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SILICON–PHOSPHORUS ANALOGIES

PARTICIPATION OF EXTERNAL NUCLEOPHILES TO ACTIVATED PROCESSES OF RACEMIZATION AND HYDROLYSIS OF CHLOROPHOSPHONO DERIVATIVES

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Abstract—Kinetic and stereochemical studies show nucleophilic assistance by dimethylformamide (DMF), dimethylacetamide (DMA), hexamethylphosphotriamide (HMPT) and N-methylimidazole (NMI) in racemization and solvolysis of menthylchloro(phenyl)phosphonate, **1a**, and O-ethylchloro(phenyl)thiophosphonate, **2**. Similar orders of nucleophilic reactivity (Nu = NMI ≫ HMPT > DMF > DMA), and identical rate-laws ($v_{rac} = k\,[M\text{–}Cl]\,[Nu]^2$ and $v_{H_2O} = k'\,[M\text{–}Cl]\,[H_2O]\,[Nu]$) are consistent with a common mechanism, governed by entropy (-60 u.e < $\Delta S^{\neq} < -40$ u.e). Analogies between reaction mechanisms at silicon and phosphorus are clearly evidenced. A two-step process, involving rate-determining attack on a pentacoordinate complex is discussed.

As part of a general comparison between the dynamic stereochemical behaviour of Si and P compounds, we have been interested by the possibility of nucleophilic assistance to nucleophilic substitutions at phosphorus.

Nucleophilic activated racemizations and solvolysis are characteristic reactions of halogeno compounds in group IV.[2,3] Kinetic data, eqn (1) for racemization and eqn (2) for hydrolysis, as well as activation parameters, $\Delta H^{\neq} \simeq 0$ and $\Delta S^{\neq} \simeq -50$ (see Table 1), agree with a two-step process, governed by entropy.

$$v^{Si}_{rac} = k^{Si}_{rac}[R_3SiCl][Nu]^2 \quad (1)$$

$$v^{Si}_{H_2O} = k'^{Si}_{H_2O}[R_3SiCl][H_2O][Nu] \quad (2)$$

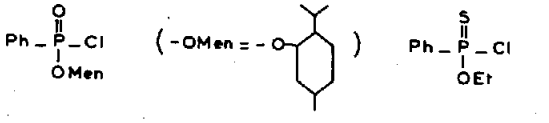
Nu = DMF, DMSO, HMPT.

For both explaining the racemization scheme and the retention of configuration at silicon observed in catalysed solvolysis, a common mechanism was proposed,[2,3b] involving coordination of the nucleophilic agent opposite to the halogen atom (Scheme 1), followed by front-side attack of a second solvent molecule or water in the rate-determining step.

In order to extend the analogies between silicon and phosphorus series, it appeared of interest to study racemization and hydrolysis of halogenophosphonates.[5]

Optical instability of halogenophosphorus compounds has been reported.[6] Phosphorylation of alcohols catalysed by nucleophilic agents has been also extensively studied.[7] Direct participation,[8] assisted solvolysis[9] or hexacoordinated species[10,14c] have been postulated, depending on reactants.

In the present paper, we report kinetic and stereochemical studies[4] of racemization and solvolysis of menthylchloro(phenyl)phosphonate **1**, and O-ethylchloro(phenyl)thiophosphonate **2**, in CCl_4 or benzene, catalysed by nucleophilic agents, DMF, DMA, HMPT or NMI.



1a, $[\alpha]_D - 80.4°$ (C. 1.16 in CCl_4) 2, $[\alpha]_D - 89°$

Kinetics

(a) *Racemization.*† In strictly anhydrous CCl_4 or benzene, **1a** and **2** are optically stable (*c*, 0.2M). Addition of nucleophilic agent slowly decreases the optical rotation value with time. The rate-law (eqn 3) determined at different concentrations of reactants (Experimental) is first-order in chloro-phosphonate and second-order in nucleophilic agent.

$$v^{P}_{rac} = k^{P}_{rac}\left[\rangle P(=O) - Cl\right][Nu]^2 \quad (3)$$

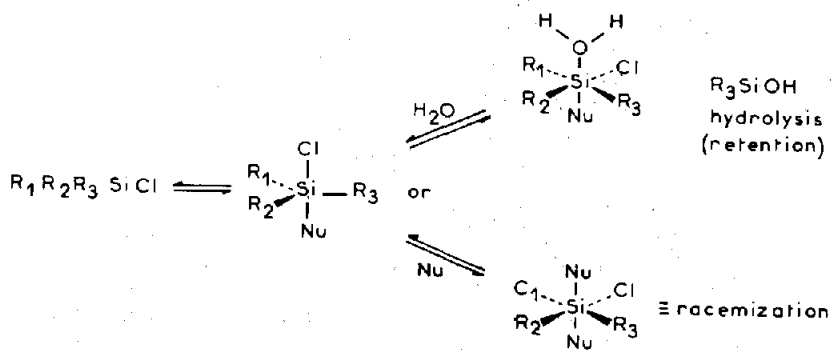
As an example, we have reported in Fig. 1 some results concerning the experimental rate-constant k_{exp} vs concentrations of the nucleophile and their square values.

