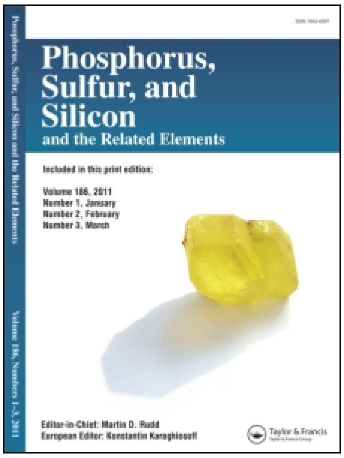

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Chen, Xin , Zhang, Nan-Ding , Yuan and Zhao, Yu-Fen(1996) 'STUDIES ON REACTION OF RIBONUCLEOSIDES WITH OXYPHOSPHORANE', Phosphorus, Sulfur, and Silicon and the Related Elements, 118: 1, 257 — 261

To link to this Article: DOI: 10.1080/10426509608038817

URL: http://dx.doi.org/10.1080/10426509608038817

Phosphorus, Sulfur, and Silicon, 1996, Vol. 118, pp. 257–261
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STUDIES ON REACTION OF RIBONUCLEOSIDES WITH OXYPHOSPHORANE

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(Received 28 April 1996; Revised 21 August 1996; In final form 21 August 1996)

Ester exchange reaction of ribonucleosides (**2**) with oxyphosphorane (**1**) afforded spirooxyphosphoranes (**3**). After hydrolysis followed by acetylation, the labile spirooxyphosphoranes such as **3a** were converted into stable nucleotide derivatives (**4**). The possible mechanism for the conversion was also discussed.

Keywords: Ribonucleosides; oxyphosphorane; ester exchange reaction

Phosphoranes have been proposed as the possible intermediates in the displacement reactions of ATP with nucleophiles,[1,2] as well as in the activation of protein kinases by cAMP for the regulatory subunit.[3,4] Recently, the kinetics and mechanism of the ester exchange reaction of oxyphosphorane (**1**) with nucleosides have been reported in this laboratory,[5] and the results indicated that ribonucleosides and 2′-deoxyribonucleosides showed much different reactivities toward the reaction with oxyphosphorane (**1**).

The ester exchange reaction of oxyphosphorane (**1**) with ribonucleosides, such as uridine (**2a**), adenosine (**2b**), guanosine (**2c**) and cytidine (**2d**), afforded selectively spirooxyphosphoranes composed of two five-membered rings (**3a–d**) (**Scheme 1**). The labile compounds **3a–d** could not been isolated, and their structures were determined by their spectral properties in solution. In order to develop this type of ester exchange reaction as a novel synthetic method for

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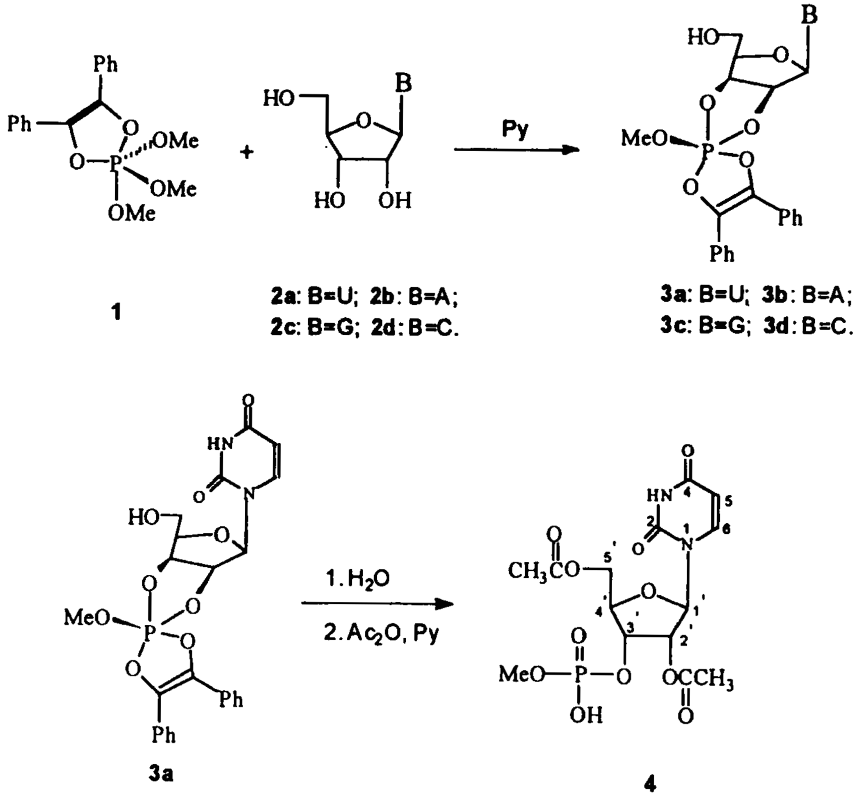
*Corresponding author.



