Oxidation of Thymine Derivatives with Superoxide Ion

Takashi Harayame, Kenya Mori, Reiko Yanada, Kumiko Iio, Yuki Fujita, and Fumio Yoneda*

Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan

Alkylated thymine and thymidine derivatives are transformed by potassium superoxide into the corresponding ring contracted imidazolone derivatives; a plausible mechanism is presented.

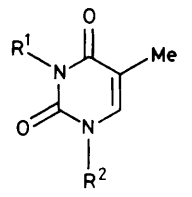
There is considerable interest on the role of superoxide ion in chemical and biochemical oxidations.[1,2] However, the biological implications of this ion are still a matter of controversy.[3] It was recently reported that superoxide ion was toxic to living cells,[4] the toxicity increasing in the presence of a halogenated compound or phosphate moiety.[5] In connection with our model studies on the oxidative damage of nucleic acids,[6] we have investigated the oxidation of the thymine and thymidine derivatives (**1**)—(**6**) with potassium superoxide (KO_2). Compounds (**4**) and (**6**), in which their active hydrogens were protected by alkylation, reacted with KO_2 in the presence of 18-crown-6 under argon using the conditions in Tables 1 and 2 to produce the corresponding ring contracted imidazolone derivatives (**7**)[7] and (**8**) in 15—53% yield. Structure assignments were based on their spectral data and mass spectrometry. This ring contraction is a novel type of reaction in nucleic acid chemistry. The reaction of (**4**) and (**6**) in tetrahydrofuran with KOH (4 equiv.), which might be formed from KO_2 and moisture in the reaction medium, led to quantitative recovery of starting material. In contrast, the reaction of compounds (**1**)—(**3**), which have an active hydrogen(s), with KO_2 produced no detectable amount of the corresponding imidazolone derivatives but resulted in >50% recovery of starting materials.† This result implies that superoxide ion is decomposed by the active hydrogens before it can attack the thymine derivatives because of its very short lifetime in a protic environment.

Interestingly, treatment of (**5**) with KO_2 in dimethyl sulphoxide (DMSO) gave thymine (**1**) in very high yield, whereas (**5**) was largely recovered in hexamethylphosphoric triamide (HMPA) or dimethylformamide (DMF) as shown in Table 3, indicating that the liberation of (**1**) is characteristic of the reaction with KO_2 in DMSO.[5b] Since superoxide produces

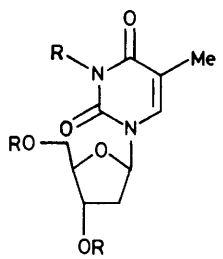
Table 1. The reaction of (**4**) with KO_2.[a]

Solvent	Time/h	(**4**) (%)	(**7**) (%)
Benzene	24	60.3	15.4
THF	24	12.3	22.4
DMF	2	—	—
DMSO	2	—	—

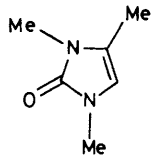
[a] KO_2 (6 equiv.), 18-crown-6 (4 equiv.), at 50 °C.



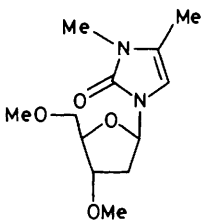
(**1**) $R^1 = R^2 = H$
(**2**) R^1 = Me, R^2 = H
(**3**) R^1 = H, R^2 = Me
(**4**) $R^1 = R^2$ = Me



(**5**) R = H
(**6**) R = Me



(**7**)

