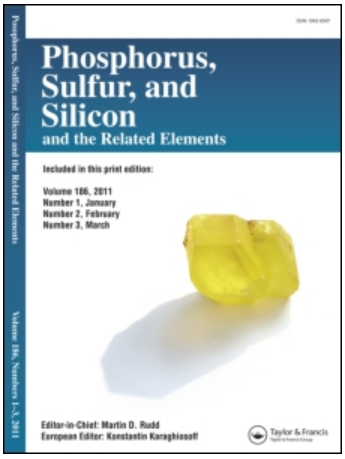

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

N-SELECTIVE PHOSPHORYLATION WITH CHLOROPHOSPHORYL DIALKYLESTERS PREPARED FROM DIALKYLPHOSPHITE/CCl_4/NEt_3

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To cite this Article Yin, Ying-Wu , Chen, Yi , Zhao, Yu-Fen and Li, Li-Pu(1993) '*N*-SELECTIVE PHOSPHORYLATION WITH CHLOROPHOSPHORYL DIALKYLESTERS PREPARED FROM DIALKYLPHOSPHITE/CCl_4/NEt_3', Phosphorus, Sulfur, and Silicon and the Related Elements, 82: 1, 67 — 72
To link to this Article: DOI: 10.1080/10426509308047409
URL: http://dx.doi.org/10.1080/10426509308047409

Phosphorus, Sulfur, and Silicon, 1993, Vol. 82, pp. 67–72
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N-SELECTIVE PHOSPHORYLATION WITH CHLOROPHOSPHORYL DIALKYLESTERS PREPARED FROM DIALKYLPHOSPHITE/CCl_4/NEt_3

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(Received January 19, 1993; in final form June 21, 1993)

By ^{31}PNMR it was found that the system: dialkylphosphite/CCl_4/NEt_3 specifically reacts with the amino group but not with the hydroxyl group.

Key words: *N*-selective phosphorylation; with dialkylphosphite/CCl_4/NEt_3; dialkyphosphoryl amino acids; ^{31}P-NMR.

INTRODUCTION

Previously, it had been reported that the amino acids and dipeptides could be phosphorylated by the dialkylphosphite/CCl_4/NEt_3-system in a mixed aqueous solution in one step. A series of *N*-phosphorylated amino acids and *N*-phosphoryl dipeptides had been synthesized.[1-2] Their structures had been determined by the FAB-MS,[3-6] ^{31}P-NMR,[7-8] ^{13}C-NMR[9] and the x-ray crystallography.[10-11] In addition, the dialkylphosphite/CCl_4/NEt_3-system was also used as the carboxyl activation reagents for the synthesis of a series of *N*-phosphoryl dipeptides, *Z*-protected dipeptides and the *N*-phosphoryl tripeptides.[2] The system: dialkylphosphite/CCl_4/NEt_3 also could be used for the synthesis of trialkylphosphates and dialkylphosphoryl chloridate. In the literature,[12] the *N*-selective phosphorylation by organophosphorus chloride was reported. In the present paper, we would like to report the selective phosphorylation of amino and hydroxyl groups by the dialkylphosphite/CCl_4/NEt_3-system. The relative reactivities of these groups were studied by tracing the reaction in different systems with ^{31}P-NMR (Tables I–IV).

RESULTS AND DISCUSSION

A. The Reaction of Dialkylphosphites with Carbon Tetrachloride and Triethylamine at 25°C (Table I)

When one eq. of dialkylphosphite was dissolved in a mixture of CCl_4, NEt_3 and $CHCl_3$, its ^{31}P-NMR spectra was checked at several intervals. It was found that

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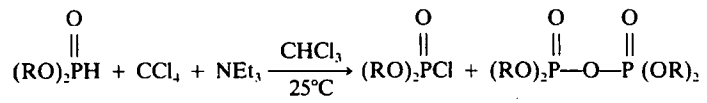
TABLE I

^{31}P-NMR tracing of the reaction of $(RO)_2P(O)H$, CCl_4, NEt_3

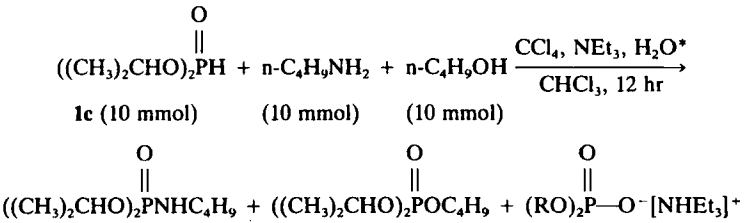


1, a, b, c **2, a, b, c** **3, a, b, c**

R	**1** δ ppm	**2** δ ppm(%)	**3** δ ppm(%)	Consuming time
a CH_3	10.5 (20%)	7.5 (50%)	5.4 ~ −26.0 (30%)	12 min
b CH_3CH_2	7.5 (13%)	4.5 (87%)		30 min
c $(CH_3)_2CH$	4.2 (60)	1.0 (35%)	−15.2 (0%)	1.5 hr