SCHEME 1 Reaction of oxyphosphorane (1) with ribonucleosides.

nucleotides,[6] the hydrolysis of the spirooxyphosphoranes was investigated. In addition, the results may provide more reliable evidences for the structural assignment of compounds **3a–d**.

Equal amounts of uridine (**2a**) and oxyphosphorane (**1**) were mixed in pyridine at room temperature under nitrogen, and the reaction was monitored by ^{31}P NMR spectra. About 5 h later, the reaction was completed. Water was added to the reaction solution to decompose the resulting spirooxyphosphorane **3a**. In order to isolate readily the hydrolytic products, acetylation was employed. By silica gel column chromatography, uridine monophosphate derivative **4** were obtained, whose structure was confirmed by its ^{31}P, ^{1}H, ^{13}C NMR and MS data, and ^{1}H-^{1}H COSY experiments (**Fig. 1**).

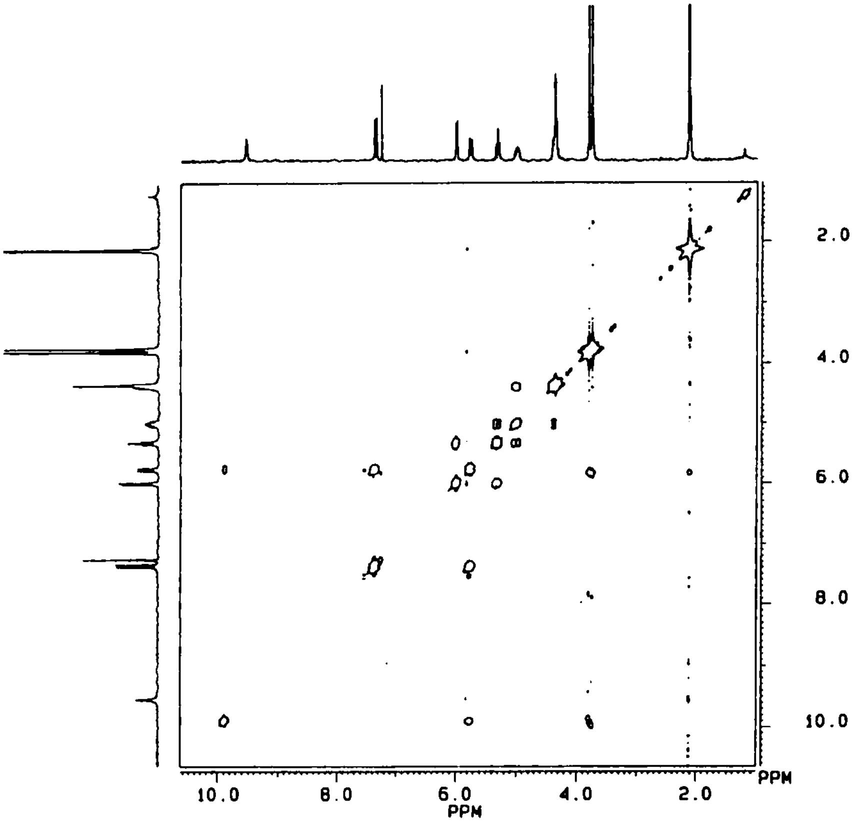
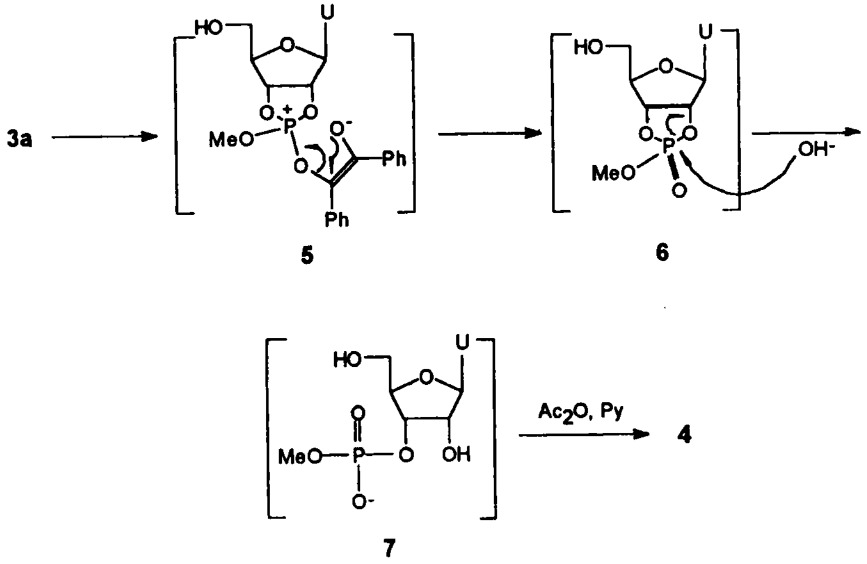


FIGURE 1 ^1H-^1H COSY Spectrum for Compound 4

The possible pathway for the conversion of spirooxyphosphorane **3a** to uridine-3′-phosphate derivative **4** was described as follows (**Scheme 2**): the unsaturated five-membered ring of spirooxyphosphorane **3a** was easily opened to give the possible P(4) intermediate **5**; removal of benzoin analogue from **5** afford cyclic phosphate **6** (uridine-2′,3′-cyclic phosphate), the latter underwent further hydrolysis to generate uridine-3′-phosphate **7**. Employing acetic anhydride—pyridine system, **7** was acetylated to afford the final product **4**.

