerases incorporating purines, which results in G·C→T·A or G·C→C·G transversions [328][329]. A structure of the replicative RB69 DNA polymerase in complex with DNA containing Gh revealed that Gh is extrahelical and rotated toward the major groove [330]. In contrast to 8-oxoG, Gh in this structure was in a *high syn*-conformation and presented the same H-bond donor and acceptor pattern as thymine, which may explain why polymerases incorporate a purine opposite Gh during error-prone bypass [330].

Aflatoxin B₁

Aflatoxin B₁ (AFB) is a mycotoxin that contaminates agricultural products [331]. It is a mutagen in bacteria [332–334], a carcinogen in fish [335][336], and a carcinogen in rodents [337][338]. AFB is mutagenic, with G→T transversions being observed in a variety of prokaryotic and eukaryotic systems [334][339][340]. Aflatoxin exposures are implicated in mutations to the p53 tumor suppressor gene [341–344], and the mycotoxin is implicated in the etiology of human liver cancer [345–348].

The reaction of N7-dG at C(8) of the electrophilic AFB-*exo*-8,9-epoxide yields the N7-dG cationic adduct (Scheme 5) [349–352]. This adduct yields the characteristic G→T mutations but is only moderately mutagenic in *E. coli* [353]. The N7-dG cationic adduct is chemically unstable [354][355]. At physiological pH, depurination occurs, to release AFB-guanine and yield an apurinic site [355]. Of greater concern is the potential for base-catalyzed cleavage of the imidazole ring to yield the formamidopyr-imidine (FAPY) derivative. Two equilibrating AFB-FAPY species in duplex DNA exhibit different biological consequences in DNA replication: one of the two species is potently mutagenic, yielding G→T mutations, while the other blocks replication [356]. These have been assigned to the α - and β -anomers of the FAPY adduct [357][358]. In duplex DNA, the β -anomer predominates [358]. In single-strand DNA, however, a 2 : 1 mixture of α - and β -anomers is observed [356].

Both the initially formed N7-dG cationic adduct and the FAPY rearrangement products have been examined as to structure in DNA. In all instances, the AFB moiety intercalates above the 5'-face of the damaged guanine [358–362]. When dC is placed opposite the N7-dG cationic adduct, *Watson-Crick* base pairing is maintained for the AFB-N7-dG-dC base pair. With regard to the highly mutagenic β -anomer of the FAPY species, *Watson-Crick* H-binding is conserved for the FAPY-dC and the flanking base pairs (Fig. 25). In duplex DNA with a 3'-neighboring adenine, both anomers adopt the (*E*)-conformation of the formyl O-atom, involving a H-bond between the formyl oxygen and the non-*Watson-Crick* H-bonded N^6 -amine H-atom of the neighboring adenine [362].

Significantly, the α -FAPY anomer decreases the stability of the DNA duplex, whereas the β -anomer increases the stability [362]. This suggests that it may be refractory to nucleotide excision repair processes *in vivo*. Favorable interstrand stacking is considered to be the main factor of the stability of AFB- β -FAPY. In contrast, the α -anomer disrupts the helical structure of DNA [362]. Intercalation of the AFB moiety induces perturbations in the phosphodiester and backbone torsion angles, ϵ and ζ , respectively, and the deoxyribose shifts to become parallel to the FAPY base and is displaced toward the minor groove. Intrastrand stacking between the AFB moiety and the 5'-neighbor thymine remains, but interstrand stacking is not observed. As a result, compared with the unmodified sequence, the α -FAPY anomer destabilizes the duplex.

Adduct-Induced DNA Cross-Linking

DNA Interstrand cross-links represent one of the most serious types of damage, since replication and transcription require separation of the complementary strands. In eukaryotes, interstrand cross-link repair requires cooperation of multiple proteins that belong to different biological pathways, including NER, homologous recombination, TLS, double-strand break repair, and the *Fanconi* anemia pathway (reviewed in [363–366]).

The 1, N^2 -dG enal adducts formed by acrolein, crotonaldehyde, and HNE discussed above are capable of forming interstrand N^2 -dG: N^2 -dG cross-links. The formation of the cross-links is sequence dependent. Enals induce interstrand cross-links in the 5'-CpG-3' sequence, but not in the 5'-GpC-3' sequence [236–238][367]. The rearrangements of the γ -OH-PdG adducts to the ring-opened N^2 -dG aldehydes is critical for cross-link formation (Scheme 6). These N^2 -dG: N^2 -dG linkages can be chemically reduced [236][237]. This implies that they exist, in part, as imines. When DNA containing the cross-links is enzymatically digested to nucleotides, the cross-links are isolated as pyrimido-purines [236–238]. However, in duplex DNA, the N^2 -dG: N^2 -dG linkages exist predominantly as carbinolamines [246][368][369]. The carbinol-amine linkage maintains *Watson-Cricking* base pairing [246][369]. The HNE-induced cross-link exhibits extraordinary chemical stability. Whereas less than 50% of acrolein and crotonaldehyde derived γ -HOPdG adducts are converted the cross-links [236][237], the HNE-derived (6*S*,8*R*,11*S*) γ -OH-PdG adduct is fully converted [238].

Formation of N^2 -dG: N^2 -dG cross-links is stereoselective. The (*R*)-carbinolamine linkage constitutes 80–90% of the cross-link induced by the γ -OH-PdG adduct [370]. Its structure has been refined in the 5'-CpG-3' sequence (Fig. 26) [370]. The carbinolamine linkage is located in the minor groove, maintaining *Watson-Crick* H-bonding of the cross-linked base pairs. The *anti*-conformation of the carbinol OH group with respect to C^α of the tether minimized steric interactions, and allowed the formation of a H-bond between the carbinol OH group and the cytosine C(2)=O located in the 5'-neighboring G-C base pair. This H-bond might explain the stability of this cross-link, and the stereochemical preference for the (*R*)-configuration of the cross-link.

The preferential formation of the cross-link in the 5'-CpG-3' sequence as compared to the 5'-GpC-3' sequence is attributed to the longer distance between the two N^2 -dG atoms in the 3'-direction than in the 5'-direction, accompanied by greater destabilization of the DNA duplex by the cross-link in the 5'-GpC-3' sequence [371][372]. Structures of the fully reduced trimethylene cross-links have been refined in both 5'-CpG-3' and 5'-GpC-3' sequences [373]. Whereas perturbation caused by the cross-link in the 5'-CpG-3' sequence is minimal, the perturbation in the 5'-GpC-3' sequence is significant (Fig. 27). Differential stacking of the base pairs at the cross-linking region explains the difference in stabilities of the trimethylene cross-links in the 5'-CpG-3' and 5'-GpC-3' sequence contexts, and, in turn, account for the sequence selectivity of the interstrand cross-link formation induced by the enal-derived 1, N^2 -dG adducts.

Configuration of the γ -OH-PdG adducts also modulates interstrand cross-link formation. The crotonaldehyde derived (*R*)-CH₃- γ -OH-PdG adduct induces N^2 -dG: N^2 -dG interstrand cross-links more efficiently than the (*S*)-CH₃- γ -OH-PdG adduct does [237]. The (*S*)-CH₃- γ -OH-PdG places the aldehyde toward the 3'-neighbor A·T base pair in the 5'-CpG-3' sequence [247]. Conformational adjustment is required to reorient the aldehyde group to the 5'-neighbor C·G base pair, and consequently results in the slow production of the cross-link. Model studies showed that re-orientation of the aldehyde in the 5'-direction led to the interference of the (*S*)-CH₃ group with the 3'-neighbor A·T base pair and decreased the stability of the DNA duplex. The structures of stereospecific α -CH₃-trimethylene cross-links, which are used as surrogates for the crotonaldehyde-derived carbinolamine cross-links, supported this conclusion (Fig. 28) [374]. The (*S*)-isomer of the α -CH₃-trimethylene cross-link exhibits lower thermal stability than the (*R*)-isomer does. Both isomers of the cross-links are located in the minor groove and retain *Watson-Crick* H-bonds at the tandem cross-linked C·G base pairs. However, the α -CH₃ group of the (*R*)-isomer is positioned in the center of the minor groove, whereas the α -Me group of the (*S*)-isomer is positioned in the 3'-direction, showing steric interference with the DNA helix.

Of the four stereoisomers of the HNE-derived γ -OH-PdG adducts, only the (6*S*,8*R*,11*S*)-configured one induces interchain cross-links [238]. All HNE-derived γ -OH-PdG adducts undergo ring-opening to N^2 -dG aldehydes and derivatives when placed opposite dC [375]. The existence of small amounts of N^2 -dG aldehyde adducts, which have been detected for the (6*S*,8*R*,11*S*)- and (6*R*,8*S*,11*R*)-stereoisomers [376], accounts for the slow formation of the cross-link. The structures of ring-opened N^2 -dG cyclic hemiacetals of (6*S*,8*R*,11*S*)- and (6*R*,8*S*,11*R*)-configurations show the HNE moiety is located in the minor groove with the directions of aldehyde group differing for the two stereoisomers (Fig. 29). The (6*S*,8*R*,11*S*)-aldehyde orients to the 5'-neighbor C·G base pair and favors cross-link formation. In contrast, the (6*R*,8*S*,11*R*)-aldehyde orients to the 3'-neighbor A·T base pair. Re-orientation of the aldehyde unit in the 5'-direction to favor the interstrand cross-link formation is disfavored due to the interference of the HNE moiety with the 3'-neighbor [377].

