EFFECT OF THYMINE HYDROPEROXIDE ON DNA BASES

Tomohisa Nagamatsu,[a] Fumio Yoneda,[a] and Shih Yi Wang[b]

Faculty of Pharmaceutical Sciences, Kumamoto University,[a] Oe-honmachi, Kumamoto 862, Japan and Division of Environmental Chemistry, The Johns Hopkins University,[b] School of Hygiene and Public Health, 3100 Wyman Park Drive, Bldg. 6, Baltimore, MD 21211, USA.

Since the discovery by Müller[1] that X-ray causes mutagenic effects, the radiation chemistry of nucleic acids has received considerable attention.[2] It has been shown[3] that radiolysis of aerated aqueous solution of nucleic acids, pyrimidine nucleotides, uracil or thymine results in the formation of the hydroxy-hydroperoxides. Among them thymine hydroperoxide (6-TOOH; cis-5-hydroxy-6-hydro-peroxy-5,6-dihydrothymine) was reported to be mutagenic on transforming DNA of Haemophilus influenzae.[4] Moreover, transition metal ions were found to enhance the mutation frequency; Cu^{++} was much more effective than other ions.

The studies presented here were undertaken to evaluate the effect of Cu^{++} on the reaction between 6-TOOH and cytosine, and to demonstrate the effect of 6-TOOH on neighbouring DNA bases. For instance, a reaction of 6-TOOH with cytosine in the presence of copper sulfate at 35 °C in H_2O produced cis-5,6-dihydroxy-5,6-dihydrothymine (cis-Thy glycol), 5-hydroxy-5-methylhydantoin, and cytosine-N(3)-oxide. On the other hand, in the absence of copper sulfate, the above reaction afforded cis-Thy glycol (53.9%), 5-hydroxy-5-methylbarbituric acid (27.7%), 5-hydroxy-5-methylhydantoin (10.1%), and an unidentified compound (8.3%). As it was presumed that the 6-TOOH might form a complex with Cu^{++}, we recrystallized the 6-TOOH from copper sulfate solution to give prisms. However, the X-ray diffraction analysis indicated that the 6-TOOH crystallized as a dihydrate in the cis configuration, and that the 6-TOOH was not coordinated to copper in the crystal.

References:
1) H.J. Müller, Pro. Natl. Acad. Sci. U.S., 44, 714 (1928). 2) G. Scholes, "Radiation Chemistry of Aqueous System", G. Stein ed., Weizman Science Press of Israel, Jerusalem, 1968. 3) G. Scholes, J. Weiss, and C.M. Wheeler, Nature, 178, 157 (1956). 4) H.F. Thomus, R.M. Herriott, B.S. Hahn, and S.Y. Wang, Nature, 259, 341, (1976).