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STRUCTURE, ACID/BASE PROPERTIES AND TRANSFORMATION REACTIONS OF PURINE RADICALS

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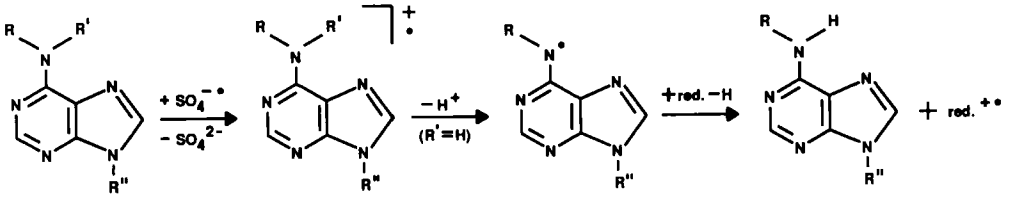
The reactions of the oxidizing radical $SO_4^{\bullet-}$ with the adenines A lead to one-electron transfer to yield the radical cations $A^{+\bullet}$. In the cases R,R' or R''=H, the one-electron oxidation is accompanied or followed by rapid deprotonation from N^6 or N^9 yielding neutral radicals[1,2] which carry sufficient unpaired electron density at the nitrogens to act as oxidants vis-a-vis reductants such as TMPD,[1-3] ascorbate,[4] or thiols (see scheme 1).[4] In the case of 2'-deoxyadenosine, the radical cation is strongly acidic, $pK_a < 1$.[5]

