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RADIATION-INDUCED HYDROXYLATION OF THYMINE SENSITIZED BY NITRO COMPOUNDS IN N_2O-SATURATED AQUEOUS SOLUTION

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Hydroxylation of thymine (**1**) to give thymine glycol (**3**) is remarkably promoted by the addition of nitro compounds (**2**a-f) in the γ-radiolysis of the N_2O-saturated aqueous solution, although overall decomposition of **1** is depressed to some extent. The G-value of **3** increases linearly with increasing the one-electron reduction potential of **2**a-f.

Radiation-induced reactions of pyrimidine bases in aqueous solution have been extensively studied to elucidate the chemical mechanism of the DNA damage by ionizing radiation. It has been reported that pyrimidine bases undergo oxidation to give pyrimidine glycols and barbituric acid derivatives in relatively high yields on γ-ray irradiation in the presence of copper (II),[1)] ferricyanide,[2)] tetranitromethane[2)] and p-nitroacetophenone.[3)] We now report that a variety of nitro compounds ; 4-nitroimidazole (**2**a), 2-nitroimidazole (**2**b), 1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanol (misonidazole,**2**c), 1-methyl-2-nitroimidazole (**2**d), p-nitroacetophenone (**2**e) and 5-nitro-2-furoic acid (**2**f) are effective for promotion of the preferential oxidation of thymine (**1**) to give thymine glycol (**3**) in the γ-radiolysis of the N_2O-saturated aqueous solution. Particular emphasis is placed to the evidence that the efficiency of the nitro compounds increases with increasing their oxidizing abilities.

On ^{60}Co γ-ray irradiation (76 krad) of a deaerated aqueous solution (5 cm^3) of thymine (1 mmol dm^{-3}) buffered at pH 7.0±0.1 with phosphate (2 mmol dm^{-3}), **1** decomposed with the G-value[4)] for conversion, G(-**1**)=1.81. Among the major products thymine glycol (**3**),[5,6)] 5-hydroxy-5,6-dihydrothymine (**4**),[7)] 6-hydroxy-5,6-dihydrothymine (**5**),[7)] 5-hydroxymethyluracil (**6**), 5,6-dihydrothymine (**7**), 5-methylbarbituric acid (**8**)[8)] and N^1-formyl-N^2-pyruvylurea (**9**)[9)] were detected by high-speed liquid

Table G-values of products in the γ-radiolysis of thymine (1)

Product	Condition	deaerated	N_2O-saturated						
	Additive	none	none	2a	2b	2c	2d	2e	2f
	$E(A/A^{\overline{\cdot}})^a$/mV			-527	-418	-398	-390	-353	-317
3 thymine glycol (cis + trans)		0.13	0.28	0.66	0.85	1.76	1.47	2.10	1.95
4 5-hydroxy-5,6-dihydrothymine		0.07^b	0.18^b	0	0	0	0	0	0
5 6-hydroxy-5,6-dihydrothymine		0.08	0.12	0.03	0.02	0.07	0.03	0.07	0.04
6 hydroxymethyl-uracil		0.14	0.49	0.10	0.10	0.17	0.18	0.22	0.09
7 dihydrothymine		0.28	0.07	0	0	0.05	0.05	0.15	0.08
8 5-methyl-barbituric acid		0.09	0.08	0.08	0.05	0.08	0.05	0.03	0
9 formylpyruvylurea		0.11	0.08	0.05	0.02	0.16	0.13	0.06	0.09
G_{total}(3-9)		0.83	1.03	0.92	1.04	2.29	1.91	2.63	2.25
G(unidentified)		0.97	2.09	0.79	1.55	0.68	0.28	0.07	0.31
G(-1)		1.81	3.17	1.71	2.59	2.97	2.19	2.70	2.56

a: one-electron reduction potential relative to normal hydrogen electrode (NHE) evaluated by means of pulse radiolysis.13-15) b: estimated value.

phase chromatography (monitored with uv absorption at 210 nm) (Table). These products (the total G-value is 0.83) were confirmed by comparison with authentic samples either prepared according to the reported method5-9) or obtained commercially. A number of the other products (G-value=0.98) have not yet been characterized.

Identical products were obtained by the radiolysis under N_2O-saturated conditions but the yield of the respective product differed significantly from the corresponding yield in the deaerated system (Table). As can be seen from the Table, the G-values of hydroxylated thymine derivatives 3, 4, 5 and 6 increase by a factor of 2-3 whereas that of hydrogenated thymine 7 falls to 1/4 in the presence of N_2O.

It has been well established that primary intermediate species involved in the radiolysis of aqueous solution are hydroxyl radical ($^{\bullet}$OH), hydrated electron (e^-_{aq}) and hydrogen atom ($^{\bullet}$H); G($^{\bullet}$OH)=2.7, G(e^-_{aq})=2.7, G($^{\bullet}$H)=0.55 at pH 7. Since e^-_{aq} is converted efficiently into $^{\bullet}$OH via the reaction 1; $N_2O + e^-_{aq} \longrightarrow {}^{\bullet}OH + OH^- + N_2$ (reaction 1), the increases in the yields of 3, 4, 5 and 6 in the N_2O saturated aqueous solution can be correlated directly with the increase in the G($^{\bullet}$OH) from 2.7 to 5.4. It is thus suggested that under the conditions of the $^{\bullet}$OH generation 1 undergoes both addition across its C5-C6 double bond to give 5- and 6-hydroxythymyl radicals (1a,b) and hydrogen abstraction from its 5-methyl group to give the allyl radical (1c) (Scheme). As illustrated in the Scheme, 3, 4 and 5 are possibly derived from the common intermediates 1a,b (Path I and III) and 6 from 1c (Path V).10,11)

The efficient conversion of e^-_{aq} (reaction 1) to $^{\bullet}$OH also accounts for lowering the G-value of 7, because the formation of 7 via reduction of 1 by e^-_{aq}12) may become negligible. Furthermore, a small amount of **7** produced in the N_2O-saturated aqueous solution may be attributed to the addition of ·H to **1**.[10)]

It should be noted that reactions of **1** due to ·OH under N_2O-saturated conditions are remarkably affected by the addition of a small amount (0.1 mmol dm^{-3}) of **2**a-f although the G(-**1**) value decreases to some extent. Table shows a general feature for the effect of **2**a-f that the formation of glycol **3** is promoted by a factor of 2.7-7.5 along with the decreases in the yields of **4**,**5** and unidentified products.

