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Review Article

Formation of ring-opened and rearranged products of guanine: Mechanisms and biological significance

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ABSTRACT

DNA damage by endogenous and exogenous agents is a serious concern, as the damaged products can affect genome integrity severely. Damage to DNA may arise from various factors such as DNA base modifications, strand break, inter- and intrastrand crosslinks, and DNA–protein crosslinks. Among these factors, DNA base modification is a common and important form of DNA damage that has been implicated in mutagenesis, carcinogenesis, and many other pathological conditions. Among the four DNA bases, guanine (G) has the smallest oxidation potential, because of which it is frequently modified by reactive species, giving rise to a plethora of lethal lesions. Similarly, 8-oxo-7,8-dihydroguanine (8-oxoG), an oxidatively damaged guanine lesion, also undergoes various degradation reactions giving rise to several mutagenic species. The various products formed from reactions of G or 8-oxoG with different reactive species are mainly 2,6-diamino-4-oxo-5-formamidopyrimidine, 2,5-diamino-4*H*-imidazolone, 2,2,4-triamino-5-(2*H*)-oxazolone, 5-guanidino-4-nitroimidazole, guanidinohydantoin, spiroiminodihydantoin, cyanuric acid, parabanic acid, oxaluric acid, and urea, among others. These products are formed from either ring opening or ring opening and subsequent rearrangement. The main aim of this review is to provide a comprehensive overview of various possible reactions and the mechanisms involved, after which these ring-opened and rearranged products of guanine would be formed in DNA. The biological significance of oxidatively damaged products of G is also discussed.

Contents

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Introduction

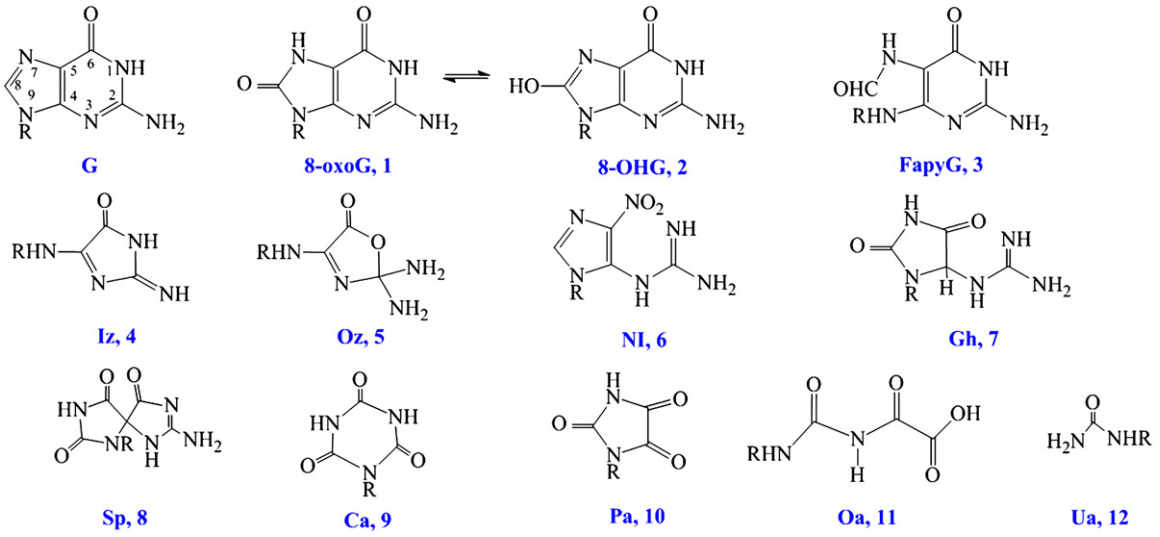
DNA damage by endogenous and exogenous agents is a matter of serious concern, as the damaged products can affect genome integrity severely [1–4]. Among the various endogenous factors, reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$), superoxide radical anion ($O_2^{\bullet -}$), hydroxyl radical ($^\bullet OH$), and peroxynitrite ($ONOO^-$) [3,4] are common and affect structures and functions of DNA severely. Ionizing radiation, chemicals, pollutants, and alkylating agents are the major exogenous factors [5–8] that damage DNA strongly. Generally, ROS are produced inside living cells during normal cellular metabolic activities. For example, one-electron reduction of the oxygen molecule (O_2) formed during normal metabolic activities can generate $O_2^{\bullet -}$, which in turn can produce hydrogen peroxide (H_2O_2) through both enzymatic [9] and nonenzymatic reactions [10,11]. Although $O_2^{\bullet -}$ is not able to damage DNA directly, it can react with the deprotonated form of the guanine radical cation through addition and reduction reactions. Similarly, H_2O_2 is not very reactive; however, $^\bullet OH$ formed from its dissociation [12–14] can modify severely structures and functions of various biomolecules present in the cell [8]. Further, generation of $ONOO^-$ and hypochlorous acid (HOCl) from reactions of nitric oxide ($NO^\bullet$) and $O_2^{\bullet -}$ [15,16] and of H_2O_2 and chloride anion [17,18], respectively, is also deleterious for biological systems [19]. Owing to a large diffusion constant and high permeativity [20], $ONOO^-$ can react with almost all biomolecules [19]. Peroxyl radicals ($^\bullet OOR$) formed during lipid peroxidation are also considered to be potent ROS [21,22] that can alter DNA structure significantly. Apart from production during normal metabolic activities, various ROS can also be generated inside living cells by various exogenous factors such as radiation [23,24].