TABLE II

Temperature effect on the phosphorylation of amine and alcohol



1c (10 mmol) (10 mmol) (10 mmol)

4c **5c** **6c**

Reaction temperature	**4c** δ ppm(%)	**5c** δ ppm(%)	**6c**[d] δ ppm(%)	Side product δ ppm(%)
0°C	7.3 (95%)	/ (0%)	−1.7 (0%)	[a]
25°C	7.3 (88%)	/ (0%)	−1.7 (3%)	8.2 (9%)[b]
50°C	7.3 (67%)	/ (0%)	−1.7 (5%)	−15.2 (5%)[c] 8.2 (18%)[b]

[a]Still 5% reactant **1c** left.
[b]An unknown compound.
[c]Pyrophosphate ester.
[d]Compound **6** comes from the trace moisture in the system and the environment.

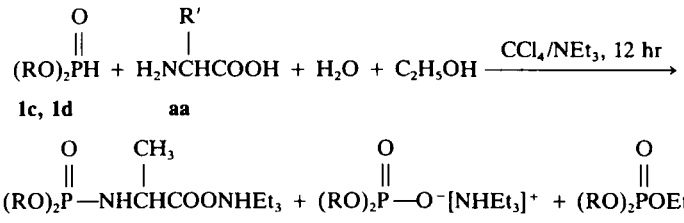
DMPH (**1a**) was the most reactive among the three compounds (**1a**–**1c**). The main product was $(RO)_2P(O)Cl$. (**2a**) formed very quickly and was easily converted into polyphosphate.

B. Selective Phosphorylation of Amine and Alcohol at Different Temperatures by the System: Diisopropylphosphite **1c**/CCl_4/NEt_3 *(Table II)*

When one eq. of *n*-butanol and one eq. of *n*-butylamine were reacted in a mixture of DIPP-H (**1c**), CCl_4 and triethylamine at 0°C (20°C or 50°C) for 12 hrs, its ^{31}P-NMR spectra were taken (Table II). It was found that for all three temperatures in general the amine was phosphorylated first. At 0°C it was the cleanest reaction with no oxygen phosphorylation at all. When the temperature was raised to 50°C,

TABLE III

Selective phosphorylation of amine, water and ethanol by dialkyl phosphites

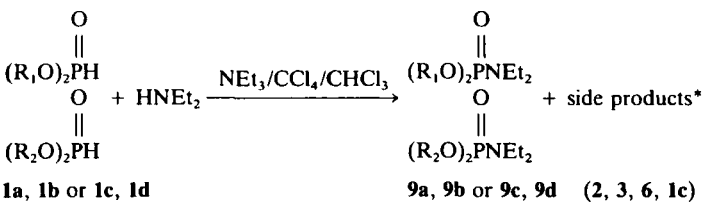


	R	Amino acid	7 δ ppm	7 yield	6 δ ppm	6 yield	8 δ ppm	8 yield
1c	i-Pr	Ala	6.6	(92%)	−1.7	(8%)	/	(0%)
1c	i-Pr	Ser	7.0	(97%)	−1.7	(3%)	/	/
1c	i-Pr	Cys	6.9	(90%)	−1.7	(10%)	/	/
1d	*n*-Bu	Ala	8.9	(83%)	0.1	(17%)	/	(0%)
1d	*n*-Bu	Ala	9.0	(70%)	0.1	(30%)	/	(0%)*

* When there was no ethanol in the system, the yield of (**7d**) decreased.

TABLE IV

The competitive reactions between different dialkylphosphites



System		Reactant	δ ppm		Product δ ppm	Product Yield
1.	**1a**	DMPH	10.1	**9a**	12.8	57%
	1b	DEPH	6.5	**9b**	10.2	43%
2.	**1c**	DIPPH	4.2	**9c**	8.2	24%
	1d	DBPH	7.6	**9d**	10.4	76%

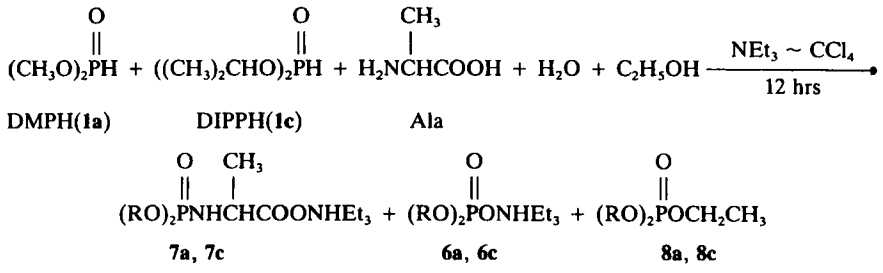
the reaction mixture easily reacted with water from trace moisture in the system and the environment. There was 5% hydrolysis product together with some side product. The selectivity decreased with increasing temperatures 0°C > R.T. > 50°C.