Butadiene-Mediated Cross-Linking

The bis-electrophile 1,2,3,4-diepoxybutane (DEB) is considered to be the ultimate carcinogenic metabolite of buta-1,3-diene. Initial DNA alkylation by DEB produces 2-hydroxy-3,4-epoxybut-1-yl adducts. These can undergo further reaction to form DNA cross-links. *Zhang* and *Elfarra* demonstrated that the reaction of DEB with dG produced nucleoside adducts resulting from alkylation at N(1) and N(7) of dG, 2'-deoxy-1-(2-hydroxyoxiran-2-ylethyl)guanosine and 2'-deoxy-7-(2-hydroxyoxiran-2-ylethyl)guanosine [378]. Incubation of the N1 adducts with dG led to formation of diastereoisomers of 1-[4-(2-amino-1,7-dihydro-6-oxo-6*H*-purin-7-yl)-2,3-dihydroxybutyl]-2'-deoxyguanosine (N7-dG-N1-dG-BD). Incubation of the N7-dG adducts with dG led to formation of the bis-dG cross-link 7,7'-(2,3-dihydroxybutane-1,4-diyl)bis[2-amino-1,7-dihydro-6*H*-purin-6-one]. The

sequence context of these cross-links is of particular interest, and not well understood. These cross-links predominate within 5'-GNC-3'/3'-CNG-5' sequences, where N is any nucleotide [379]. The efficiencies of cross-linking are dependent upon configuration, with (S,S)- >(R,R)- >meso-DEB [380]. Other DEB-mediated cross-links have been reported. *Tretyakova* and co-workers reported regioisomeric dG-dA cross-linking products involving the N7-dG N-atom, and the N1-, N3-, N⁶-, and N7-dA N-atoms [381]. The 1-(hypoxanthin-1-yl)-4-(guanin-7-yl)butane-2,3-diol (N1 HX-N7-dG-BD) cross-link has also been identified [382]. It was proposed that the latter was formed by the hydrolytic deamination of 1-(adenin-1-yl)-4-(guanin-7-yl)butane-2,3-diol. Alternatively, DEB can form exocyclic lesions by alkylating two sites of the same DNA base. *Zhang* and *Elfarra* have identified bis-alkylation products of dG [378][383][384]. *Tretyakova* and co-workers identified bis-alkylation products of dA [385][386]. They proposed that DEB alkylates the N(1)-position of dA to form N1-(2-hydroxy-3,4-epoxybut-1-yl)-dA adducts, which undergo an S_N2-type intramolecular nucleophilic substitution and rearrangement to give 1,N⁶-[2-hydroxy-3-(hydroxymethyl)propane-1,3-diyl]-2'-dA and 1,N⁶-[2-hydroxy-1-(hydroxymethyl)propane-1,3-diyl]-2'-dA. Both annelation products were identified in DNA treated with DEB *in vitro* and in liver DNA of mice exposed to BD by inhalation. Their formation provides a possible mechanism of mutagenesis at A:T base pairs. The initially formed 2-hydroxy-3,4-epoxybut-1-yl adducts may also interact with nucleophilic side chains within DNA-binding proteins to form DNA-protein conjugates, *e.g.*, with DNA repair proteins [387]. Structural studies of these adducts have not been reported but will be of considerable interest. However, the synthetically accessible and stable N⁶,N⁶-dA intrastrand cross-links have been used as model systems to probe the structures of DEB-induced cross-links in the major groove of DNA, and their consequent biological processing. The structures reveal that the major conformational difference between the (R,R)- and (S,S)-BD cross-links (Fig. 19) regards the conformation of the C₄ butadiene chain (27,28). The (R,R)-BD cross-link exists in the extended chain conformation with minimal perturbation of the DNA (27), while the (S,S)-BD cross-link creates a greater structural perturbation (28). Although both (R,R)- and (S,S)-BD cross-links were mutagenic in both *E. coli* and COS-7 cells, the (S,S)-BD cross-link exhibited a lower overall mutagenic frequency (20%) than that of the (R,R)-BD cross-link (54%) (29).

Summary

Early on, it was recognized that the alkylation of DNA, particularly when forming sterically bulky lesions, can be accommodated by conformational rearrangements at the damage sites, which do not involve bond breaking. Numerous examples now exist, particularly involving conformational rearrangement about the glycosyl torsion angle. These conformational interconversions have sufficiently large activation barriers that, under physiologically relevant conditions, interconversion occurs slowly at ms or slower time scales, and it is anticipated that different conformers may elicit differential biological responses. It has also been increasingly recognized that DNA damage may result in configurational rearrangements involving bond breakage; such rearrangements may be either reversible or irreversible and may alter the biological response to the damage. Finally, the ability of bis-electrophiles, such as α,β -unsaturated aldehydes or diepoxybutane, to cross-link DNA has been of considerable interest. Such cross-links, if not repaired, are anticipated to be highly genotoxic, interfering both with replication and repair processes.

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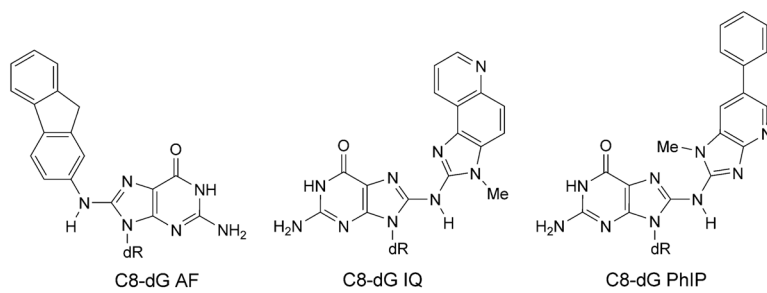


Fig. 1.
DNA Adducts derived from aromatic amines and heterocyclic amines

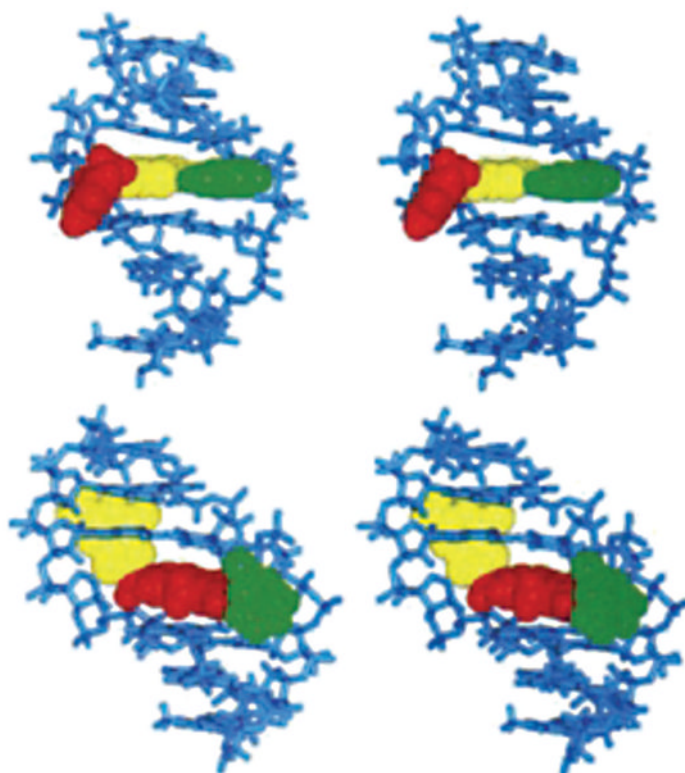


Fig. 2. Stereoview of duplexes containing a C8-dG AF adduct

The top panel shows the external-AF conformation, and the bottom panel shows the inserted-AF conformation as viewed from the major groove. The AF adduct is in red, the adducted guanine is in yellow, and the complementary dC is in green.

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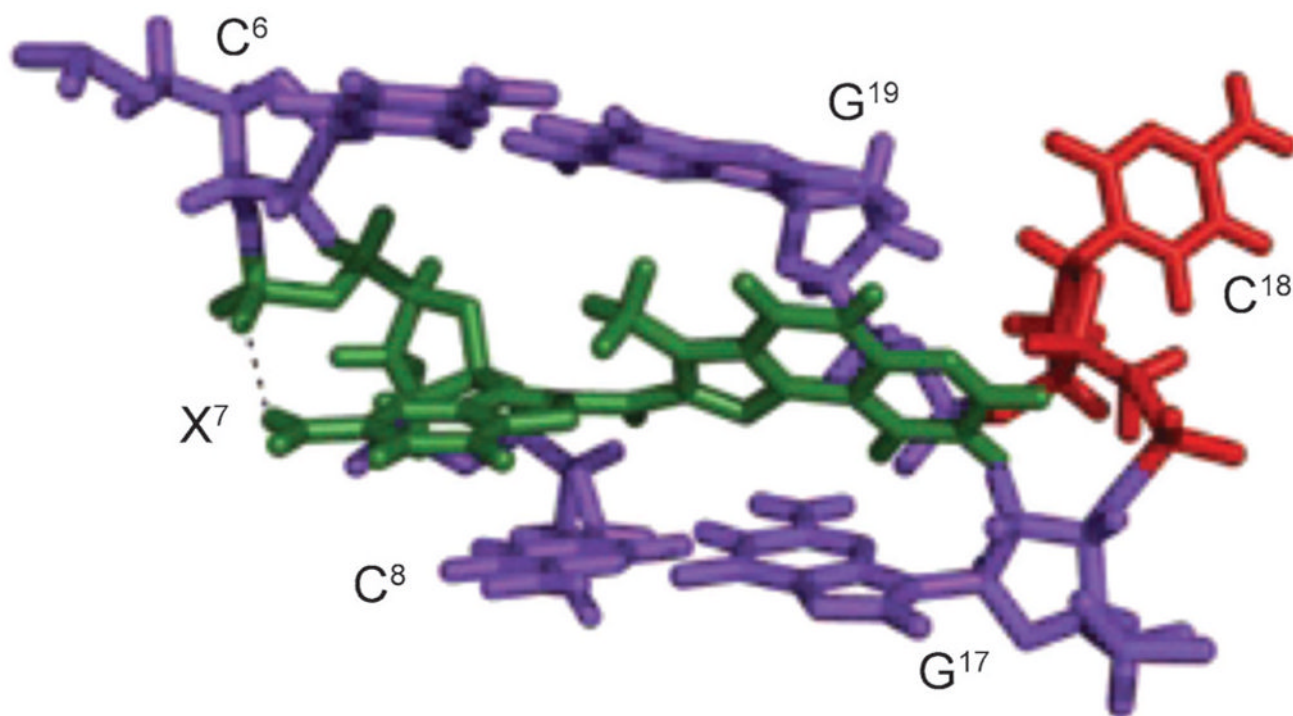


