Direct Transformation of Ribonucleoside Cyclic 3′,5′-Phosphorothioates into Cyclic 2′,3′-Phosphates

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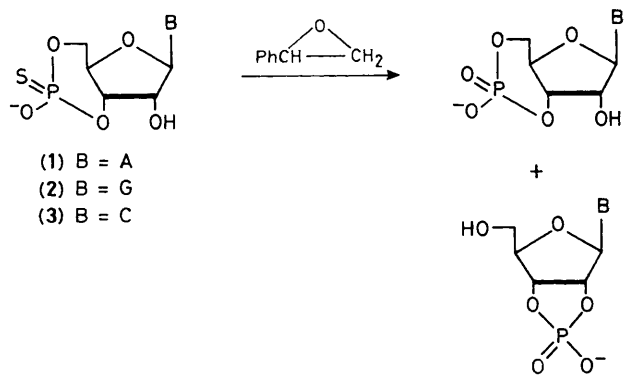
Ribonucleoside cyclic 3′,5′-phosphorothioates react with oxiranes to give preferentially ribonucleoside cyclic 2′,3′-phosphates.

It has been demonstrated in our recent report[1] that styrene [^{18}O]oxide can be successfully used for the stereospecific conversion of *P*-chiral thymidine cyclic 3′,5′-phosphorothioates into the corresponding 3′,5′-[^{18}O]phosphates. However, the reaction of styrene oxide with S_P-adenosine cyclic 3′,5′-phosphorothioate (**1**) gave only 38% of the

Table 1. Reactions of nucleoside cyclic phosphorothioate (**1**)—(**3**) with oxiranes.

Expt.	Substrate[a]	Oxirane RCHCH$_2$O, R	Conditions	% Yield of cyclic phosphate[c] 3′,5′	2′,3′
1	(**1**)	Ph	H_2O–DMF, 60 °C, 4 h	38[b]	49[b]
2	(**2**)	Ph	H_2O–DMF, 60 °C, 4 h	28	38
3	(**3**)	Ph	H_2O–DMF, 60 °C, 4 h	15	58
4	(**1**)	Ph	EtOH, 60 °C, 4 h	14	77
5	(**1**)	Et	H_2O, 60 °C, 2 h	13	76
6	(**1**)	H	H_2O, 20 °C, 30 min	7	81

[a] The phosphorothioates (**1**)—(**3**) (Et_3N salts) were taken as the mixture of diastereoisomers R_P and S_P in *ca.* 1:1 ratio. [b] A similar composition of isomeric phosphates was obtained from the reaction of pure R_P- and S_P-(**1**) with styrene oxide. [c] The mixture of isomeric phosphates was isolated by ion-exchange chromatography (DEAE Sephadex) and further separated by preparative h.p.l.c. The identity of the products was proved by comparison of their u.v., ^{31}P and ^{1}H n.m.r. spectra as well as h.p.l.c. retention time with those of authentic samples.

