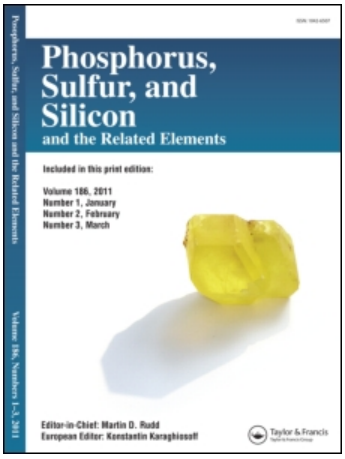

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NUCLEOPHILIC ASSISTANCE IN THE FORMATION OF PYROPHOSPHONATE: EFFECTIVE SIDE-REACTION OF HALOGENOPHOSPHORUS COMPOUNDS WITH WATER IN APROTIC SOLVENTS

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NUCLEOPHILIC ASSISTANCE IN THE FORMATION OF PYROPHOSPHONATE: EFFECTIVE SIDE-REACTION OF HALOGENOPHOSPHORUS COMPOUNDS WITH WATER IN APROTIC SOLVENTS

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Aside from racemization and direct solvolysis of halogenophosphonates, nucleophilic assistance by dimethylformamide, hexamethylphosphotriamide, N-methylimidazole, pyridine or triethylphosphite in wet solvents brings about P—O—P bond formation.

The nucleophiles are not directly involved in the chemical reaction. The oxygen atom originates from H_2O. The reaction does not nevertheless take place via consecutive coupling reaction between preliminary formed phosphonic acid and a second molecule of phosphonic chloride. As proposed in the case of activated racemization and hydrolysis of halogenophosphonates, the mechanistic pathway envisaged involves nucleophilic assistance to dimerization, prior to hydrolysis.

In the course of the dynamic stereochemical study of alkyl chloro phenylphosphonates or alkyl chloro phenylthiophosphonates in the presence of nucleophilic agents (dimethylformamide (DMF), hexamethylphosphotriamide (HMPT), N-methylimidazole (NMI), pyridine or triethylphosphite), we have mentioned secondary reactions giving variable amounts of oxo (or thio) pyrophosphonic esters, with P—O—P linkages.[1]

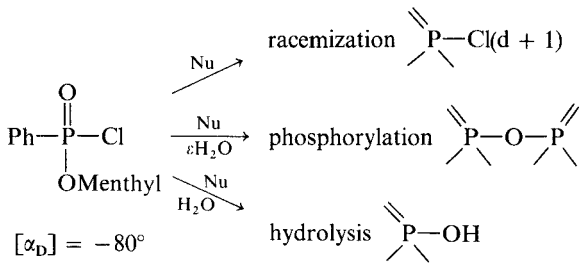
Ester formation, although unimportant in the direct hydrolysis, can dominate in nucleophilic catalysed racemization performed in wet solvents.

In the present note, we describe quantitative and stereochemical experiments designed to elucidate the formation of such compounds.

RESULTS AND DISCUSSION

Careful examination of ^{31}P nmr spectroscopy showed the formation of the title compounds whatever the nucleophiles DMF, DMA, HMPT, C_5H_5N, $(EtO)_3P$, NMI. Since nucleophiles containing no oxygen atom react similarly to oxygen containing nucleophiles, any chemical reaction of the oxygenated activating agents can be excluded. The oxygen atom of the P—O—P linkage does not originate from DMF or HMPT. The source of this oxygen can be assumed to be residual water in organic solvents.[2]

In order to test this hypothesis, increasing percentages of water were added to methyl-chlorophenylphosphonate in the presence of DMF or HMPT. At very low concentration of water (very carefully dried solvents and nucleophiles), only racemization was observed by ^{31}P nmr spectroscopy. With one added equivalent water, hydrolysis was preponderant, without formation of P—O—P linkage. At lower concentration of H_2O, racemization and phosphorylation† were competitive.