Fig. 3. Structure of the C8-dG IQ (*green*)-modified three-base-pair duplex, looking into the major groove and normal to the helix axis

The IQ ring is in red and is inserted between flanking base pairs. The dotted line indicates a H-bond formed between the amino group of modified dG and the O-atom of the 5' phosphodiester linkage. This illustration was prepared from PDB entry 2 HKC using PyMol [39] software.

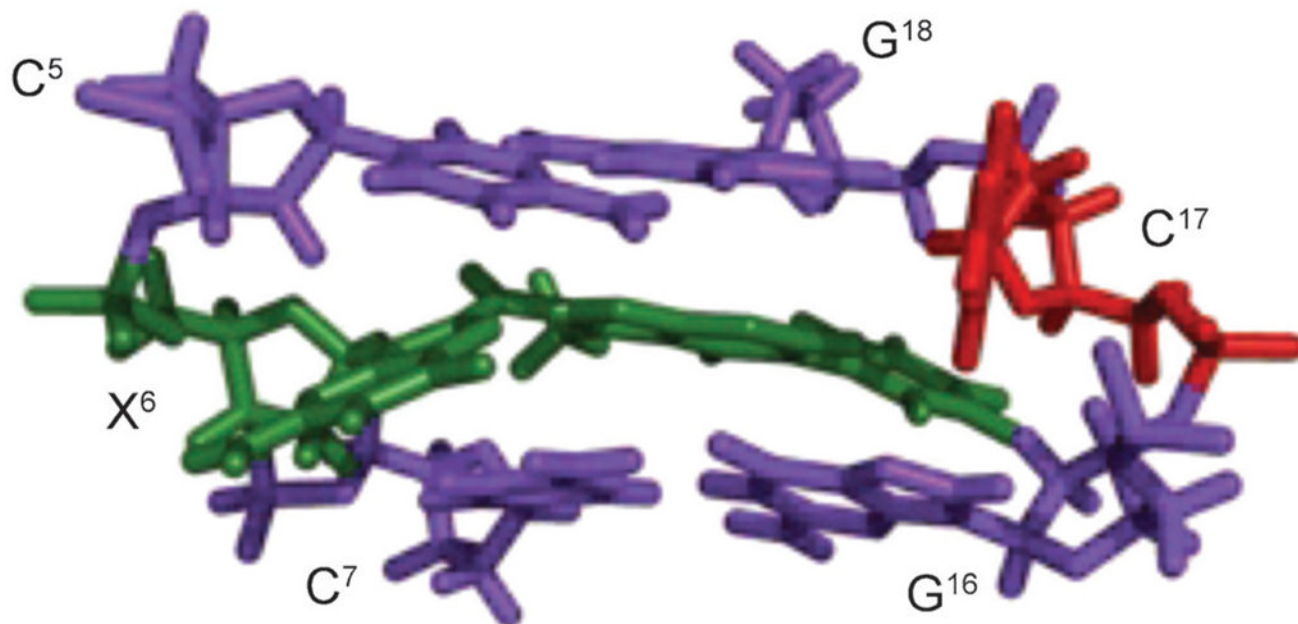


Fig. 4. Structure of a C8-dG PhIP (*green*)-modified three-base-pair duplex, looking into the major groove and normal to the helix axis
This illustration was prepared from PDB entry 1 HZO using PyMol [39] software.

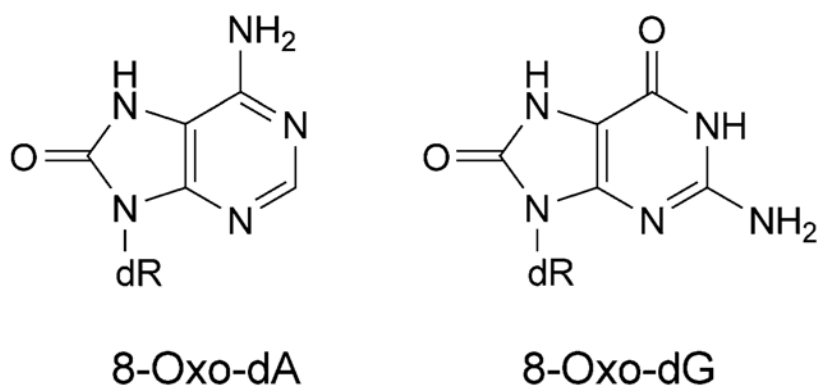


Fig. 5.
8-Oxo-dG and 8-oxo-dA adducts

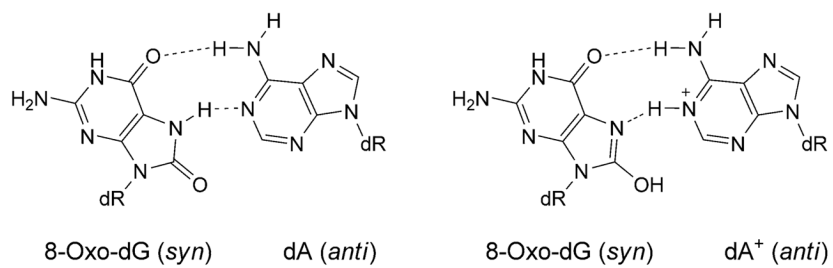


Fig. 6. H-Bonding patterns involving the 8-oxo-dG (*syn*)·A (*anti*) and 8-oxo-dG (*syn*)·A⁺ (*anti*) base pairs

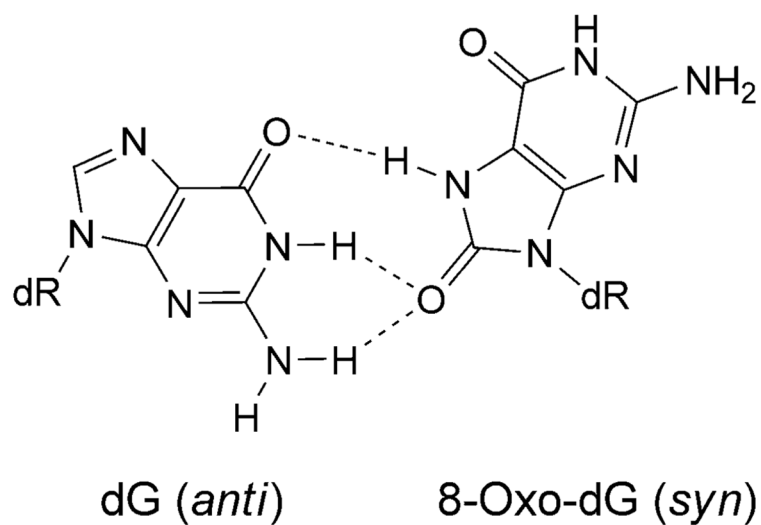


Fig. 7. Base pair showing the three-centered H-bonding between C(8)=O of 8-oxo-dG and the imino, and one of the amino H-atoms of the complementary dG