Furthermore, the value of G(**3**) increases linearly with increasing one-electron reduction potential $E(A/A^{\cdot -})$ of **2**a-f as shown in the Figure. This linear correlation suggests that the ability of **2**a-f as an oxidizing agent determines the preferential formation of **3**. Since **1**a and **1**b are possible intermediates leading to **3**,**4** and **5**, it is most likely that **1**a and **1**b undergo preferentially one-electron oxidation by **2**a-f to give the corresponding carbonium ions **1**a′ and **1**b′, respectively (Path II). The carbonium ions thus formed may undergo solvolytic substitution to give **3**. The ready formation of **1**a′,b′ is responsible for the increase in G(**3**) value.

The decreases in the yields of **4** and **5** occurring in the presence of **2**a-f are consistent with the efficient conversion of **1**a,b to **1**a′,b′. Since the formation of unidentified products is depressed by the addition of **2**a-f, it may be possible to predict that these products are derived from radical inter-

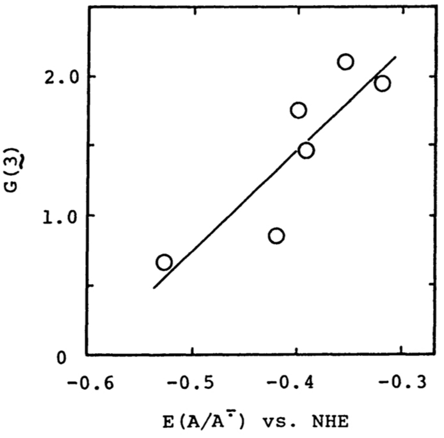
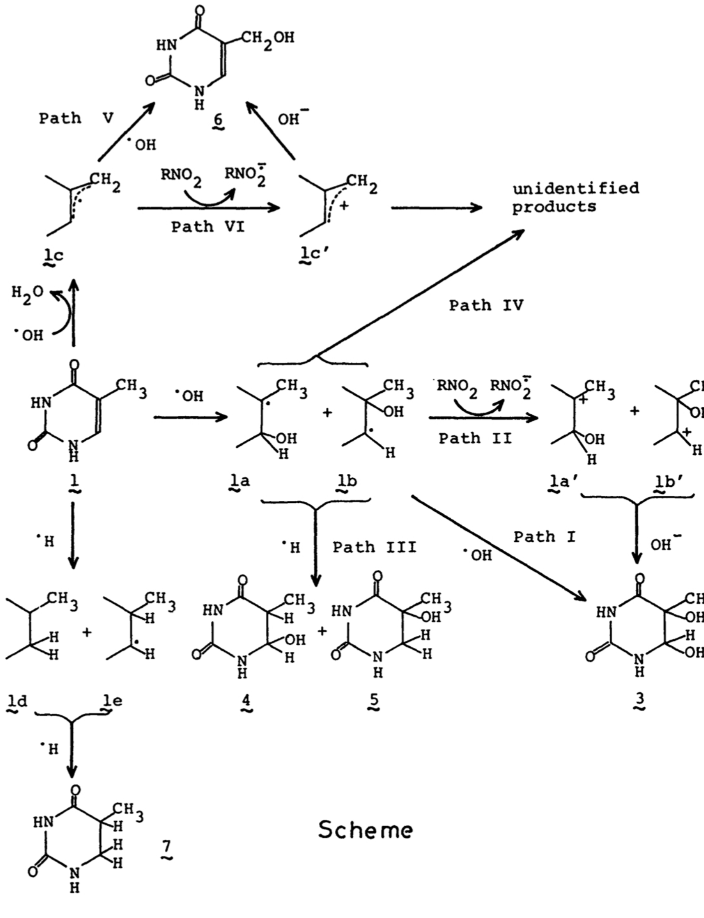


Figure Correlation between G(**3**) and $E(A/A^{\cdot -})$.



Scheme

mediates 1a and 1b (Path IV).

The formation of 6 was also depressed to less than 1/2 in the presence of 2a-f (Table). It seems likely that electron transfer from 1c to 2a-f occurs to give a carbonium ion 1c′ (Path VI) which partly decomposes in competition with its conversion to 6.

Further study on the detailed mechanism of the sensitization by nitro compounds will be reported in a subsequent paper.

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10) The disproportionations among radical intermediates 1a-e are responsible for the formation of 3-7. For example, a set of reactions $1 + {}^{\bullet}OH \longrightarrow 1a$ and $2 \cdot 1a \longrightarrow 1 + 3$ lead to 3. Since the formal chemical change can be represented by $1 + 2{}^{\bullet}OH \longrightarrow 3$, the above processes involving disproportionation are illustrated as $1 \xrightarrow{{}^{\bullet}OH} 1a \xrightarrow{{}^{\bullet}OH} 3$ for convenience in Scheme.

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