Cyclic Phosphorylation Reaction of Diols with Tri(1-imidazolyl)phosphine

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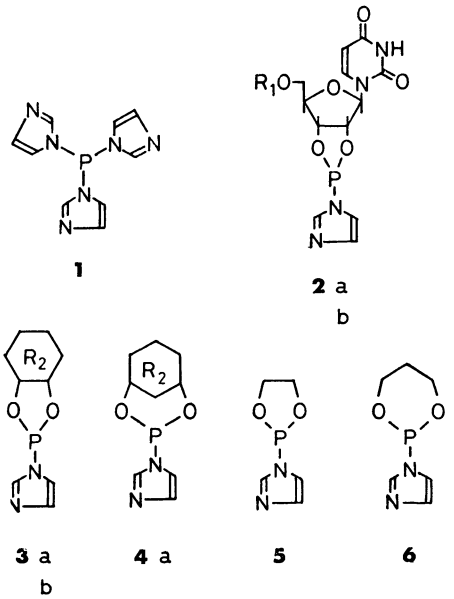
Tri(1-imidazolyl)phosphine (**1**) gave the cyclic phosphite quantitatively in the reactions with the diols possessing favorably placed hydroxyl groups in which the distance between the two oxygen atoms is 2.7—3.0 Å. The both five- and six-membered cyclic phosphites were obtained quantitatively from the reactions of the diols possessing flexible chains with **1**. The course of the selective formation of ribonucleoside 2′,3′-cyclic 1-imidazolylphosphonite was interpretated by the higher reactivity of **1** toward the 2′- or 3′-hydroxyl group than toward the 5′-hydroxyl group of ribonucleoside.

It is well-known that many active phosphorus compounds readily react with vicinal diols to give the cyclic phosphites.[1—7] Recently, we have developed a new sort of phosphorylating reagent such as tri(1-imidazolyl)phosphine (**1**) which reacts selectively with the 2′- and 3′-hydroxyl groups of ribonucleoside to give a ribonucleoside 2′,3′-cyclic 1-imidazolylphosphonite (**2a**).[8] This reaction was extended by the use of tri(azol-1-yl)phosphines and has been successfully adopted to the synthesis of oligoribonucleotides directly from unprotected ribonucleosides.[9,10] It is significant to elucidate the aspect of this cyclic phosphorylation reaction which is directed toward the use for a selective phosphorylation of some important substances possessing diol group, *e.g.* sugars, some steroids, *etc.* For this purpose, the reaction of some simple diols with **1** is performed. In this paper, we describe the cyclic phosphorylation reaction of diols with **1** in connection with the phosphorylation of the ribonucleosides.



1 **2** a b **3** a b **4** a **5** **6**

R_1 a) H–
b) monomethoxytrityl–

R_2 a) cyclohexane
b) benzene

Results and Discussion

We first focused our attention on the reaction of diols possessing different degree of distance between the reacting hydroxyl groups with **1**. Cyclohexanediols have a variety of stereoisomeric conformers. The distances between the two oxygen atoms in the diols can be calculated[11] and listed in Table 1. Compounds 1,2-cyclohexanediol, 1,3-cyclohexanediol, and 1,4-cyclohexanediol were allowed to react with equimolar amounts of **1** and then ethanol. The products were analyzed by ^{31}P NMR spectroscopy. All the cyclohexanediols were completely phoshorylated by the reaction with **1** at −78 °C within 5 min. The yields of cyclic phosphite derivatives are given in Table 1. Both *cis*- and *trans*-1,2-cyclohexanediol gave the five-membered cyclic phosphonite (**3a**) quantitatively. Inspection of models shows that the phosphonite ring can be formed readily both with the *cis*-diol having one axial and one equatorial hydroxyl(O–O distance, 2.96 Å), and the *trans*-diol having two equatorial hydroxyl groups(O–O distance, 2.96 Å). Neither of the two stereoisomeric(*cis* and *trans*) cyclic phosphonites is greatly strained and their formation can require little or no distortion of the cyclohexane ring from its

TABLE 1. YIELDS OF CYCLIC PHOSPHITE DERIVATIVES IN THE REACTIONS OF TRI(1-IMIDAZOLYL)PHOSPHINE WITH VARIOUS DIOLS AND NUCLEOSIDES