Secondly, racemization of (−)-ethyl-chlorophenylthiophosphonate **1** in $HMPT/CCl_4$, checked by polarimetry (Figure 1) showed the optical

† In the present note *phosphorylation* is used to express the formation of pyrophosphonic derivatives in contrast to hydrolysis which gives directly phosphonic acids.

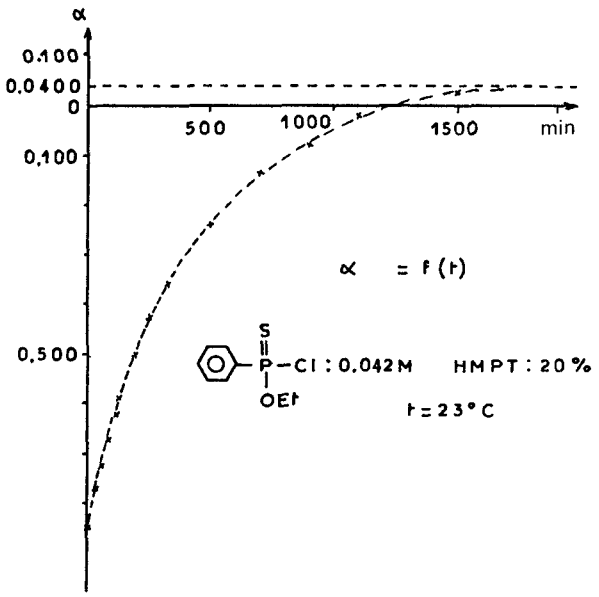
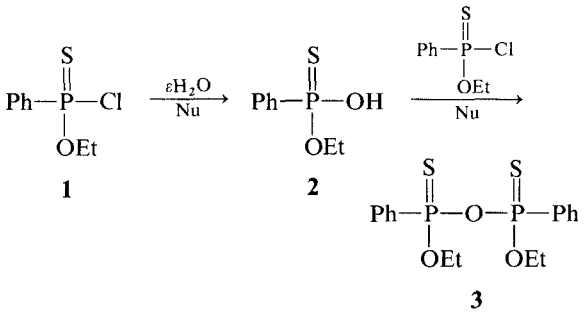


FIGURE 1

activity changing to positive value after 20 hrs in that medium.

Since the only other product detected by ^{31}P nmr is the sym pyrophosphonate, **3**, at least partial stereospecific conversion has to be considered.

The most reasonable pathway supposes preliminary formation of phosphonic acid, **2**, followed by fast coupling reaction[3] with **1** to give the sym-pyrophosphonic ester **3** (Scheme 1).



SCHEME 1

When stoechiometric amounts of **1** and **2** are mixed in DMF/CCl_4 with a low water content, the thiophosphonic acid is completely recovered after usual work-up (Table I (exp 1–3)). The P—OH compound is not involved in the formation of P—O—P linkage. The small amount of sym-pyrophosphonate **3** corresponds to the reaction of water on the chlorophosphonate. When more water is added (exp 3), partial direct hydrolysis of **1** is also detected.

A second experiment was performed in order to eliminate the hypothesis of P—OH as possible intermediate in the formation of P—O—P. When **2** is replaced by methyl-phenyl-thiophosphonic acid **4** and mixed with equivalent **1** in DMF/CCl_4, plus water, we do not observe any formation of the mixed pyrophosphonic derivative **5**. The only P—O—P type product is **3** (Scheme 2) corresponding to the transformation of **1**.[4]

Stereochemical investigations on **3** implied the formation of the two diastereoisomers (threo and meso) of known configuration.[5]

The sodium salt of the thiophosphonic acid, (−) **2**, reacts with inversion[5] on the chlorophosphonate, (−) **1**, of opposite configuration to give the (+) threo-pyrophosphonate as the major isomer. The two phosphorus atoms are inverted relative to (−) **1**. (Scheme 3).

The meso compound is obtained from the same sodium salt of (−) **2**, by addition of excess (+) **1**.

