THE CHEMICAL REPAIR REACTION OF THYMINE AND THYMIDINE DIOL DERIVATIVES, MODELS OF OXIDATIVELY DAMAGED NUCLEIC ACIDS, BY TRIVALENT PHOSPHORUS COMPOUNDS

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When treated with trivalent phosphorus compounds, thymine and thymidine diol derivatives, models of oxidatively damaged nucleic acids, were reductively repaired to regenerate the original thymine and thymidine derivatives. A possible mechanism is proposed.

KEYWORDS 1,3-dimethylthymine diol; thymidine diol derivative; phosphite; phosphine; reduction; repair reaction; damaged nucleic acid model; mechanism

It has been reported recently that the *cis* isomers of thymine and thymidine diols are released in human and rat urine as the result of excision repair of oxidatively damaged DNA.¹⁾ Although the several kinds of excision repairs for the abnormal nucleic acids by endonucleases are known in biological systems, we considered that there would possibly be other types of repair mechanism for oxidatively modified nucleic acids. Thus, we have examined the repair reactions of thymine and thymidine diols as models of damaged nucleic acids, using a wide variety of reducing agents.²⁾ The results so far showed that only trivalent phosphorus compounds effectively repaired the diol derivatives to the original thymine and thymidine derivatives, as reported here.

A mixture of 1,3-dimethylthymine diol (*cis* **1** or *trans* **2**)³⁾ (1 mmol) with phosphorus compounds was treated under the conditions in Table I. After the reaction, the solution was concentrated *in vacuo* and the residue was purified by preparative T.L.C. with ether to give 1,3-dimethylthymine (**3**) in good yield.⁴⁾

Chart 1

In both **1** and **2**, the reaction proceeded at the same rate to give almost the same yield of **3** in spite of their different stereochemistry, therefore the same reaction intermediate could be considered. The results using several tri and pentavalent phosphorus compounds, summarized in Table I, showed that only trivalent phosphorus compounds were effective for this repair reaction. The reaction of thymidine diol derivative (**4**) with triphenylphosphite gave β -thymidine derivative (**5**)⁵⁾ in 89% yield, and not α -thymidine isomer. Therefore it seemed reasonable to assume that the movement of the lone pair of N₁ followed by the scission of the C1'-O bond in ribosyl moiety,⁶⁾ did not take place.

The nucleophilic attack on carbonyl carbon by trivalent phosphorus compounds at the initial stage is generally accepted as the mechanism of the Perkow reaction (reaction of α -halocarbonyl compound

with trivalent phosphorus compound), although the details are still not completely resolved.^{7,8)}

Therefore, we would like to propose tentatively a Perkow type of reaction mechanism shown in Chart 2 for the reductive repair reaction.

To our knowledge, natural and stable trivalent phosphorus compounds have not yet been reported in the field of biochemistry. However, if a trivalent phosphorus derivative is brought about transiently in living cells, this type of repair reaction for oxidatively modified nucleic acids might occur under certain conditions in live bodies.

Table I. The Results of Reaction of **1** and **2** with Phosphorus Compounds

Compound	Reagent	Equivalent	Solvent	Conditions	Yield of 3 (%)
1	PBr ₃	10.0	THF	R.T. 20 h	61.0
2					74.4
1	PCl ₃	2.4	THF	Reflux 20 h	73.2
2					72.0
1	(PhO) ₃ P	Neat	—	100 °C 3 h	86.7
2					85.7
1	(MeO) ₃ P	Neat	—	100 °C 16 h	86.0
2					85.3
1	n-Bu ₃ P	Neat	—	100 °C 24 h	20.0
2					20.0
1	PCl ₅	2.4	THF	Reflux 20 h	0
2					0
1	POCl ₃	2.4	THF	Reflux 40 h	0
2					0

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(Received February 19, 1991)