	Yield[a]/%	O–O Distance[b]/Å
cis-1,2-Cyclohexanediol	≈100	2.96
trans-1,2-Cyclohexanediol	≈100	2.96[d]
cis-1,3-Cyclohexanediol	44	2.53[e]
trans-1,3-Cyclohexanediol	0[c]	5.30
cis-1,4-Cyclohexanediol	0[c]	4.49
trans-1,4-Cyclohexanediol	0[c]	5.70
1,2-Benzenediol	74	2.72
1,3-Benzenediol	0[c]	4.71
1,4-Benzenediol	0[c]	5.44
Thymidine	0[c]	3.73
5′-*O*-Monomethoxytrityluridine	93	2.77

a) Yields determined by ^{31}P NMR spectroscopy or HPLC. b) Distance between the two oxgen atoms in the hydroxyl groups: L. E. Sutton, "Tables of Interatomic Distance and Configuration in Molecules and Ions." c) Polymeric product. d) Two equatorial hydroxyl groups. e) Two axial hydroxyl groups.

preferred chair conformation. On the other hand, of the two 1,3-cyclohexanediols, only the *cis*-compound having two axial hydroxyl groups (O–O distance, 2.53 Å), gave the six-membered cyclic phosphonite (**4a**), but *trans*-compound(O–O distance, 5.3 Å) did not give the cyclic phosphonite. Inspite of no distortion of the cyclohexane ring from the chair conformation, the yield(44%) of the six-membered cyclic phosphonite was less than that of the five-membered one. *cis*-1,4-Cyclohexanediol(O–O distance, 4.49 Å), and *trans*-1,4-cyclohexanediol(O–O distance, 5.70 Å) did not give the cyclic phosphonite. They yielded gel-like polymeric material. These results show that the selectivity of the cyclic phosphorylation reaction with **1** depends on the distance between the two oxygen atoms of the hydroxyl groups in diols; in the case of diols possessing the favorably adjacent hydroxyl groups, only the cyclic phosphorylation reaction proceeds, which involves the formation of the monophosphorylated diol and then the successive intramolecular reaction to give the cyclic phosphonite. When the two hydroxyl groups of diols are not favorably placed, the intermolecular reaction of the monophosphorylated diols leads to the formation of the polymer.

Further investigation on the reactions of benzenediol derivatives with equimolar amounts of **1** was carried out. The yields of the cyclic phosphite derivatives are shown also in Table 1. 1,2-Benzenediol(O–O distance, 2.72 Å) was favored to give the five-membered cyclic phosphonite (**3b**). The six-membered cyclic phosphonite from 1,3-benzenediol (O–O distance, 4.71 Å) was not obtained. 1,4-Benzenediol (O–O distance 5.44 Å) gave polymeric material.

The question arose whether a six-membered ring could be formed in the reaction of a nucleoside possessing the 5′- and 3′-hydroxyl groups(O–O distance, 3.73 Å) with **1**. To study this problem the reaction of thymidine with equimolar amount of **1** was performed. The result is shown in Table 1. Thymidine 3′,5′-cyclic phosphonite was not formed, but polymeric compounds were obtained. On the other hand, the reaction of 5′-monomethoxytrityluridine having free 2′- and 3′-hydroxyl groups(O–O distance, 2.77 Å) with equimolar amount of **1** gave only the five-membered cyclic phosphonite (**2b**), but no polymeric compound was obtained. It is concluded therefore that **1** gave the cyclic phosphites quantitatively in the reaction with diols possessing the favorably placed hydroxyl groups in which the distance between the two oxygen atoms is 2.7—3.0 Å.

Another problem was to examine the ease of the formation of five-membered cyclic phosphonite and six-membered one in the reaction of diols with **1**. The reaction of aliphatic diols which have flexible chains with equimolar amounts of **1** were carried out (−78 °C, 30 min). After the treatment with methanol, ^{31}P NMR spectra of the products show that the cyclic phosphites were formed quantitatively both from ethylene glycol and 1,3-propanediol. These results indicate that **1** has a potential activity to give the both five- and six-membered cyclic phosphonite (**5** and **6**) from the flexible chain diols. It was reported that, in the similar reactions, phosphorus trichloride,[1–3] triphenylphosphine,[4] and hexamethylphosphorous triamide[12] gave the cyclic phosphite in moderate yields. Therefore, from the practical point of view, **1** is useful for the preparation of cyclic phosphites.

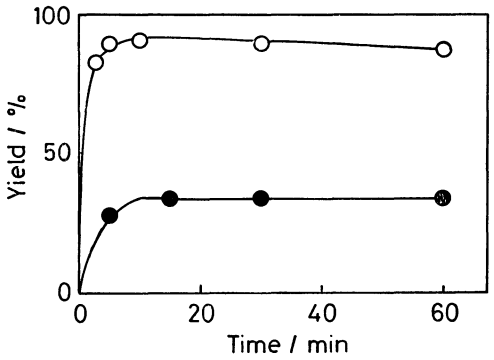


Fig. 1. The time course of the phosphorylation reaction of 5′-*O*-monomethoxytrityluridine and 2′,3′-*O*-isopropylideneuridine with tri(1-imidazolyl)phosphine. ○: 5′-*O*-Monomethoxytrityluridine, ●: 2′,3′-*O*-isopropylideneuridine.