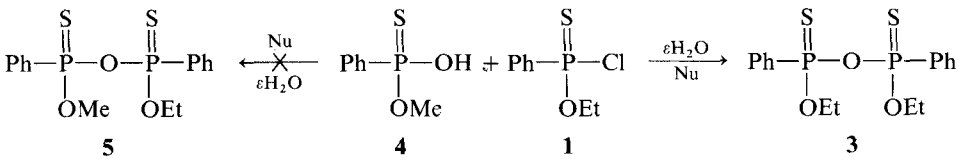
Proton nmr study of the DMF catalysed racemization of **1** showed the formation of threo-**3**, as major isomer (Scheme 4).

Formation of preponderant (+) threo-3 isomer from (−) **1** in HMPT (Figure 1) supposes that the configurations of the two P atoms have been inverted.

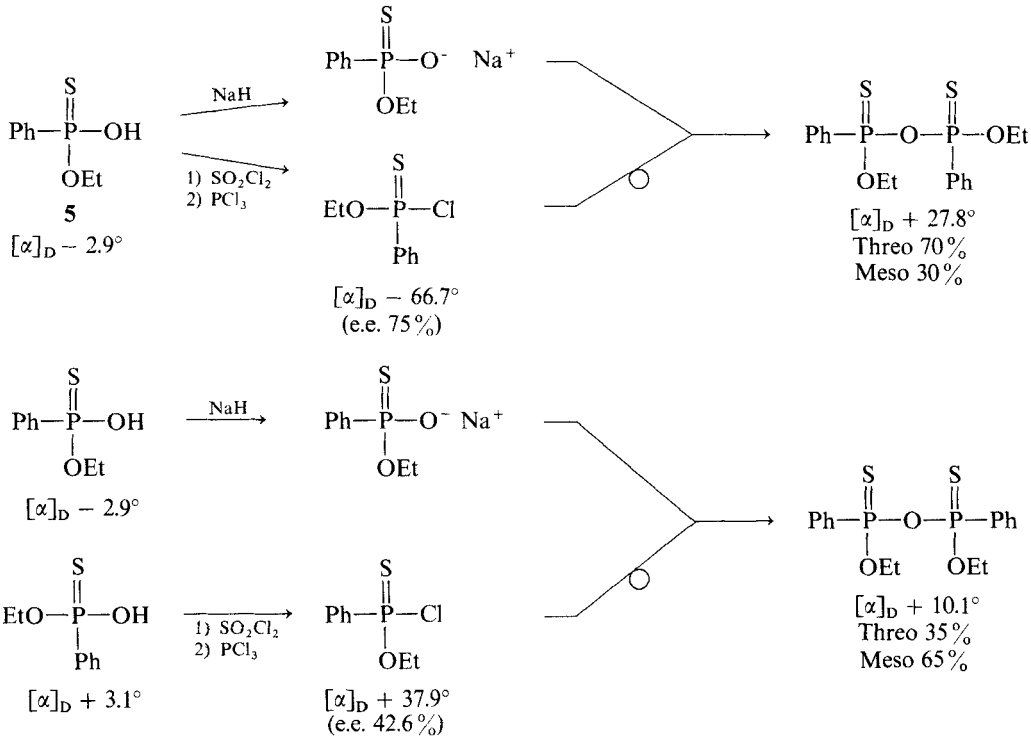
From these experimental data, we can conclude:

1) Phosphorylation involves participation of residual water.

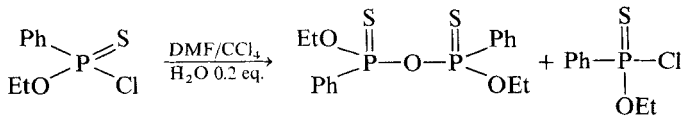
2) Phosphonic acid is excluded as intermediate in the formation of P—O—P linkage from the reaction between water and P—Cl compounds.