C. *Selective Phosphorylation of Amino Acid, Water, Ethanol by the Systems: Dialkylphosphites/CCl_4/NEt_3 (Table III)*

Similarly, when one eq. of dialkylphosphite (**1c**) or (**1d**)/CCl_4/NET_3 was added to an aqueous media containing one eq. of amino acid and excess ethanol, the ^{31}P-NMR tracing experiments showed that only the amino acids were *N*-phosphorylated. DIPPH (**1c**) was the cleaner reagent because only 3 ~ 10% hydrolysis

TABLE V

Comprehensive study of phosphorylation selectivity by dialkyl phosphite.



	By **1a**	By **1c**
N-phosphorylation	**7a** (81%) (12.3, 11.0 ppm)	**7c** (26%) (7.4, 6.8 ppm)
O-phosphorylation	**8a** (2%) (1.8 ppm)	**8c** (11%) (−2.3 ppm)
Hydrolysis	**6a** (17%) (2.9 ppm)	**6c** (63%) (−0.8 ppm)

occurred in the system. When alanine was replaced by serine or cysteine the same results were obtained, in spite of the presence of —OH, —SH, —COOH groups respectively. This indicates that —OH, —SH, —COOH in the amino acids were not easily phosphorylated.

D. The Competitive Reactions between Different Dialkylphosphites (Table IV)

In Section A it was shown that the DMPH (**1a**) was converted into the phosphoryl chloridate (**2a**) much faster than DEPH (**1b**). But in Table IV is shown that in the competition reaction of molar amounts of DMPH (**1a**), DEPH (**1b**) and diethylamine in the presence of CCl_4/NEt_3 give the products **9a/9b** in the ratio 57%/43%. In the analogous system 2 the DIPPH (**1c**) was less reactive than the DBPH (**1d**) to give **9c/9d** in the ratio of 24/76. The greater steric hindrance in (**1c**) than (**1d**) could be responsible (see Table IV).

E. Comprehensive Study of Competition and Selectivity for the N-Phosphorylation of Amino Acids (Table V)

When one eq. of DMPH (**1a**), and one eq. of DIPPH (**1c**) was mixed with one eq. of alanine in the $CCl_4/NEt_3/H_2O$/EtOH-system, it was found that the DMPH (**1a**) had a better *N*-phosphorylation selectivity (**7a**: 79%) in comparison to the *O*-phosphorylation (**8a**: 3%). Also, the hydrolysis (**6c**: 63%) of **1c** is easier than that of **1a**. A greater amount of **6c** was hydrolized (**6c**: 63%) than of **1a** (**6a**: 17%). It seems that the competitive phosphorylation between water and ethanol is dependent on the steric hindrance around the phosphoryl group. Therefore, the order of the phosphorylation tendency by **1a** and **1c** is as follows:

1a and **1c**: $—NH_2 > H_2O > EtOH$

In conclusion, in the alcoholic aqueous media in the presence of hydroxyl (serine) or thiol (cysteine) groups, the amino groups in amino acids were first *N*-phosphorylated by the diisopropyl phosphite/CCl_4/NEt_3-system at 0°C.

EXPERIMENTAL

Experiment 1: The Reaction of Dialkylphosphite with CCl_4 and Et_3N

A mixture of dialkylphosphite (10 mmol) and carbon tetrachloride (2 ml) was added dropwise to a solution of triethylamine (2 ml) and trichloromethane (2 ml) and stirred at 22°C. Immediately the sample was investigated by ^{31}P-NMR. The compounds **2a**, **2b** and **2c** were obtained from the reaction system directly with vacuum distillation. **2c**: bp 68 ~ 69°C/4 ~ 5 mmHg yield 82%. ^{1}H NMR: 1.3 ~ 1.5 (d, 12H); 4.3 ~ 5.1 (m, 2H); ^{31}P-NMR: 1.0 ppm ($CDCl_3$). **3c**: ^{13}C-NMR: 73.7 (2.9), 73.6 (3.0), 23.0 (3.0), 22.9 (2.9); ^{1}H NMR: 1.3 ~ 1.5 (d, 2H); 4.4 ~ 5.4 (w, 4H); ^{31}P-NMR: −15.2 ppm; (*p*-FAB-MS: 346 (30), 304 (15), 262 (20), 220 (40), 178 (100), 183 (4), 99 (100).