We have already shown that, in the reaction of unprotected ribonucleoside, the ribonucleoside 2′,3′-cyclic 1-imidazolylphosphonite (**2a**) is formed by the selective attack of **1** to the 2′- and 3′-hydroxyl groups of ribonucleoside.[8–10] In order to examine the course of the selective formation of the ribonucleoside 2′,3′-cyclic 1-imidazolylphosphonite(**2a**), the reactivity of **1** toward the different hydroxyl groups(5′- or 2′,3′-OH) of ribonucleoside was investigated. The time course of the phosphorylation reaction of 5′-*O*-monomethoxytrityluridine and 2′,3′-*O*-isopropylideneuridine with equimolar amount of **1** was shown in Fig. 1. 5′-*O*-Monomethoxytrityluridine was phosphorylated to 90% within 3 min, whereas the rate of the phosphorylation of 2′,3′-*O*-isopropylideneuridine was considerably slow and the yield of the phosphorylated product was less than 35%. That is, the reactivity of **1** toward the 2′- and 3′-hydroxyl groups of ribonucleoside is much higher than toward the 5′-hydroxyl group. Consequently, it is considered that the formation of ribonucleoside 2′,3′-cyclic 1-imidazolylphosphonite (**2a**) is obviously kinetically controlled.

Experimental

High-performance liquid chromatography was carried out on a Shimadzu-Dupont LC 830 instrument using Partisil 10 SAX(ion exchange) column; the linear gradient was 0.001 M†† KH_2PO_4 to 0.3 M KH_2PO_4 containing 10% ethanol(3% min^{-1}) at 70 atm, or on a Shimadzu LC 3A instrument using Nucleosil $7C_{18}$(reverse-phase) column; solvent was 2—20% CH_3CN in 0.1 M ammonium acetate(pH 6.0) at a flow rate of 1.0 ml min^{-1}. ^{31}P NMR spectra were recorded on a JEOL FX-200 instrument. ^{13}C NMR spectra were obtained on a JEOL FX-100 instrument.

Pyridine was distilled from *p*-toluenesulfonyl chloride, redistilled from calcium hydride, and stored over 4A molecular sieves. Tetrahydrofuran was refluxed in the presence of $LiAlH_4$ for overnight, distilled, and stored over 5A molecular sieves. Phosphorus trichloride was distilled and stored in

†† 1 M=1 mol dm^{-3}.

a brown ampule. Ethanol was distilled in the presence of benzene and stored over 3A molecular sieves. Methanol was distilled and stored over 3A molecular sieves. Imidazole, thymidine, *cis*- and *trans*-1,2-cyclohexanediol(*cis*:*trans*=67:33),[13] *trans*-1,2-cyclohexanediol, *cis*- and *trans*-1,3-cyclohexanediol(*cis*:*trans*=50:50),[13] *cis*- and *trans*-1,4-cyclohexanediol(*cis*:*trans*=44:56),[13] ethylene glycol, 1,3-propanediol, 1,2-benzenediol, 1,3-benzenediol, and 1,4-benzenediol were purchased from Nakarai Chemical Co. 5′-*O*-Monomethoxytrityluridine and 2′,3′-*O*-isopropylidene uridine were synthesized by the usual method.[14]

Tri(1-imidazolyl)phosphine. The preparation of tri(1-imidazolyl)phosphine was carried out under argon; phosphorus trichloride(300 μl, 3.45 mmol) was added dropwise to a solution of imidazole(1.41 g, 20.7 mmol) in 24 ml of tetrahydrofuran (THF). Then the mixture was stirred at 0 °C for 20 min. After the filtration of the imidazolium hydrochloride, the filtrate was used as a phosphorylating reagent. Tri(1-imidazolyl)phosphine was contained *ca.* 0.14 mmol in 1 ml of the filtrate. This phosphorylating reagent was stable at least for a week in anhydrous THF under argon.

Reaction with Cyclohexanediols. Generally, the reactions of cyclohexanediols with tri(1-imidazolyl)phosphine were carried out in THF; the reaction mixtures consisted of cyclohexanediols (400.8 mg, 3.45 mmol) in 5 ml of THF and tri(1-imidazolyl)phosphine (approximately equimolar amount to cyclohexanediols) in 24 ml of THF. The mixtures were stirred at −78 °C for 60 min and then evaporated to nearly dryness. The residues were dissolved in pyridine-d_5. The solutions were sealed into the NMR tube under argon and then analyzed by ^{31}P NMR.