SCHEME 2



SCHEME 3

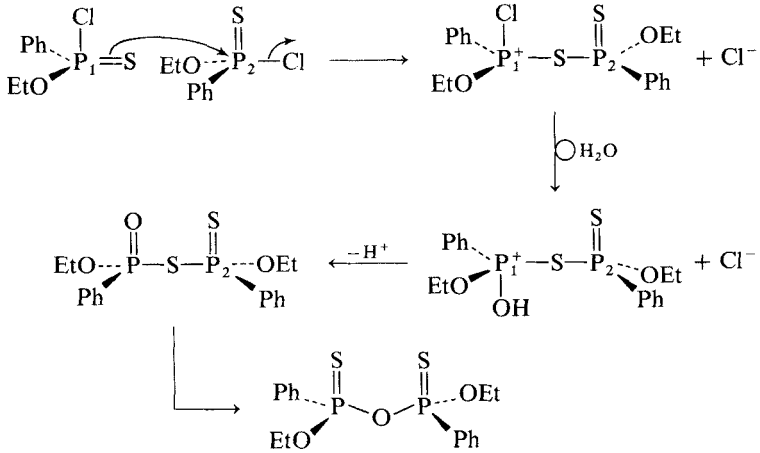


1 $[\alpha]_D$ + 37.9°
e.e. 42.6%

3 threo 12%
meso 8%

80%

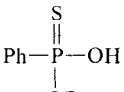
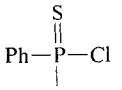
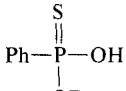
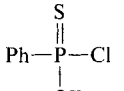
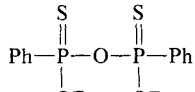
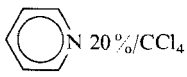
SCHEME 4



SCHEME 5

TABLE I

Reaction of phosphonic acid, **2**, with chlorophosphonate, **1**, in the presence of H_2O, with different nucleophiles

No.			Experimental			
1	0.435 g 2.15×10^{-3} mole	0.478 g 2.17×10^{-3} mole	DMF: 20%/CCl_4 $[H_2O] = 0.042 \times 10^{-3}$ mole reaction: 12 h	0.444 g 2.19×10^{-3} mole	90%	0.412 g 10%
2	0.360 g 1.78×10^{-3} mole	0.395 g 1.79×10^{-3} mole	DMF: 20%/CCl_4 $[H_2O] = 0.234 \times 10^{-3}$ mole reaction: 12 h	0.401 g 1.99×10^{-3} mole	90%	0.272 g 10%
3	0.447 g 2.21×10^{-3} mole	0.483 g 2.19×10^{-3} mole	DMF: 20%/CCl_4 $[H_2O] = 0.063 \times 10^{-3}$ mole HCl reaction: 7 h	0.461 g 2.28×10^{-3} mole	90%	0.308 g 10%
4	0.204 g 1.01×10^{-3} mole	0.230 g 1.04×10^{-3} mole	HMPT: 20%/CCl_4 reaction: 18 h	0.292 g (+ residual HMPT)	60%	0.208 g 40%
5	0.209 g 1.03×10^{-3} mole	0.233 g 1.06×10^{-3} mole	 N 20%/CCl_4 reaction: 18 h	0.208 g 1.03×10^{-3} mole	20%	0.221 g 80%

3) Stereochemical evidences suggest inversion of the two P atoms in the mechanistic pathway.

Nucleophilic substitution by phosphoryl oxygen atom on dialkylphosphorochloridate has been described by Simpson and Zwierzak.[3]

A similar reaction pathway is proposed in Scheme 5.