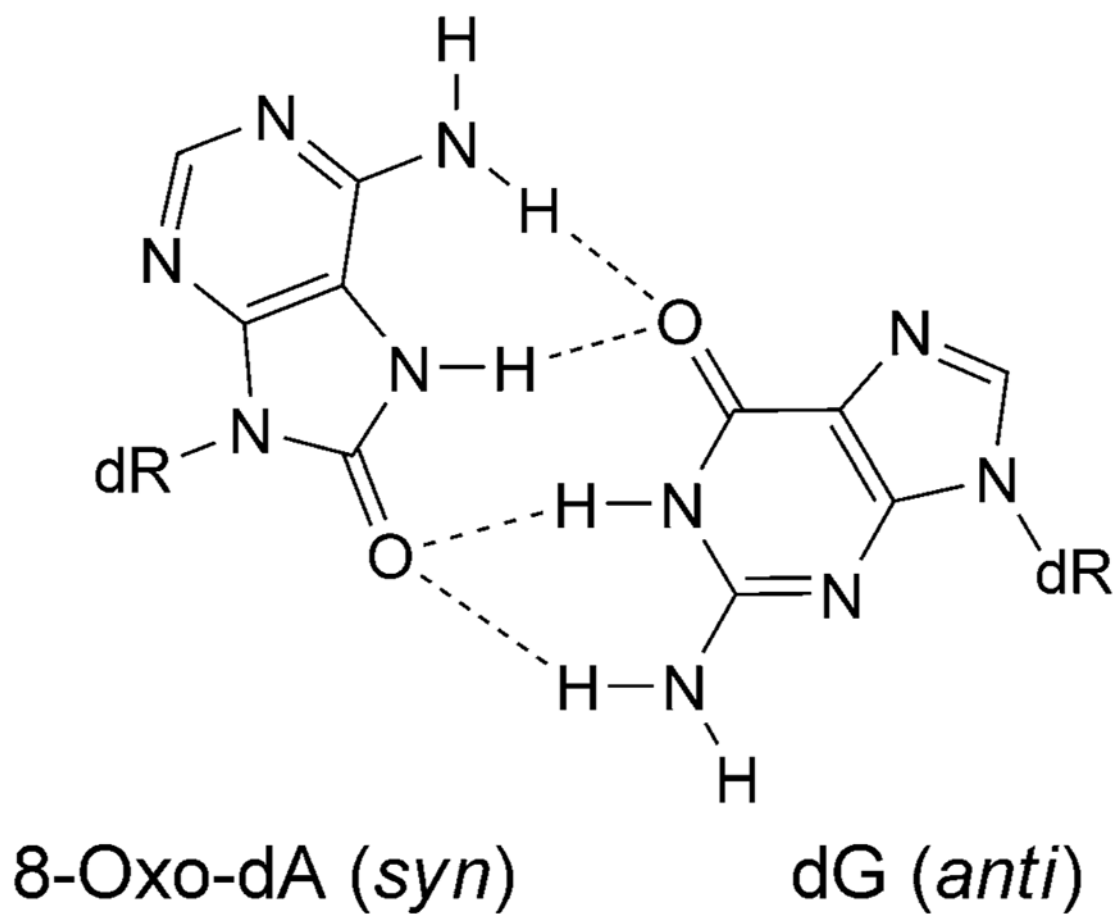


Fig. 8. Base pair showing the proposed reverse three-center H-bonding for the 8-oxo-dA (*syn*)-G (*anti*) base pair

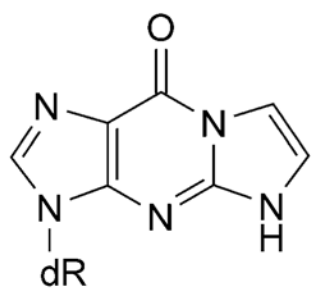
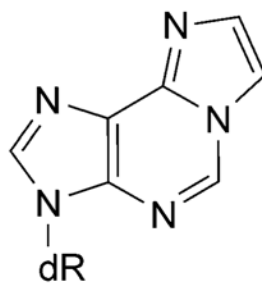
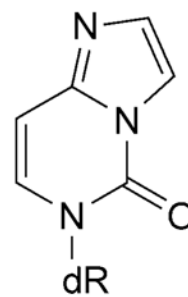
 $1,N^2\text{-}\epsilon\text{dG}$  $1,N^6\text{-}\epsilon\text{dA}$  $3,N^4\text{-}\epsilon\text{dC}$

Fig. 9.
Structures of etheno adducts

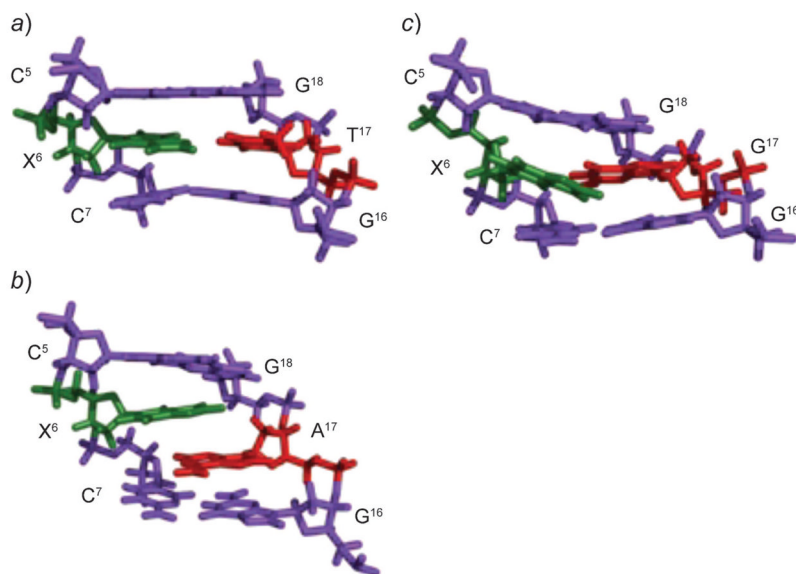


Fig. 10. Structures of the 3,*N*⁴-edC adduct (*X*⁶) opposite dT, dA, and dG in the 5′-C⁵X⁶C⁷-3′ sequence

a) The 3,*N*⁴-edC (*syn*)·T (*anti*) base pair. The etheno moiety is in the major groove. *b*) The 3,*N*⁴-edC (*anti*)·A (*anti*) base pair, showing partial intercalation within the 3,*N*⁴-edC (*anti*)·A (*anti*) alignment. *c*) The 3,*N*⁴-edC (*anti*)·G (*anti*) base pair. The 3,*N*⁴-edC and complementary base are shown in green and red, respectively. These illustrations were prepared from PDB entries 1B5K and 1B6Y using PyMol [39] software.

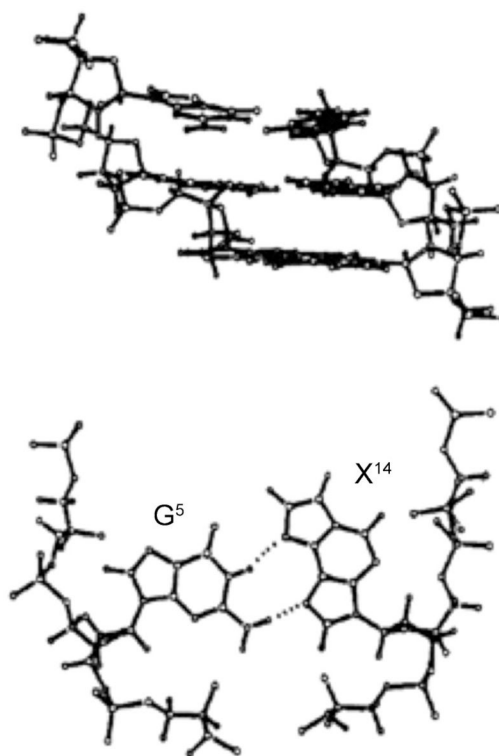


Fig. 11. Structure of the 1, N^6 -edA adduct (X^{14}) opposite dG, in the 5'-C¹³ X^{14} C¹⁵-3' sequence The top panel shows the three base pairs with the 1, N^6 -edA adduct (*syn* conformation) located in the major groove. The bottom panel shows the 1, N^6 -edA (*syn*)-G (*anti*) base pair alignment viewed down the axis and the two H-bonds that stabilize this base pair. Reproduced with permission from [92] (© 2002 *American Chemical Society*).

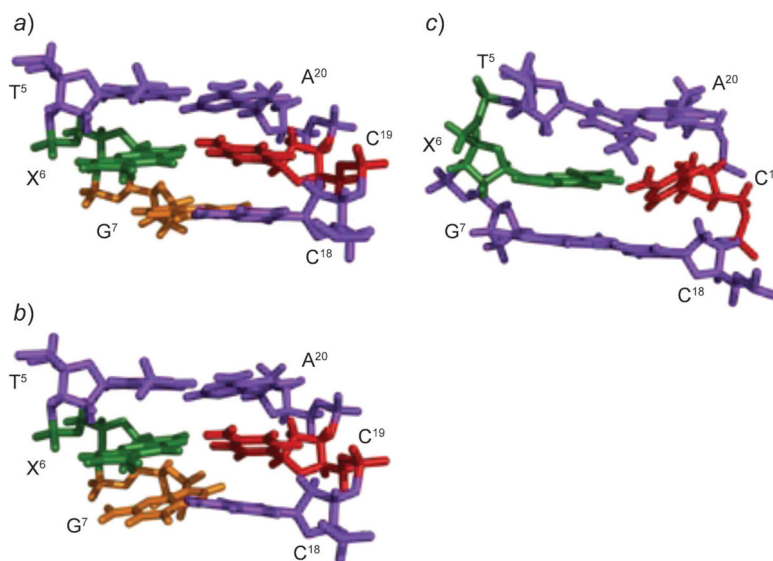


Fig. 12. Structures of the 5'-T⁵X⁶G⁷-3'-5'-C¹⁸C¹⁹A²⁰-3' duplex containing the 1,N²-edG adduct (X⁶), opposite dC, as a function of pH
a) At pH 5.2, the major conformation features the 1,N²-edG (*syn*)-C (*anti*) pair in the *Hoogsteen* conformation. *b)* At pH 5.2, a second conformation exists in which both the 1,N²-edG (*syn*)-C (*anti*) base pair and its 3'-neighbor dG (*syn*)-C (*anti*) base pair are in *Hoogsteen* conformation. *c)* At pH 8.6, the 1,N²-edG lesion (green) adopts the *anti*-conformation. The X⁶, G⁷, and C¹⁹ nucleotides are in green, orange, and red, respectively. These illustrations were prepared from PDB files used in [95][96], using PyMol [39] software.