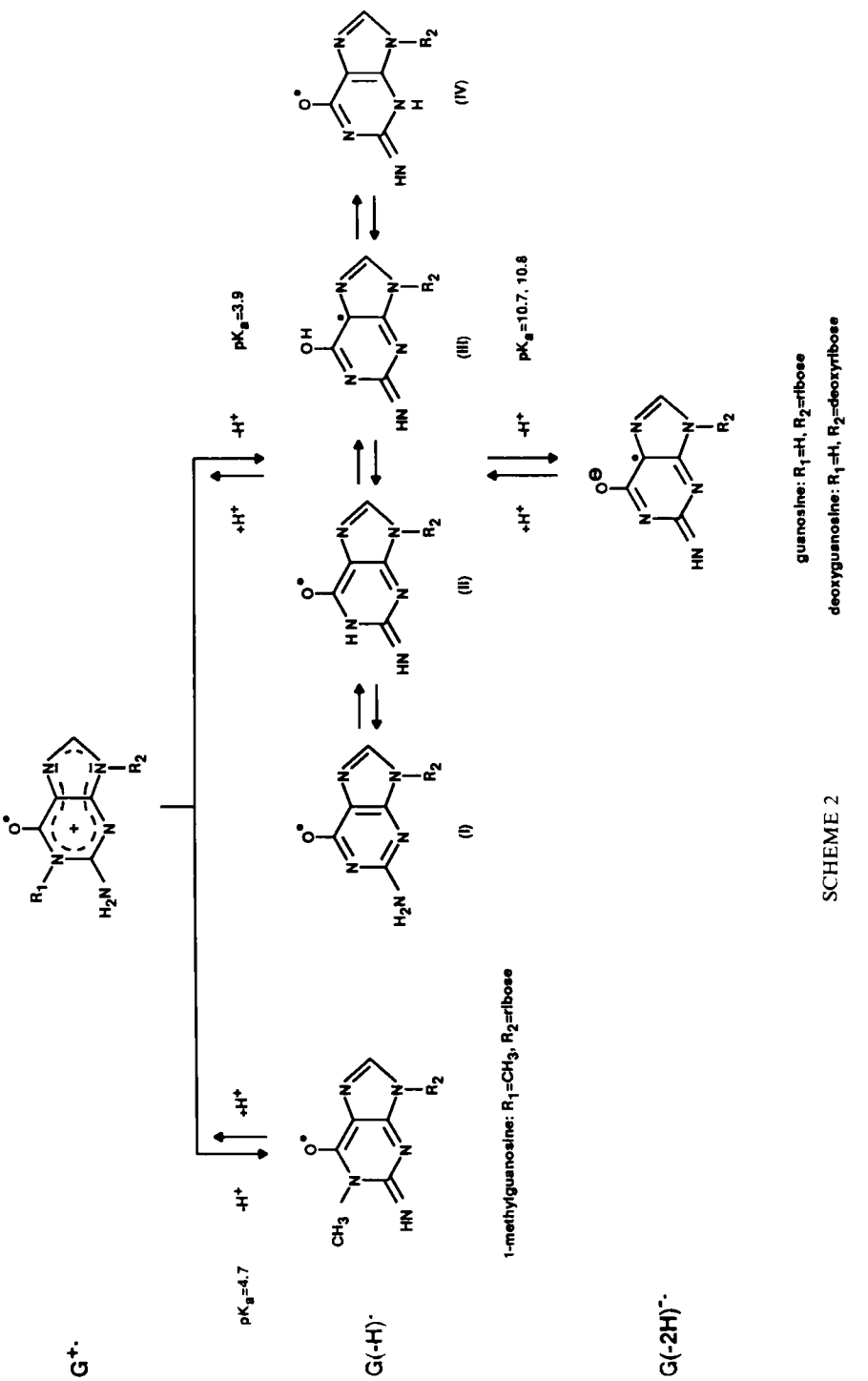


A : R , R' , R'' = H , alkyl

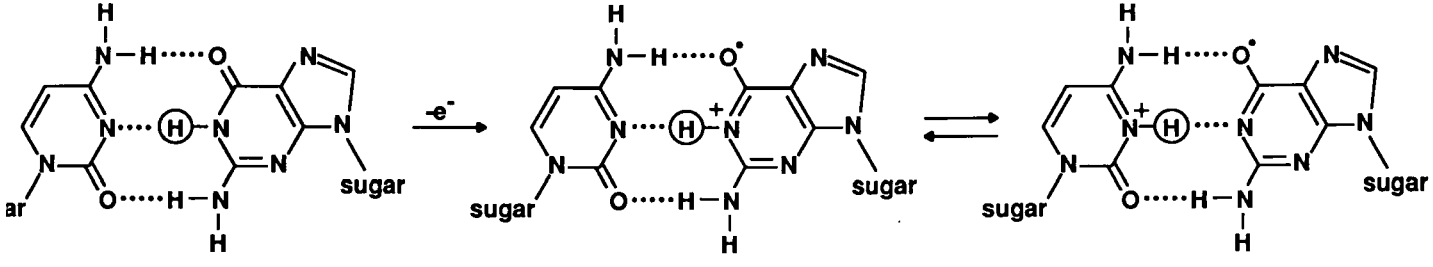
SCHEME 1

The electrophilic OH reacts with the purines by addition ($k = 1.3 \times 10^8$ to $8.4 \times 10^9\ M^{-1}s^{-1}$) via a polar transition state ($\varrho^+ = -0.9$) to give isomeric radicals by attachment to C-4 and C-8 and, possibly, to other positions. The adduct to C-4 (A-4-OH) undergoes a unimolecular dehydration reaction to give a radical with oxidizing properties. Substituents at C-6 exert a strong influence on the rate of this dehydration ($\varrho^+ = -3$). The adduct to C-8 (A-8-OH) also undergoes a unimolecular transformation reaction which is assigned to opening of the imidazole ring. Substituents at C-6 have only a small influence on the rate of the ring-opening reaction ($\varrho^+ = -0.3$). A ribose substituent at N(9) decreases the rates of both dehydration and ring opening. The transformation reactions of A-4-OH and A-8-OH can be distinguished not only by their different response to substituents at C-6 but also by their activation parameters: E_A and $\Delta S^{\neq}$ values for dehydration of A-4-OH are typically ~ 9 kcal mol^{-1} and -6 eu, respectively, whereas they are ~ 6 kcal mol^{-1} and -19 eu for ring opening of A-8-OH.[1]