Time Course of the Reaction with Cyclohexanediols. *trans*-1,2-Cyclohexanediol was reacted with tri(1-imidazolyl)phosphine under the same conditions above for 5, 15, 30, and 60 min. After these time intervals, the reaction mixtures were treated with excess ethanol at 0 °C for 30 min. The solutions were evaporated to nearly dryness and dissolved in benzene-d_6. They were sealed into the NMR tube and then analyzed by ^{31}P NMR. Similar experiments were done for *cis*- and *trans*-1,2-cyclohexanediol, and *cis*- and *trans*-1,3-cyclohexanediol.

Reaction with Glycols. Glycols (ethylene glycol, 62.1 mg, 1,3-propanediol, 76.1 mg; 1 mmol) were dissolved in THF (7 ml) and then cooled to −78 °C. To these solutions, tri(1-imidazolyl)phosphine (1.0 mmol) in 7 ml of THF was added and stirred for 30 min. After treatment of methanol (0.2 ml, 4.9 mmol), the solutions were evaporated to nearly dryness. The residue were dissolved in $CDCl_3$. The solutions were transferred into the NMR tube and then analyzed by ^{31}P NMR.

Reaction with Benzenediols. Benzenediols (30.8 mg, 0.28 mmol) were reacted with tri(1-imidazolyl)phosphine(equimolar amount to benzenediols) in 3 ml of THF at −78 °C for 60 min. The reaction mixtures were added to a solution of iodine (71.2 mg, 0.28 mmol) in 3 ml of THF–water(2:1, v/v) with a few drops of pyridine. Then the solutions were evaporated to dryness. The residues were dissolved in 1 ml of water and then analyzed by HPLC.

Reaction with Thymidine. Thymidine (36.2 mg, 0.1 mmol) was reacted with tri(1-imidazolyl)phosphine (equimolar amount to nucleoside) in 2.4 ml of pyridine–THF (1:4, v/v) at −78 °C for 60 min. After the oxidation with iodine and water, the mixtures were evaporated to dryness. The residues were dissolved in 1 ml of water and then analyzed by HPLC.

Reaction with 5′-O-Monomethoxytrityluridine and 2′,3′-O-Isopropylideneuridine. 5′-*O*-Monomethoxytrityluridine (72.3 mg, 0.14 mmol) was dissolved in 1.4 ml of pyridine–THF (5:2, v/v) and then cooled to −78 °C. To this solution, tri(1-imidazolyl)phosphine (equimolar amount to nucleoside) in 1 ml of THF was added and stirred. After the appropriate time intervals, the mixture was oxidized with iodine and water. The mixture was evaporated to dryness and dissolved in the buffer(20% CH_3CN) and then analyzed by HPLC. Similar experiment was done for 2′,3′-*O*-isopropylideneuridine under the same conditions. In order to confirm the cyclic structure, the phosphorylated derivative from 5′-*O*-monomethoxytrityluridine was treated with $ZnBr_2$ in methanol and then analyzed by HPLC. Only the peak due to uridine 2′,3′-cyclic phosphate was appeared.

Determination of Yields. Yields(%) of the cyclic phosphite derivatives from the reaction of tri(1-imidazolyl)phosphine with cyclohexanediols and glycols were determined by ^{31}P NMR spectroscopy. The cyclic structure was confirmed after the conversion of the cyclic 1-imidazolylphosphonite to the corresponding cyclic phosphites of which ^{31}P chemical shifts (downfield from external 85% H_3PO_4) were reported in the literatures.[15,16] 2-Ethoxy-4,5-(*cis*-1,2-cyclohexanedihydroxy)-1,3,2-dioxaphospholane (from **3a**): δ+136 ppm (lit,[15] δ+136 ppm); 2-ethoxy-4,5-(*trans*-1,2-cyclohexanedihydroxy)-1,3,2-dioxaphospholane (from **3a**): δ=139 (lit,[15] δ=139); 2-ethoxy-4,5-(*cis*-cyclohexanedihydroxy)-1,3,2-dioxaphosphorinane (from **4a**): δ=124 (lit,[15] δ=124); 2-methoxy-1,3,2-dioxaphospholane (from **5**): δ=132 (lit,[16] δ=132); 2-methoxy-1,3,2-dioxaphosphorinane (from **6**): δ=129 (lit,[16] δ=129).

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