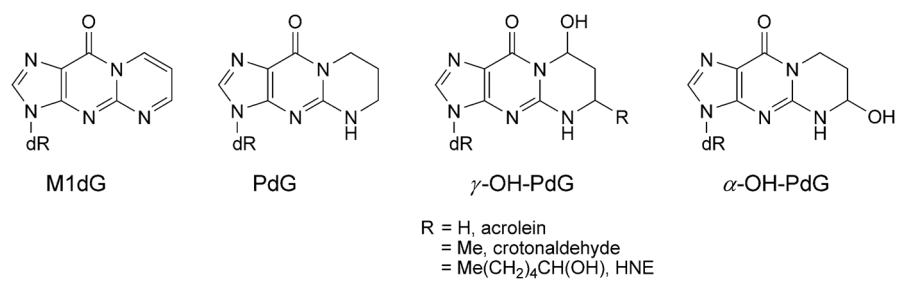


Fig. 13.
Structures of M₁dG, PdG, γ -OH-PdG, and α -OH-PdG

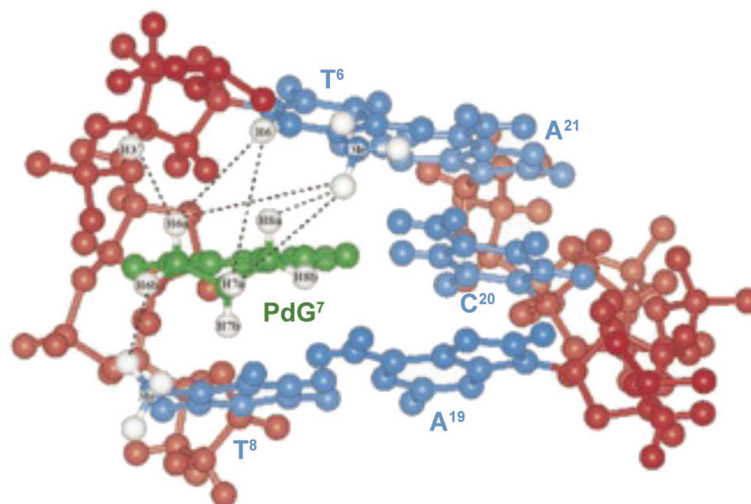


Fig. 14. Structure of the PdG adduct (green) in the 5'-T⁵X⁶T⁷-3' sequence
The PdG adduct is in the *syn*-conformation, and the propano moiety faces into the major groove. The dotted lines represent the NOEs observed between PdG and flanking bases T⁵ and T⁷. Reproduced with permission from [102] (© 2002 *American Chemical Society*).

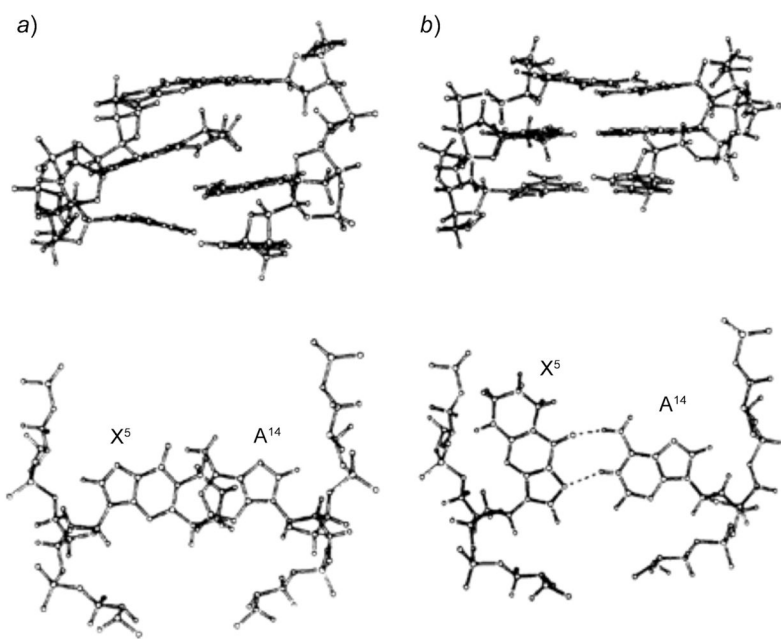


Fig. 15. Structures of the PdG adduct (X^5) opposite dA, in the 5'-G⁴X⁵G⁶-3' sequence
a) At basic pH, the PdG (*anti*)-A (*anti*) base pair alignment as viewed from major groove (*top*) and down the axis (*bottom*). *b*) At acidic pH, the PdG (*syn*)-A (*anti*) base pair alignment as viewed from major groove (*top*) and down the axis (*bottom*), showing the two H-bonds that stabilize this base pair. Reproduced with permission from [105] (© 2002 American Chemical Society).

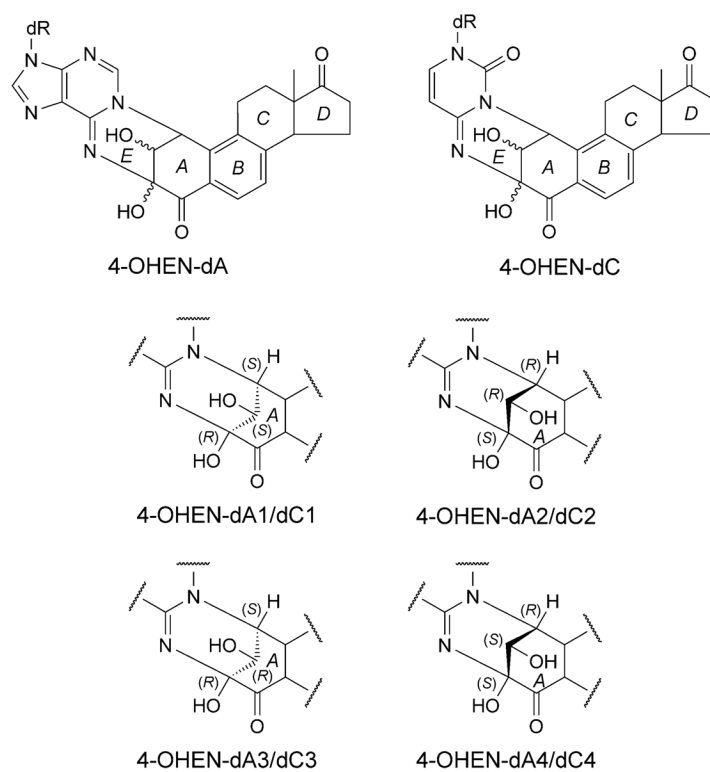


Fig. 16. Chemical structures and configurational characteristics of the 4-OHEN-dA and dC adducts