It should be pointed out that there was no uridine-2′-phosphate derivative isolated. This result indicated that the hydrolysis of spirooxyphosphorane **3a** possessed highly regioselectivity, and the ester exchange reaction of ribonucleosides with oxyphosphorane (**1**) shows promise for the synthesis of ribonucleotides with natural 3′-5′ phosphodiester links.



SCHEME 2 The possible pathway for the conversion of compound **3a** to **4**.

EXPERIMENTAL SECTION

All glassware was dried in an oven for at least 3 h at 120°C before use. Air-sensitive materials were transfered under nitrogen atmosphere. Commercial solvents and reagents were all purified before use. Pyridine was dried over anhydrous KOH. Ribonucleosides were purchased from Aldrich or Sigma Chemical Co., and dried by P_2O_5 in a small oven.

^1H and ^{13}C NMR spectra were recorded on Bruker AC 200 or Varian 90 spectrometers. ^{31}P NMR spectra were taken on a Bruker AC 200 spectormeter at 81 MHz under proton decoupling conditions. ^{31}P chemical shifts were reported in ppm downfield (+) or upfield (−) from external 85% H_3PO_4. Mass spectra were run on a Finnigan MAT 90 MS double focusing magnetic mass spectrometer operated in negative FAB mode using a direct sample inlet.