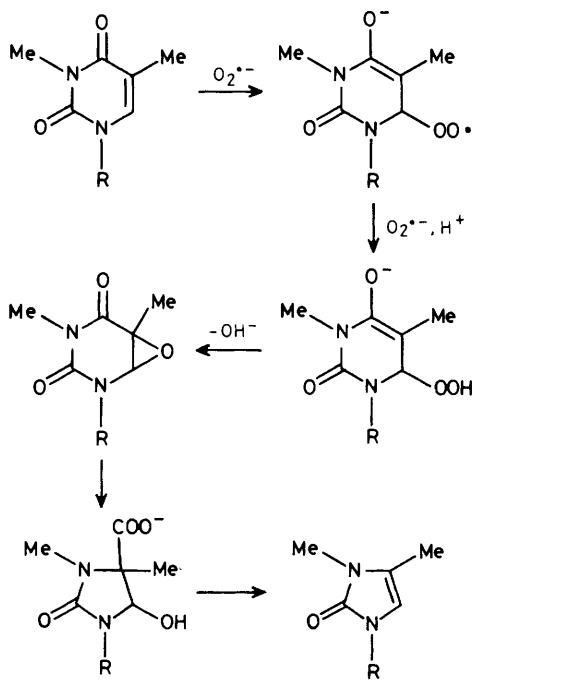


(**8**)

Table 2. The reaction of (**6**) with KO_2.[a]

Solvent	Time/h	(**6**) (%)	(**8**) (%)
Benzene	25	79.4	20.6
THF	25	8.9	39.8
DMF	2	—	27.3
DMSO	2	—	53.6

[a] Conditions as in Table 1.



Scheme 1

† 5-Fluoro-1,3-dimethyluracil was decomposed in a reaction with KO_2 under similar conditions and gave no identifiable products.

Table 3. The reaction of (**5**) with KO_2.[a]

Solvent	Time/h	(**5**) (%)	(**1**) (%)
HMPA	24	95.0	3.8
DMF	72	80.0	19.2
DMSO	36	2.6	97.3

[a] Conditions as in Table 1.

other active oxygen species such as hydroxyl radicals and hydrogen peroxide by disproportionation,[2,3] the nature of the genuine active species in the reaction is difficult to determine. However, hydroxyl radicals can be ruled out, because imidazolones are obtained even in DMSO (see Table 2), which is known to be a hydroxyl radical scavenger.[8] A plausible mechanism for the formation of the imidazolones (**7**) and (**8**) from the thymine derivatives (**4**) and (**6**) is shown in Scheme 1. It is considered that in the double-stranded DNA there are no active hydrogens on the thymidine units, because they are included inside the double helix in a hydrogen-bonded state. Therefore we propose that this type of transformation of thymidine by superoxide might take place in biological systems under certain circumstances.

Received, 25th April 1988; Com. 8/01603H

References

1 E. Lee-Ruff, *Chem. Soc. Rev.*, 1977, **6**, 195.
2 I. Fridovich, *Arch. Biochem. Biophys.*, 1986, **247**, 1.
3 D. T. Sawyer and J. S. Valentine, *Acc. Chem. Res.*, 1981, **14**, 393; I. Fridovich, *ibid.*, 1982, **15**, 200.
4 A. C. Bagley, J. Krall, and R. T. Lynch, *Proc. Natl. Acad. Sci. USA*, 1986, **83**, 3189.
5 (a) H. Yamamoto, T. Mashino, T. Nagano, and M. Hirobe, *J. Am. Chem. Soc.*, 1986, **108**, 539; (b) H. Yamane, N. Yada, E. Katori, T. Mashino, T. Nagano, and M. Hirobe, *Biochem. Biophys. Res. Commun.*, 1987, **142**, 1104, and references cited therein.
6 T. Harayama, R. Yanada, T. Taga, K. Machida, and F. Yoneda, *Chem. Pharm. Bull.*, 1986, **34**, 4961; T. Harayama, R. Yanada, M. Tanaka, T. Taga, K. Machida, J. Cadet, and F. Yoneda, *J. Chem. Soc., Perkin Trans. 1*, in the press.
7 S. Cortes and H. Kohn, *J. Org. Chem.*, 1983, **48**, 2246.
8 S. A. Lesko, R. J. Lorentzen, and P. O. P. Ts'o, *Biochemistry*, 1980, **19**, 3023.