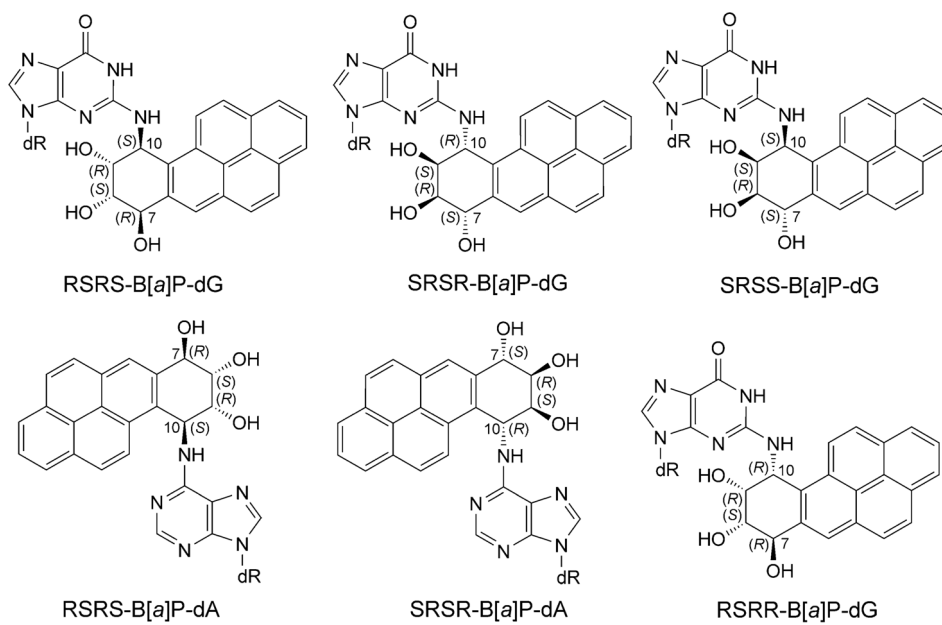


Fig. 17.
Structures of dG and dA adducts derived from B[a]P

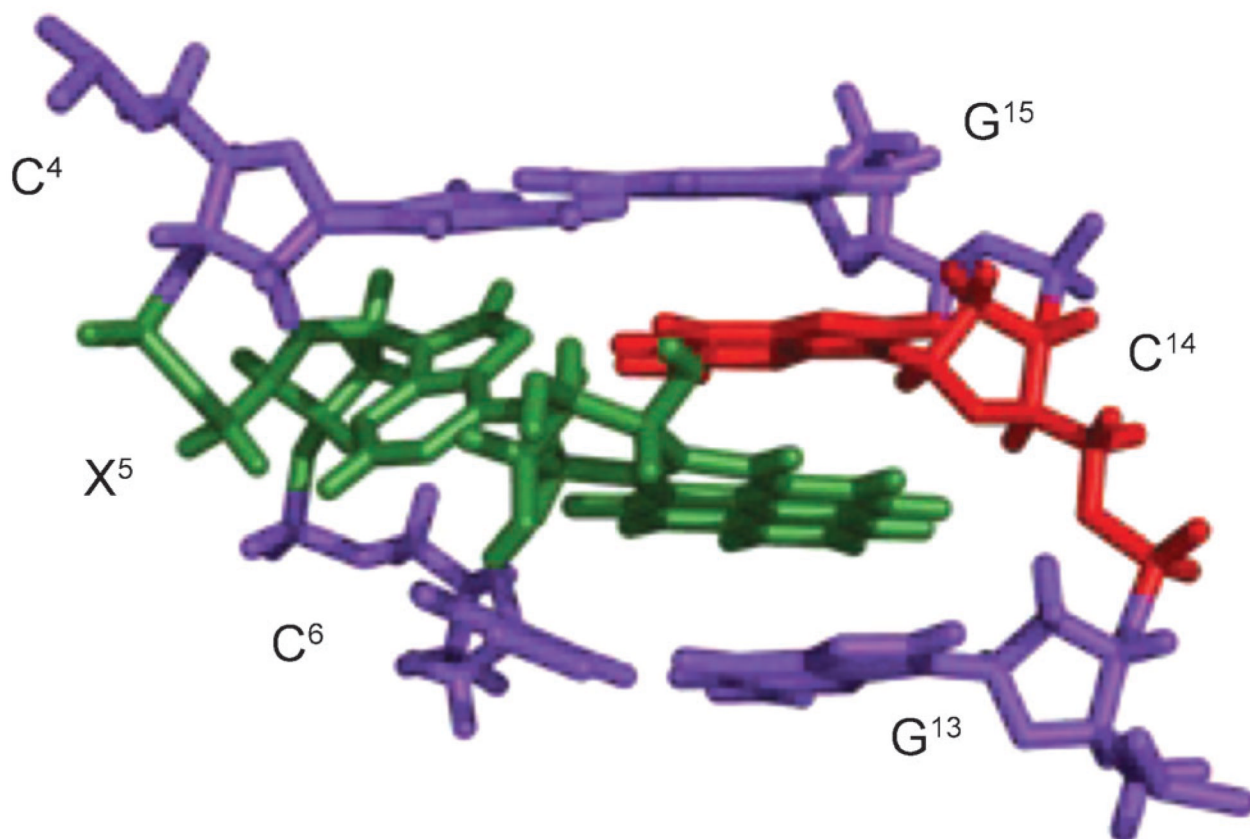


Fig. 18. Structure of the N^6 -dA (*RSRS*)-B[a]P adduct (*green*) opposite dG (*red*) in a three-base-pair segment of duplex DNA. This illustration was prepared from PDB entry 1DXA using PyMol [39] software.

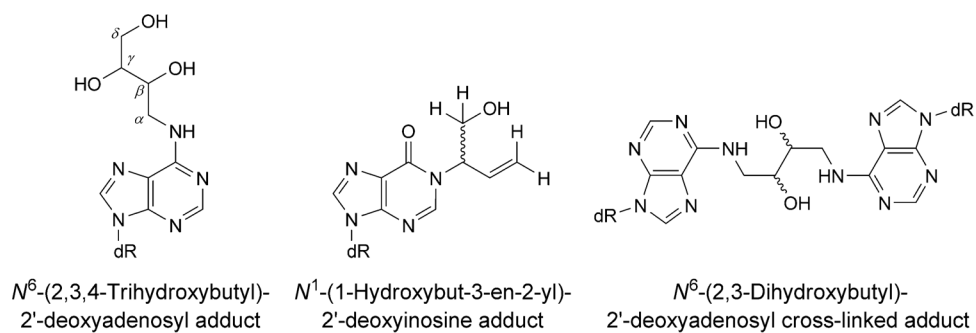


Fig. 19.
Chemical structures of BD-derived adenine adducts

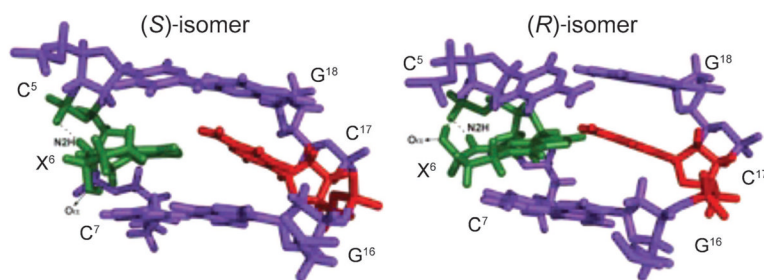


Fig. 20. Structures of diastereoisomeric α -OH-PdG adducts (X^6 ; green) in the 5'- $C^5X^6C^7$ -3' sequence

The α -OH-PdG adducts are in the *syn* conformation with the propano ring facing the major groove. The dotted lines represent H-bonds that are proposed to stabilize the *syn* conformations of the (*R*)- and (*S*)-diastereoisomers of the α -OH-PdG adduct. These illustrations were prepared from PDB entries 2KD9 and 2KDA using PyMol [39] software.

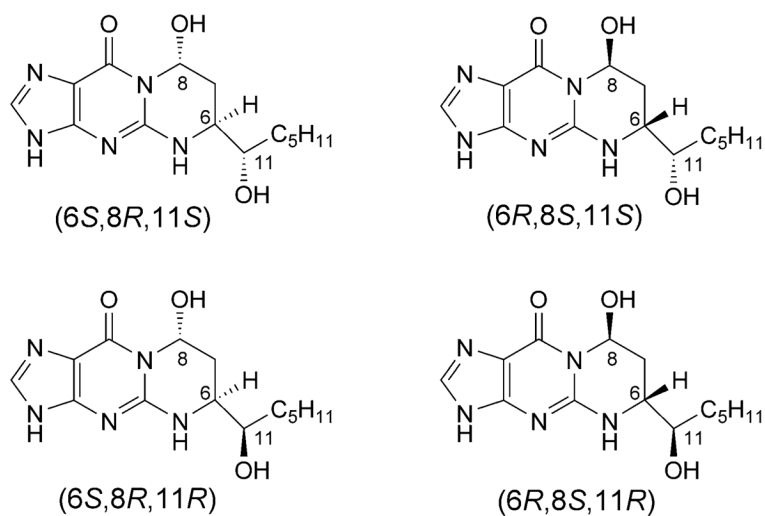


Fig. 21.
Four stereoisomers of HNE-derived exocyclic 1,N²-dG adducts

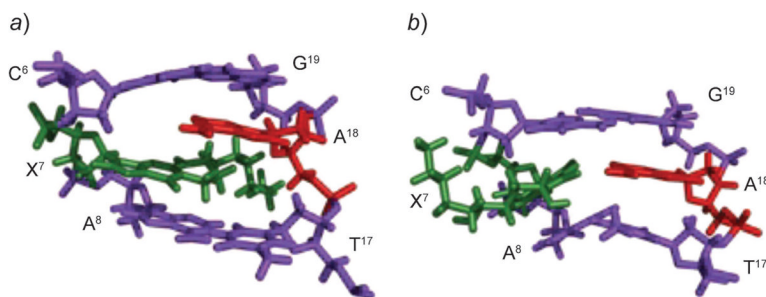


Fig. 22. Structures of the 1,*N*²-dG (6*S*,8*R*,11*S*)-HNE-adduct (*X*⁷; green) opposite dA (red), in the 5'-C⁶X⁷A⁸-3' sequence context

a) At basic pH, *X*⁷ adopts the *anti*-conformation and intercalates. The complementary dA is displaced in the 5'-direction, and the HNE moiety is oriented toward the minor groove. *b*) At acidic pH, *X*⁷ adopts the *syn*-conformation allowing formation of H-bonds with protonated adenine, and the HNE moiety is placed into the major groove. These illustrations were prepared from PDB entries 2KAS and 2KAR using PyMol [39] software.

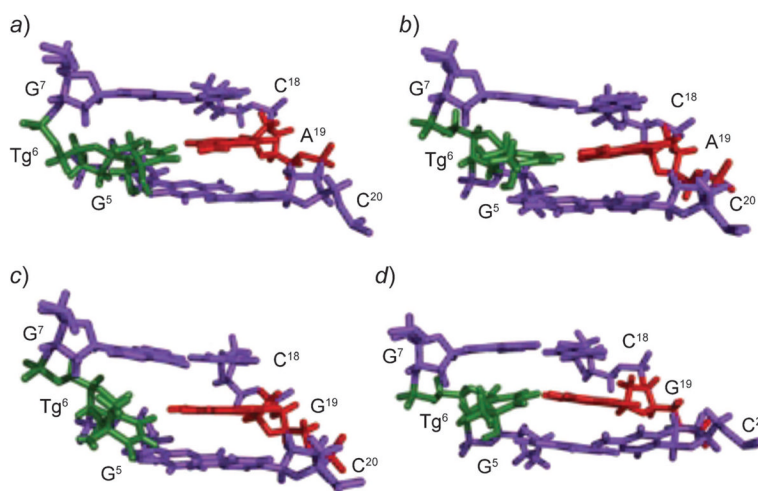


Fig. 23. Structures of Tg (green)-containing duplexes

a) The axial conformation of the Tg moiety when placed opposite dA. *b)* The equatorial conformation of the Tg moiety when placed opposite dA. *c)* The axial conformation of the Tg moiety when placed opposite dG. *d)* The equatorial conformation of the Tg moiety when placed opposite dG. These illustrations were prepared from PDB entries 2KH5, 2KH6, 2KH7, and 2KH8 using PyMol [39] software.