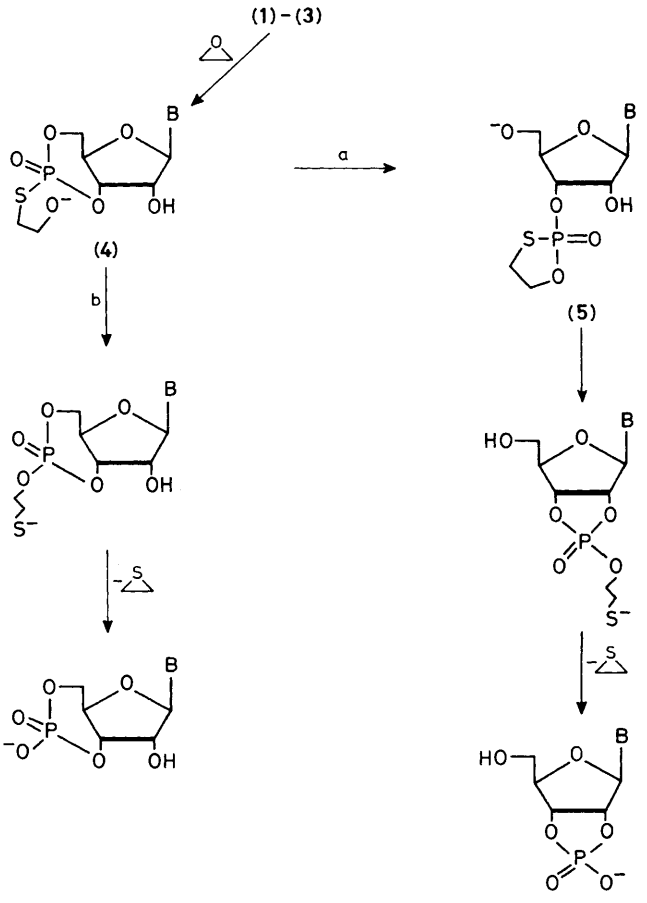


Scheme 1

expected oxo-product, thus suggesting its more complex character in ribonucleotide series.

We describe here the results of our further studies on the reaction of cyclic 3′,5′-phosphorothioate derivatives of adenosine (**1**) as well as guanosine (**2**) and cytidine (**3**) with styrene oxide. The cyclic nucleotides (**1**)—(**3**) employed in these studies were prepared according to our previous reports.[2] We have found that P(:S) → P(:O) exchange proceeds in high yield; the product, however, was isolated as a mixture of two isomeric cyclic nucleotides in which the phosphate moiety was incorporated into either a 6- or a 5-membered ring (Scheme 1). The relative ratio of isomeric phosphates was found to be strongly dependent upon the reaction conditions (see Table 1). The fraction of cyclic 2′,3′-nucleotide, being the major product in all reactions studied, was much higher when the conversion of (**1**) was performed in ethanol solution instead of dimethylformamide (DMF)–water. A similar tendency for the formation of cyclic 2′,3′-phosphate to be favoured was observed when (**1**)† was treated with aliphatic oxiranes such as 1,2-butylene or ethylene oxides in aqueous solution (Table 1, expts. 5 and 6). The experiment with (**1**) and styrene [^{18}O]oxide (55% isotope enrichment) in DMF–water resulted in the incorporation of the oxygen isotope into both 5- and 6-membered ring phosphates without any loss of isotope enrichment. On the other hand, no incorporation of oxygen label into either of the phosphate products was observed when (**1**) was treated with unlabelled styrene oxide in DMF–[^{18}O]water.

The bidirectional reactivity of ribonucleoside cyclic 3′,5′-phosphorothioates with oxiranes can be rationalized in terms of Hamer's classical mechanism[3,4] (see Scheme 2). The intermediate (**4**), resulting from the initial addition of phosphorothioate to the oxirane molecule, undergoes intramolecular rearrangement by nucleophilic attack of the vicinal hydroxy group at phosphorus with opening of the dioxaphosphorinane ring and the formation of the intermediate 3′-thioxaphospholane (**5**) (path a). Subsequent intramolecular attack of the 2′-hydroxy group at phosphorus in (**5**) leads to the



Scheme 2

formation of 2′,3′-dioxaphospholane ring products. This particular step is strongly favoured by the entropy factor owing to the close proximity of the 2′-hydroxy group to the phosphorus centre. Cyclic 3′,5′-phosphates are formed *via* path b with full preservation of the dioxaphosphorinane ring. The relatively low proportion of cyclic 3′,5′-phosphate products in ribonucleotide series is in clear contrast to the almost quantitative yield of 3′,5′-cTMP obtained in the reaction of *P*-chiral thymidine cyclic 3′,5′-phosphorothioates with styrene oxide[1] and reflects the dramatic change in reactivity of nucleotides introduced by the presence of the 2′-hydroxy group.

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† Detailed spectroscopic studies revealed that no base modification occurred under the conditions used for these reactions. Similarly no reaction was observed when 3′,5′-cAMP (Et_3N salt) was treated with either 1,2-butylene or ethylene oxide under the same conditions.

References

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