Experiment 2: Temperature Effect

The carbon tetrachloride solution (5 ml) containing 10 mmol DIPPH (**1c**) was added dropwise to a solution of 50 ml trichloromethane, 10 ml triethylamine, 10 mmol *n*-butanol and 10 mmol *n*-butylamine within 30 min. The mixture was stirred at 0°C (20°C or 50°C), respectively for 12 h, then checked by ^{31}P-NMR (Table II). Compounds **4c** and **5c** were made according to Todd's method.[13] **4c**: ^{1}H NMR 0.8 ~ 0.95 (t, 3H); 1.2 ~ 1.4 (m, 14H); 1.4 ~ 1.5 (m, 2H); 2.6 ~ 2.7 (w, N—H); 2.8 ~ 2.9 (t, 2H); 4.6 ~ 4.7 (m, 2H); ^{31}P-NMR: 7.5 ppm; (p)-FAB-MS ($M^+ + 1$); 238 (100), 196 (20), 98 (90), 141 (40); **6c**: ^{1}H NMR: 1.3 ~ 1.4 (m, 21H); 4.5 ~ 4.7 (m, 6H); 4.7 ~ 4.8 (m, 2H); 7.5 (w, ^{1}H); ^{31}P-NMR: −1.7 ppm (H_2O/EtOH/NEt_3).

Experiment 3: Selective Phosphorylation of Amino Acid

Alanine or serine (10 mmol) was dissolved in water (5 ml), ethanol (5 ml) and triethylamine (10 ml) and the solution was cooled in an ice bath. To this solution was added dialkylphosphite (10 mmol) in carbon tetrachloride (5 ml) within 30 min. Then the solution was stirred for 2 h–3 h in an ice bath and then at room temperature for 9 h–10 h. In order to transform the two phase system into a one phase system, ethanol (0.2 ml) was added and then the ^{31}P-NMR taken (Table III). Compounds **7c** and **7d** were prepared according to the literature.[1] DIPP-AlaOH: ^{1}H NMR: 1.2 ~ 1.5 (m, 15H); 3.4 ~ 4.2 (m, 1H); 4.3 ~ 4.9 (w, 3H); 12.1 ~ 12.5 (w, 1H); ^{31}P-NMR: 5.5 ppm; ^{13}C NMR: 176.1 (10.9), 49.7, 21.0 (2.4); 23.9 (t) (4.8, 4.3), 71.6 (t) (5.4, 5.3); DIPP-SerOH: ^{1}H NMR: 1.2 ~ 1.4 (d, 12H); 1.8 ~ 1.4 (w, 12H); 3.0 ~ 3.5 (w, 2h); 4.1 ~ 5.1 (m, 4H); 7.5 ~ 7.9 (w, 2H); ^{31}P-NMR: 5.7 ppm; ^{13}C NMR: 173.1 (5.9), 55.5, 63.3 (5.9), 22.4 (7.5); 69.6 (5.1); DBP-AlaOH: ^{1}H NMR: 0.8 ~ 1.2 (t, 6H); 1.2 ~ 2.0 (w, 11H); 3.4 ~ 4.2 (w, 7H); ^{31}P-NMR: 7.6 ppm; ^{13}C NMR: 175.8 (4.8), 49.5, 20.6, 65.8 (5.9), 31.7 (5.3), 18.2, 13; **8c**: ^{1}H NMR: 1.1 ~ 1.4 (m, 15H); 3.7 ~ 4.3 (m, 2H); 4.2 ~ 4.8 (m, 2H); ^{31}P-NMR; −2.8 ppm.

Experiment 4: Competitive Reactions between Different Dialkylphosphites

To a solution of diethylamine (10 ml), triethylamine (10 ml), trichloromethane (50 ml) were added the same molar amount of $(R_1O)_2P(O)H$ (10 mmol) $(R_2O)_2P(O)H$ (10 mmol) and carbontetrachloride (5 ml). After the workup as in Experiment 3, the ^{31}P-NMR, were taken (Table IV). **9c**: ^{13}C NMR: 69.5 (6.3), 23.4 (4.6), 38.8 (4.2), 13.4 (2.5); ^{31}P-NMR: 8.3 ppm.

Experiment 5: Comprehensive Study

Alanine (10 mmol) was dissolved in water (5 ml), ethanol (5 ml) and triethylamine (10 ml) and the solution was cooled in an ice bath. To this solution DMPH (**1a**) (10 mmol) and DIPPH (**1c**) (10 mmol) in carbon tetrachloride (5 ml) were added within 30 min. Then the solution was stirred for 2 h–3 h in an ice bath, then at room temperature for 9 h–10 h. In order to get homogenous phase, ethanol was added to the sample. The final sample was checked by ^{31}P-NMR (Table V). The compounds **6a**, **6c**, **8a** and **8c** were identified by comparison with authentical samples.

ACKNOWLEDGEMENT

This work was supported by the Chinese National Science Fund.

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