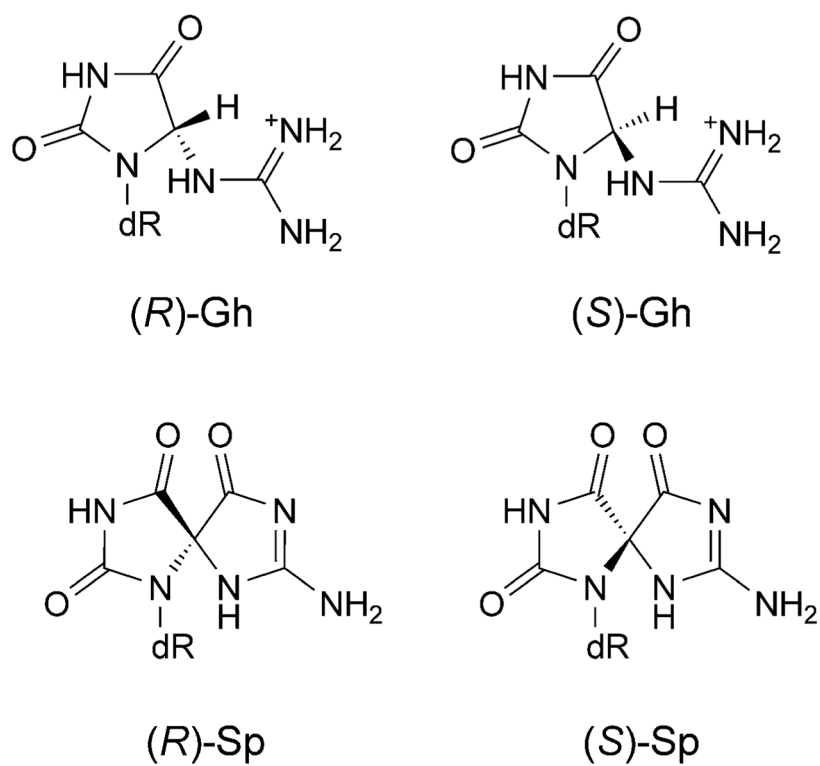


Fig. 24.
Chemical structures of DNA adducts derived from oxidation of 8-oxo-dG

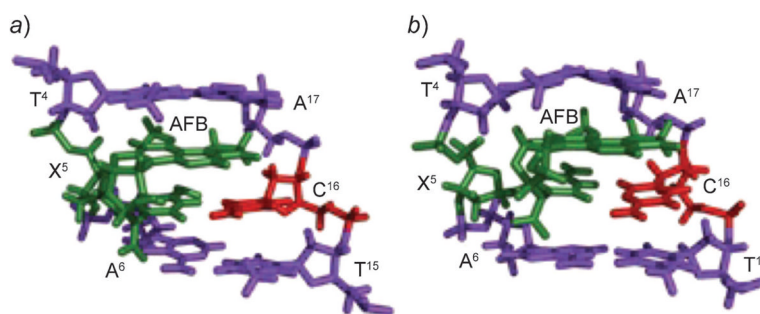


Fig. 25.
a) Structure of the AFB₁- α -FAPY adduct (*green*) in duplex DNA. *b)* Structure of the AFB- β -FAPY adduct (*green*) in duplex DNA. These illustrations were prepared from PDB entries 2KH3 and 1 HM1 using PyMol [39] software.

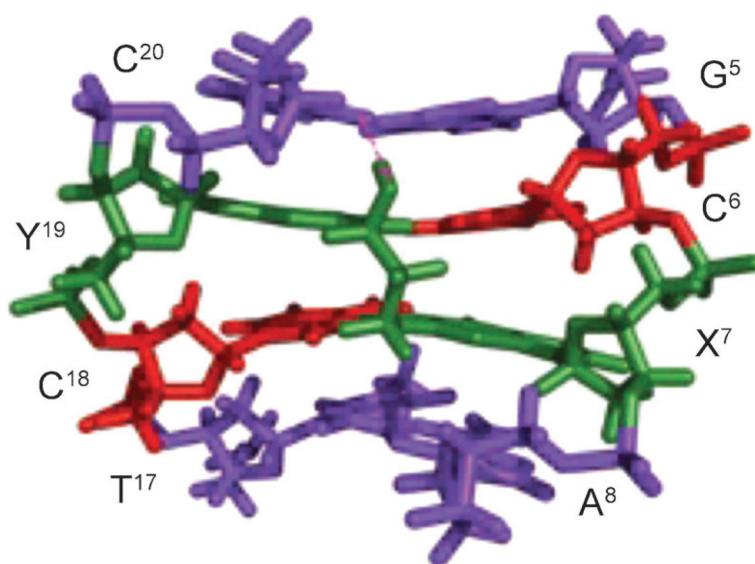


Fig. 26. Structure of the (*R*)- γ -hydroxytrimethylene-*N*²-dG:*N*²-dG interstrand cross-link (green) in a three-base-pair duplex suggests the presence of a H-bond between the OH group and 5'-neighbor C²⁰, which may account for the stability of the interstrand cross-link
This illustration was prepared from the PDB file used in the article [370] using PyMol software [39].

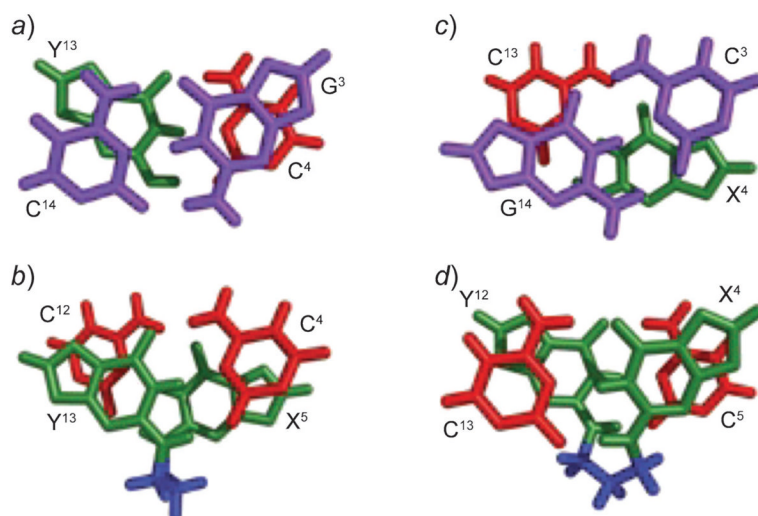


Fig. 27. Differential base stacking at the cross-linking region explains the difference in stabilities of the trimethylene- N^2 -dG: N^2 -dG interstrand cross-links in the 5'-CpG-3' vs. the 5'-GpC-3' sequences, and, in turn, accounts for the same sequence selectivity of interstrand cross-link formation induced by the enal-derived 1, N^2 -dG adducts
a) and b) show base stacking in the 5'-CpG-3' sequence; c) and d) show base stacking in the 5'-GpC-3' sequence. This illustration was prepared from PDB entries 2KNK and 2KNL using PyMol software [39] (© 2009 American Chemical Society).

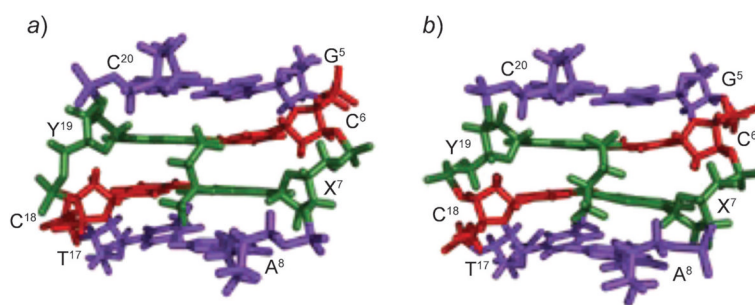


Fig. 28. Structures of the (*R*)- and (*S*)- γ -CH₃-trimethylene-*N*²-dG:*N*²-dG interstrand cross-links (*green*) viewed from the minor groove showing different orientations of the CH₃ group. *a*) (*R*)-Configuration. *b*) (*S*)-Configuration. These illustrations were prepared from PDB entries 2 HMD and 2 HMR using PyMol [39] software.

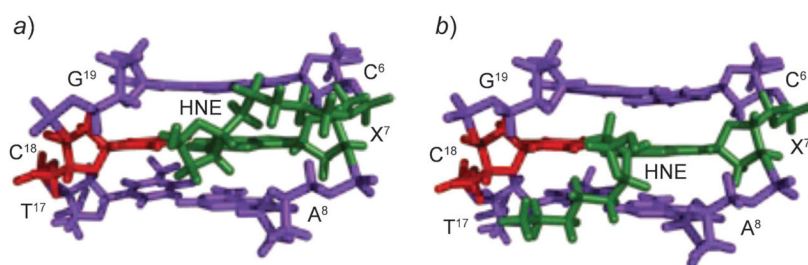
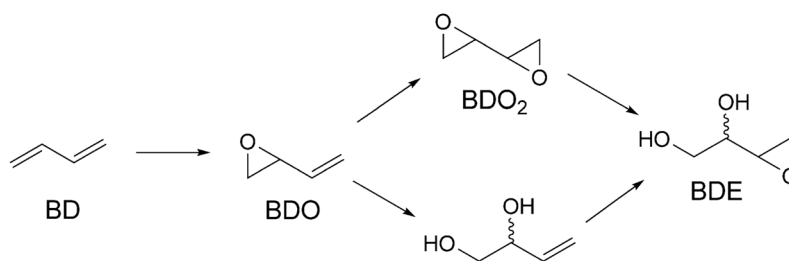
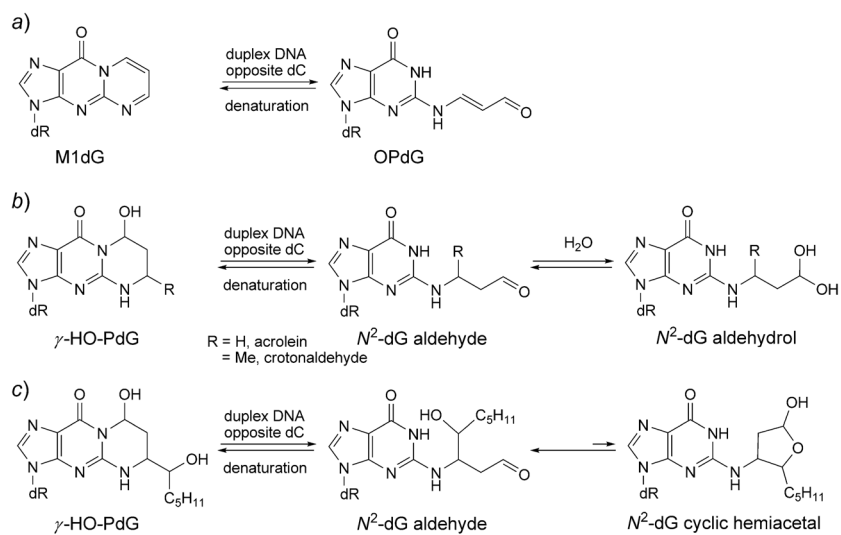