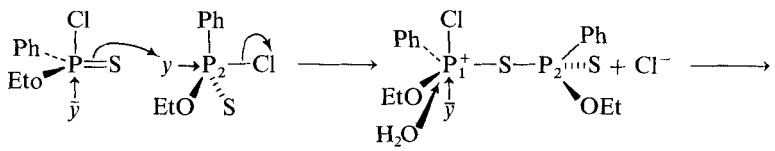
Nucleophilic attack of the thiophosphoryl center on the chlorophosphonate proceeds with inversion of configuration at P_2. Then, P_1 is inverted by hydrolysis of the labilized P_1—Cl bond. The last step corresponds to thermodynamic rearrangement[7] of the non-symmetric thiopyrophosphonate derivative with retention of configuration.[8]

In fact, kinetic and stereochemical evidences showed direct participation of nucleophiles in nucleophilic catalysed solvolysis and racemization of **1**.

Reasonably, a similar two-step process involving participation of the nucleophile has also to be envisaged here since the formation of P—O—P does not take place between P—Cl bond and H_2O in the absence of nucleophile (Scheme 6).

For the sake of clarity, all pentacoordinate P(5) geometries are not represented. Stereochemical conclusions are similar to those found for the P(4) species. The two substitution steps proceed with inversion at P_1, P_2.

By analogy with the activated hydrolysis of **1**, we can admit that, initially, the formation of the pyrophosphonate is highly stereoselective. But since formation of **3** and racemization of **1** are competitive, we cannot avoid formation of the meso compound, as experimentally characterized.



$\bar{y}$ ~ nucleophile

SCHEME 6

CONCLUSION

The very efficient activation of chlorophosphono compounds by added nucleophiles allows these products to react stereospecifically with residual water in organic solvents to give sym-pyrophosphonates. That reaction which has not been hitherto recognized is characteristic of nucleophilic catalysed substitution at phosphorus. The activating agent is not directly involved in the chemical reaction: its participation only consists of nucleophilic assistance to nucleophilic substitution. On the other hand, the present data eliminate the possibility of the hydrolysis product as intermediate in the formation of P—O—P linkage.

Seen as a whole, the general phenomenon may be summarized.

$$\text{Nu} + \text{dry solvent} \longrightarrow \text{racemization} + \varepsilon\ \text{P—O—P}$$

$$\text{Nu} + \text{aqueous solvent} \longrightarrow \text{hydrolysis (P—OH)}$$

$$\text{Nu} + \text{solvent} + \varepsilon\ \text{water} \longrightarrow \varepsilon\ \text{racemization} + \text{P—O—P} + \varepsilon\ \text{POH}$$

The three processes are competitive; three involve initial coordination of the nucleophile at phosphorus.

EXPERIMENTAL

Materials

The following compounds have been prepared according to described procedures (1) (6) (9): menthyl-chloro-phenyl-phosphonate ($\delta\ 31_P$ + 26, + 26.8 ppm); menthyl-phenyl-phosphonic acid, ($\delta\ 31_P \simeq +16.8$ ppm); dimethyl-phenyl-pyrophosphonate ($\delta\ 31_P$ + 7.4 ppm); O-ethyl-chloro-phenyl-thiophosphonate ($\delta\ 31_P$ + 86.4); O-Odiethyl-diphenyl-dithiopyrophosphonate ($\delta\ 31_P \simeq +75$ ppm); O-ethyl-phenyl-thiophosphonic acid ($\delta\ 31_P$ + 79.7 ppm) O-methyl-phenyl-thiophosphonic acid ($\delta\ 31_P$ + 81.3 ppm); O-ethyl-chloro-phenyl-phosphonate ($\delta\ 31_P$ + 26.8 ppm); O - ethyl - phenyl - phosphonic acid ($\delta\ 31_P$ + 16.8 ppm), O,O-diethyl-diphenyl-pyrophosphonate ($\delta\ 31_P$ + 8.6 ppm).

Techniques used for quantitative determinations by proton or phosphorus nmr spectroscopy have been previously described (1).