General Procedure for the Ester Exchange Reaction of Oxyphosphorane (1) with Ribonucleosides (2a–d)

A mixture of oxyphosphorane (**1**)[7] (2.0 mmol) and ribonucleosides (**2a–d**) (2.0 mmol) dissolved in anhydrous pyridine (10–30 mL) was stirred at 23°C under N_2 for 5–12 h (5 h for uridine **2a**). ^{31}P NMR signals indicated that the reaction was completed, resulting labile spirooxyphosphoranes **3a–d**. The spectral data for compound **3a**: ^{31}P NMR (81 MHz): δ-23.32 (major), −24.86 (minor); ^{1}H NMR (200 MHz, pyridine-d$_5$): δ2.92 (d, 3H, $^3J_{PH}$ = 13.8 Hz, CH_3O), 3.30 (m, 2H, 5'-H), 3.68 (m, 1H, 4'-H), 4.22 (m, 1H, 3'-H), 4.45 (m, 1H, 2'-H), 4.90 (d, 1H, J = 8.0 Hz, 5-H), 5.63 (brs, 1H, 1'-H), 6.80–7.38 (m, 10H, Ar-H), 7.64 (d, J = 8.0 Hz, 6-H); MS (EI): *m/z* 514 (M^+).

To the above reaction solution was added H_2O (0.5 mL), and the stirring was continued for further 5 min. Pyridine was removed under reduced pressure, and the light yellow solid was dissolved in pyridine (1 mL) and acetic anhydride (1 mL) with N-methylimidazole (0.2 mL), and kept at room temperature overnight. After evaporating the solvents under reduced pressure, dissolving the residue in CH_2Cl_2 (50 mL) followed by washed with H_2O (2 × 20 mL) and dried with anhydrous Na_2SO_4, the crude products were purified by silica gel (200–300 mesh) column chromatography eluting with CH_2Cl_2-MeOH (10:1) to afford almost colorless solid **4** in 81% yield (based on the consumed **2a**).

Spectral data for **4**: ^{31}P NMR (81 MHz, $CDCl_3$): δ1.83; ^{1}H NMR (200 MHz, $CDCl_3$): δ2.12 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 3.78 (d, 3H, $^3J_{PH}$ = 11.3 Hz; CH_3O), 4.36 (m, 2H, 5'-H), 4.39 (m, 1H, 4'-H), 5.01 (m, 1H, 3'-H), 5.33 (dd, 1H, J = 5.5, 5.6 Hz, 2'-H), 5.78 (d, 1H, J = 8.0 Hz, 5-H), 6.02 (d, 1H, J = 5.5 Hz, 1'-H), 7.39 (d, 1H, J = 8.0 Hz, 6-H), 9.81 (br, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ20.49, 20.75 (2 × CH_3CO), 54.96 (d, $^2J_{PC}$ = 3.8 Hz, CH_3O), 62.97 (5'-C), 72.80 (d, $^3J_{PC}$ = 4.1 Hz, 2'-C), 73.63 (d, $^2J_{PC}$ = 3.6 Hz, 3'-C), 80.90 (d, $^3J_{PC}$ = 4.1 Hz, 4'-C), 87.59 (1'-C), 103.45 (5-C), 139.59 (6-C), 150.17 (2-C), 162.99 (4-C), 169.76, 170.10 (MeC═O); HRMS (negative FAB) calcd. for $C_{14}H_{18}N_2O_{11}P$: *m/z* 421.0648 $(M-1)^-$. Found: *m/z* 421.0652.

Acknowledgement

The authors wish to acknowledge the financial support of the National Natural Science Foundation of China and the National Science and Technology Committee for Y. F. Zhao, and China Postdoctoral Science Foundation for X. Chen.

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