Fig. 29. Structures of the ring-opened 1, N^2 -dG (6*R*,8*S*,11*R*)- and (6*S*,8*R*,11*S*)-HNE adducts in a three-base-pair duplex

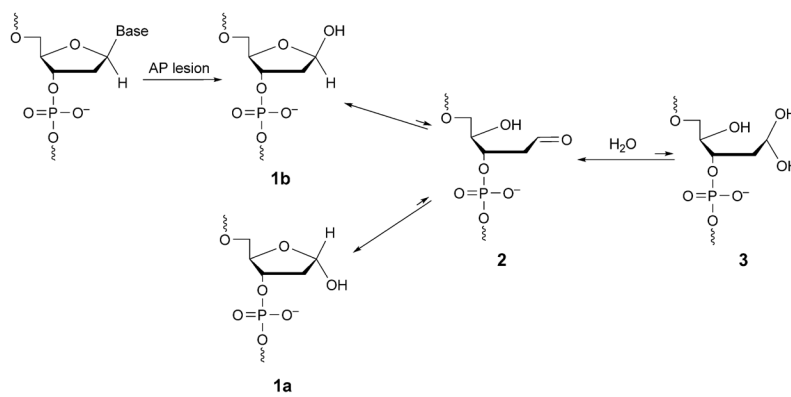
Differential orientations of the HNE moiety in the ring-opened species determine the capabilities to induce N^2 -dG : N^2 -dG interstrand cross-links (green) by diastereoisomeric 1, N^2 -dG HNE adducts. *a*) (6*R*,8*S*,11*R*)-Configuration. *b*) (6*S*,8*R*,11*S*)-Configuration. These illustrations were prepared from PDB entries 2K8T and 2K8U using PyMol [39] software.



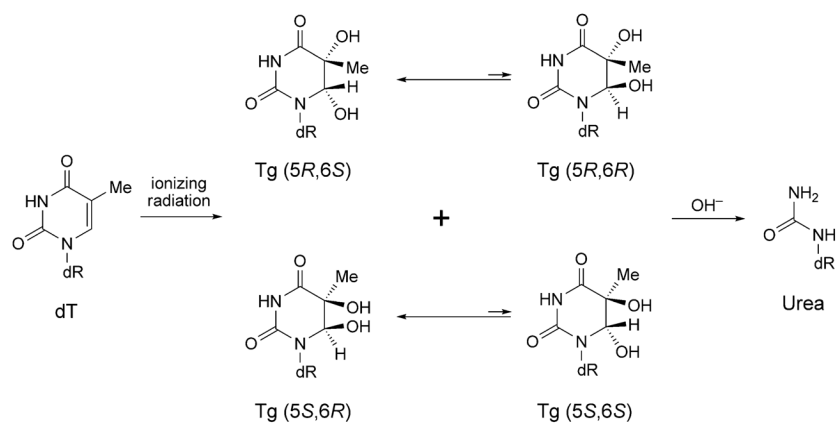
Scheme 1.
Reactive Metabolites of BD



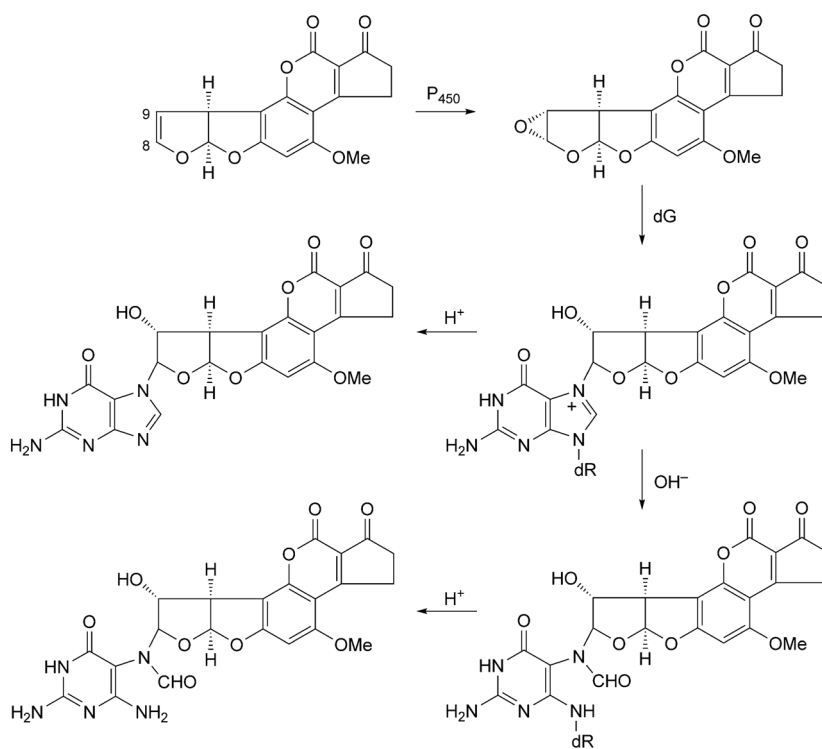
Scheme 2.
Reorganization of M₁dG and γ -HO-PdG to the Ring-Opened Forms in DNA



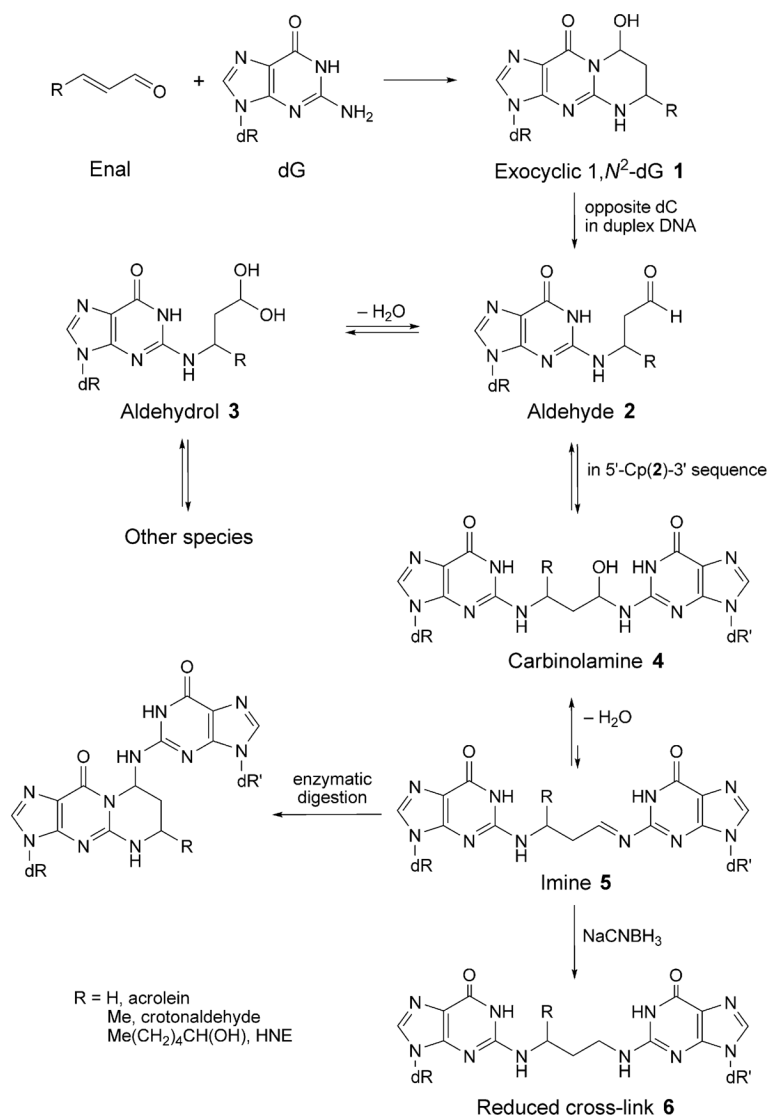
Scheme 3.
Epimerization of Abasic Sites



Scheme 4.
Production of Thymine Glycol (*Tg*) and Urea Adducts by Exposure of Thymine to Ionizing Radiation



Scheme 5.
Formation of Aflatoxin B₁ DNA Adducts



Scheme 6.
Formation of the N^2 -dG: N^2 -dG Interstrand Cross-Link When Enal-Derived γ -HO-PdG Adduct Is Placed Opposite dC in DNA