DNA damage by ROS can arise in various ways such as base modifications [25–28], normal and oxidized abasic sites [29], strand breaks [30–32], DNA interstrand and intrastrand crosslinks [33,34], DNA–protein crosslinks [35,36], etc. Any of these processes can lead to serious consequences and have been implicated in various pathological conditions such as cancer, aging, neurodegenerative diseases, rheumatoid arthritis, and AIDS [27,37–41]. Hence, understanding the mechanisms of DNA damage and the biological significance of the damaged products is of paramount importance in chemistry, biology, toxicology, and medicine.

It has been demonstrated that among the various DNA damage pathways, base modification is most common. DNA base modification generally refers to changes in the structures and chemical properties of the bases, because of which their functionality is lost. Because it has the smallest oxidation potential among all the DNA bases (guanine (1.29 V) < adenine (1.42 V) < cytosine (1.6 V) < thymine (1.7 V)), guanine (G) is frequently modified by one-electron oxidants [32,42,43]. Its reactivity is enhanced when it is present in GG and GGG sequences [44–46]. It has been found that reactions of G with various reactive species can produce different mutagenic products such as 8-oxo-7,8-dihydroguanine (8-oxoG; **1**) [47–61], 8-hydroxyguanine (8-OHG; **2**) [47], 2,6-diamino-4-oxo-5-formamidopyrimidine (FapyG; **3**), [47,50,62–66], 2,5-diamino-4*H*-imidazolone (imidazolone, Iz; **4**) [67–71], 2,2,4-triamino-5-(2*H*)-oxazolone (oxazolone, Oz; **5**) [67–71], and 5-guanidino-4-nitroimidazole (NI; **6**) [72–74] (Scheme 1).

It is interesting to note that although prolonged presence of 8-oxoG (**1**) in cells is lethal, it is very reactive and hence readily degrades to various other stable products. This is because the oxidation potential of **1** (0.58 to 0.75 V) is even lower than that of G (1.29 V) [75–79]. Despite the high reactivity of **1**, its degradation to several other lesions has not been accurately detected in cellular DNA. However, formation of Iz (**4**), Oz (**5**), guanidinohydantoin (Gh; **7**), spiroiminodihydantoin (Sp; **8**), cyanuric acid (Ca; **9**), parabanic acid (Pa; **10**), oxaluric acid (Oa; **11**), urea (Ua; **12**), etc. (Scheme 1) from **1** because of its reaction with various ROS such as $^1O_2$ [80–83], $ONOO^-$ [84–87], and other oxidants [88–92] has been observed in several model studies by considering base, nucleoside, nucleotide, and isolated DNA as probes. All these products are formed from either ring opening (**3, 6, 7**) or both ring-opening and subsequent rearrangement (**4**, **5**, **8–12**).

It is noteworthy that the above-mentioned ring-opened and rearranged products of guanine can be formed in DNA in various possible ways involving reduction, oxidation, alkylation, etc., and some of them are even more mutagenic than **1.** Unlike **1,** these products of G are quite stable under physiological conditions and do not degrade further. Moreover, depending on the reaction conditions, yields of the above products may be even more than that of **1** [18,63,73]. Despite this, the mechanisms of formation of these products are less studied than that of **1.** The main aim of this review is to provide a comprehensive overview of various possible reactions and the mechanisms involved after which these ring-opened and rearranged products of guanine would be formed in DNA. We also discuss the biological significance of oxidatively damaged products of guanine in detail, emphasizing why they pose serious threats to genome integrity.



Scheme 1. Structures of guanine (G) and its various ring-opened and rearranged (**3–12**) derivatives. The adopted atomic numbering scheme for G is also shown. R stands for the sugar moiety.