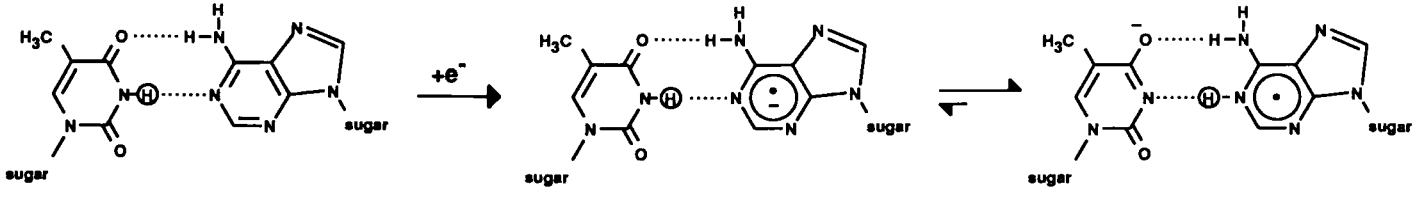
Deoxyguanosine, guanosine and 1-methylguanosine react in aqueous solution by electron transfer with $SO_4^{\bullet-}$ with nearly diffusion-controlled rates, and with $Br_2^{\bullet-}$ with rate constants close to $\sim 5 \times 10^7\ M^{-1}s^{-1}$. The resulting radical cations have pK_a values of 3.9 and 4.7 for the non-methylated and methylated systems, respectively, so that at pH 7 the products of one-electron oxidation are neutral radicals, formed by deprotonation from N(1) in the case of guanosine and deoxyguanosine and from the exocyclic N^2 in the case of 1-methylguanosine.[6] The radicals of deoxyguanosine and



SCHEME 2



SCHEME 3



SCHEME 4

guanosine further deprotonate to give radical anions with pK_a values of 10.8 and 10.7, respectively, but not that from 1-methylguanosine (see scheme 2).[6]

An implication of these results to the radiation chemistry of DNA is that the radical cation formed upon ionization of a guanine moiety shifts a proton (and thereby a positive charge) to its complementary base cytosine, i.e. that separation of charge from spin occurs by proton transfer: Deoxyguanosine is a weak acid with a pK_a of 9.6. The radical cation, however, is a much stronger acid (pK_a = 3.9, see above). The equilibrium positions of one or all of the three protons involved in the hydrogen bonds with the cytosine moiety will therefore be shifted towards the cytosine which results in an overall transfer of positive charge to that base. Since the pK value for protonation of cytidine (4.2) is similar to that for *de*protonation of the (deoxy)guanosine radical cation, the proton will not be transferred fully to the cytidine (see scheme 3). Analogous proton transfer processes are likely to occur on ionization of the other bases.[5]

If the opposite to ionization takes place, i.e. electron *addition* rather than removal, the Brönsted basicities of the bases are drastically *in*creased. This leads to proton transfer towards the base radical anion, the complementary base now serving as a proton *donor* (see scheme 4 for an example), rather than as an acceptor as in the case of one-electron *removal* from the complementary base.[5]

Proton transfer leads to separation of charge and spin and it thus converts radicals cations (positive holes) or radical anions (localized but mobile electrons) into neutral radicals. This means that proton transfer inhibits or at least slows down the mobility of the charge and spin carriers, which are thereby "frozen" or trapped. Proton-transfer-modulation of electron transfer is likely to influence the migration distance of charge carriers in DNA. Proton transfer from a hetero atom to another hetero atom is usually reversible, whereas proton transfer from a hetero atom to a carbon is usually *ir*reversible and it leads to a change in the redox properties of the radical.[7,8]

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