Reaction of O-ethyl-phenyl-thiophosphonic acid **2** *with* **1**, *in the presence of nucleophiles.* In a typical experiment, 0.468 g (2.17 mmole) of O-ethyl-chloro-phenyl-thiophosphonate and 0.435 g (2.15 mmole) of O-ethyl-phenyl-thiophosphonic acid are mixed with 4 ml of dimethylformamide and 16 ml of CCl_4. The concentration of residual water in the 20% DMF/CCl_4 cosolvents is measured by titration with Karl Fischer's reagent with a Methrom E 408 A apparatus: $[H_2O] = 2.1 \times 10^{-3}$ M. After 12 hours, the mixture is washed with 50 ml of NaOH (0.5 N), and extracted with petroleum ether. The organic portion is dried with magnesium sulfate and concentrated **in vacuo** giving 0.412 g of viscous oil. The nmr proton spectrum corresponds to O,O-diethyl-diphenyl-dithio-pyrophosphonate and O-ethyl-chloro-phenyl-thio-phosphonate in the ratio 10/90 (by relative integration of different methyl groups). The basic aqueous medium is acidified with HCl and extracted with Et_2O; 0.444 g of O-ethyl-phenyl-thiophosphonic acid is isolated.

Similar experiments have been performed in the case of HMPT, or C_5H_5N (see Table I).

Reaction of O-methyl-phenyl-thiophosphonic acid with **1**, *plus DMF.*

To 0.445 g (2.017 mmoles) of O-ethyl-chloro-phenyl-thiophosphonate is added 0.383 g (2.036 mmoles) of O-methyl-phenyl-thiophosphonic acid in 20 ml of DMF-benzene (1/4). After treatment with NaOH, 0.39 g is obtained from the petroleum ether portion (O,O-diethyl-diphenyl-dithiopyrophosphonate and O-ethyl-chloro-phenyl-thiophosphonate 10/90). From the aqueous solution, 0.58 g of viscous oil is isolated after acidification, corresponding to DMF (46%), O-methyl-phenyl-thiophosphonic acid (40%) and O-ethyl-phenyl-thiophosphonic acid (14%).

Preparation of diastereoisomeric O-O-diethyl-diphenyl-dithiopyrophosphonate, **3**

The soldium salt is obtained from 3.07 g (0.0152 mole) of (−) O-ethyl-phenyl-phosphonic acid ($[\alpha]_D$ − 2.9°, CCl_4) in benzene (40 ml) and 0.0152 mole of NaH after 12 hours; yield 70%.

To 0.416g (1.8 mole) of sodium salt dissolved in 5 ml of freshly distilled acetonitrile is added dropwise 0.41 g (1.8 mmole) of (−) O-ethyl-chloro-phenyl-thiophosphonate, **1** ($[\alpha]_D$ − 66.7°, CCl_4). After 4 hours, the mixture is filtered, and the filtrate concentrated **in vacuo**: 0.687 g of threo (+) O,O-diethyl-diphenyl-dithiopyrophosphonate (yield 98%) ($[\alpha]_D$ + 27.8°, CCl_4). I.R. ν_{P-O-P} 920 cm^{-1} $\nu_{P=S}$ 800–650 cm^{-1}.

NMR ^1H − Methyle (threo) δ + 1.32 ppm J = 7.2 Hz (70%)
(meso) δ + 1.26 ppm J = 7.2 Hz (30%)

NMR ^{31}P threo + 74.7 ppm (67%, meso + 75.0 ppm (33%)

Mass spectrometry M^+ 386.

From the same sodium salt of (−) **2**, and 0.4 g of (+) **1** ($[\alpha]_D$ + 37.9°, CCl_4), the major isomer meso is characterized: $[\alpha]_D$ + 10.1°, CCl_4). IR idem characteristics.

NMR ^1H threo δ_{CH_3} + 1.32 (35%); meso δ_{CH_3} + 1.26 (65%)
^{31}P threo $\delta 31_P$ + 74.7 (37%); meso $\delta 31_P$ + 75.0 (63%).

$C_{16}H_{20}P_2O_3S_2$ Found: C, 50.14; H, 5.32; P, 15.13
Calcd.; C, 49.6; H, 5.23; P, 16.06.

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