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HETEROCYCLIC RESONANT RADICALS

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Polyunsaturated and heterocyclic radicals due to delocalization of the unpaired electron (resonance) may exhibit unusual reactivities with oxygen and H-atom donors.

Bisallyl, a simple resonant polyunsaturated radical, does not react with oxygen. The two mesomeric conjugate forms, however, do react, as observed in linoleic acid,[1]

$$\begin{tikzcd}
 & \mathrm{RCH{=}CH\text{-}\dot{C}H\text{-}CH{=}CHR'} \arrow[dr] \arrow[dd, "O_2"] & \\
\mathrm{R\dot{C}H\text{-}CH{=}CH\text{-}CH{=}CHR'} \arrow[ur] \arrow[d, "O_2"] & & \mathrm{RCH{=}CH\text{-}CH{=}CH\dot{C}HR''} \arrow[d, "O_2"] \\
\mathrm{\cdot OORCH\text{-}CH{=}CH\text{-}CH{=}CHR'} & \text{no reaction} & \mathrm{RCH{=}CH\text{-}CH{=}CH\text{-}CHR'OO\cdot}
\end{tikzcd} \qquad (1)$$

The rate of reaction of oxygen with the above radical is lower ($k < 10^8\,M^{-1}s^{-1}$) than the expected rates for localized C-centered radicals ($k \sim 10^9\,M^{-1}s^{-1}$).[2] Distribution of the unpaired electron[3] appears to be responsible for this characteristic behavior of polyunsaturtaed fatty acids.[1]

The guanyl radical was generated on oxidation of G or any other molecule containing guanine using Tl(II),[4]

$$\mathrm{Tl(I)} + \cdot\mathrm{OH} \rightarrow \mathrm{Tl(II)} + \mathrm{OH}^- \qquad (2)$$

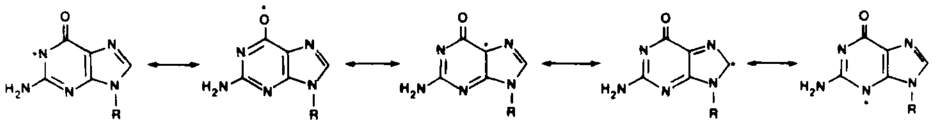
$$\mathrm{G} + \mathrm{Tl(II)} \rightarrow \cdot\mathrm{G}^+ + \mathrm{Tl(I)} \qquad (3)$$

Formation of $\cdot G^+$ on oxidation of dGMP by $\cdot Br_2^-$ in alkaline media was observed previously,[5] the charge of the guanyl radical, however, could not be determined. From the ionic strength effect on the decay of the guanyl radical at pH 6–7 and [3] it was concluded that the guanyl radical is not charged in biological media. Hence,

$$\begin{gathered} \cdot\mathrm{G}^+ \rightleftharpoons \cdot\mathrm{G}(-\mathrm{H}) + \mathrm{H}^+ \\ pK_a < 3 \end{gathered} \qquad (4)$$

The guanyl radical resulting from one electron oxidation of guanine (G) is a highly delocalized heterocyclic radical.[4]

The mesomeric forms of the neutral guanyl radical, $\cdot G(-H)$, which is the biologically relevant form, are shown below



(5)

TABLE I

Oxygen uptake, $G(-O_2)$, by free radicals generated from Tl(II) + S and •OH + S reactions for selected substrates measured by a Clark electrode at pH 7. Aqueous solutions saturated with N_2O: O_2 = 4:1 mixture, irradiated at 0.052 $Gy\,s^{-1}$, and 20°C.

Substrate, S	$G(-O_2)$[a]	
	Tl(II) + S[b]	•OH + S[c]
Formate ion	3.0	3.0
Guanosine	0.7(0.5)	1.5

[a] Estimated to be accurate to ± 0.1 G-unit.

[b] Obtained in solutions containing 2 mM Tl_2SO_4 and 0.2 mM substrates. Values in parenthesis pertain to 1 mM Tl_2SO_4 and 0.1 mM substrates.

[c] 0.2 mM substrate.

Oxygen does not affect the lifetime of the guanyl radical under pulse radiolysis conditions from which an upper limit for the rate constant can be calculated, $k(\cdot G(-H) + O_2) < 10^5\,M^{-1}s^{-1}$. Stationary state experiments also do not indicate any reactivity with oxygen.[4] The oxygen uptake values for the $\cdot CO_2^-$, guanyl and guanine OH-adduct are shown in Table 1.

Consequently

$$\begin{gathered}\cdot G(-H) + O_2 \rightarrow \text{not observed} \\ k < 1\,M^{-1}s^{-1}\end{gathered} \tag{6}$$

In contrast to the guanyl radical, the OH-adducts to guanine react with oxygen

$$\cdot G-OH + O_2 \rightarrow \cdot OOG - OH \tag{7}$$

since $G(-O_2) = 1.5$, Table 1.

From spectral differences determined by pulse radiolysis one can conclude that about 50% of OH-adducts of guanine lose water,

$$\cdot G-OH \rightarrow \cdot G(-H) + H_2O \tag{8}$$

Since $k(\cdot G-OH + O_2) < 10^5\,M^{-1}s^{-1}$, some of the four $\cdot G-OH$ isomers undergo reaction (8) whereby oxygen uptake drops from the expected $G(-O_2) = 3$.

The guanyl radical is also unreactive towards aliphatic thiols

$$\begin{gathered}\cdot G(-H) + RSH \rightarrow G + RS\cdot \\ k < 10^5\,M^{-1}s^{-1}\end{gathered} \tag{9}$$

Similar conclusions were reached for adenine.

Electron donors, in contrast to the H-atom donors, are excellent repair agents of the guanyl and adenyl radicals. For example, 5-hydroxytryptophan, fully restitutes either guanine or adenine, e.g.,

$$\begin{gathered}\cdot G(-H) + \text{R-Ind-OH} \rightarrow G + \text{R-Ind-O}\cdot \\ k = 1.4 \times 10^9\,M^{-1}s^{-1}\end{gathered} \tag{10}$$

CONCLUSIONS

It is suggested that at low unpaired electron densities, reduced by resonance, the free radical sites become less reactive with oxygen and H-atom donors, and cease to react entirely below certain critical values, encountered in highly resonant forms. Properties of these purine radicals generated by chemiionization[4] have significant implications to the mechanisms of the direct effect of ionizing radiation on DNA, and the oxygen effect in radiation biology.

References

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