$$v = k_{exp}[PCl] \text{ with } k_{exp} = k^{P}_{rac}[Nu]^n$$

Nucleophilic reactivity is in the order NMI ≫ HMPT > DMF > DMA. Activation parameters are characterized (Table 1) by large negative $\Delta S_P^{\neq}$ values, and $\Delta H_P^{\neq}$ terms higher than in the case of silicon ($0 < \Delta H^{\neq}_{Si} < 3$).

A kinetic evaluation of racemization of **1a** by means of proton decoupled ^{31}P Fourier transform NMR spectroscopy is also possible, since the signals of diastereoisomeric **1a**, **1b** are well-separated singlets ($\Delta\delta^{31}_P = 0.4$ ppm). Kinetic data obtained by NMR and

†In the case of **1a**, the term "racemization" is improper, since the reaction is an epimerization between two diastereoisomers with a final equilibrium 54/46, as shown by ^{31}P NMR spectroscopy. However, since we consider only the P atom, "racemization" will be held along these lines.



Scheme 1.

Table 1.

Reactant	Nucleophile	$k^{25°C}$ $mol^{-2}l^2s^{-1}$	$E_a^{\neq}$ kcal·mol^{-1}	$\Delta H^{\neq}$ kcal·mol^{-1}	$\Delta G^{\neq}$ kcal·mol^{-1}	$\Delta S^{\neq}$ cal·K^{-1}mol^{-1}
		Racemization				
MePhNpSiCl[2]	DMF	0.46×10^2	0	0	20.6	−70
PhNp(MenO)SiCl[2]	HMPT	1.2	0.98	0.39	17.3	−57
Ph(MenO)P(O)Cl	DMF	4.5×10^{-5}	10.4	9.8	23.3	−45
	DMA	1.8×10^{-5}	6.5	5.9	23.8	−60
	HMPT	7.6×10^{-4}	7.7	7.1	21.6	−49
Ph(EtO)P(S)Cl	HMPT	2.5×10^{-5}	4.8	4.2	23.7	−65
		Hydrolysis				
MePhNpSiCl[3]	DMF	$40^{(20°C)}$	—	2.6	—	−40
PhNp(MenO)SiCl[3]	HMPT	$220^{(20°C)}$	—	(−2.9)	—	−46
Ph(MenO)P(O)Cl	DMF	2.6×10^{-3}	7.3	6.7	21	−48
	DMA	1.6×10^{-3}	5.0	4.4	21	−56

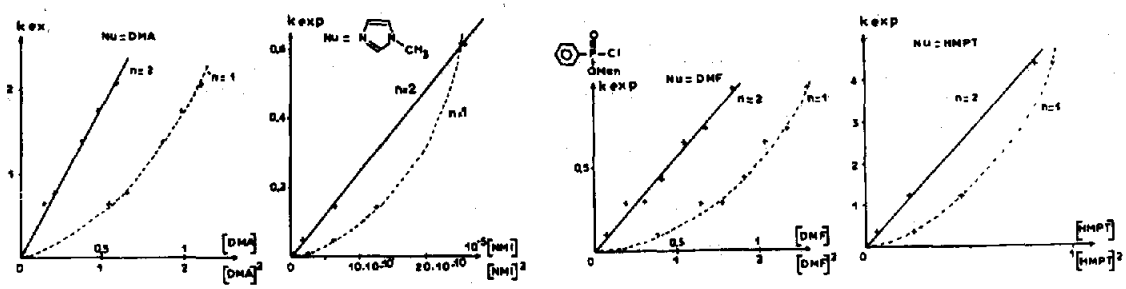


Fig. 1. $v = k_{exp}[PCl]$ with $k_{exp} = k^P_{nuc}[Nu]^n$

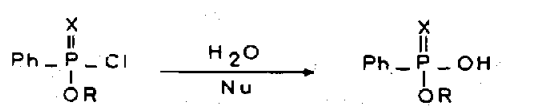
Table 2.

	[1a] mol·l^{-1}	k mol^{-2}l^2 mn^{-1} NMR ^{31}P	polarimetry
DMF/CCl_4 1.947M	0.199	2.6×10^{-3}	2.2×10^{-3}
DMA/CCl_4 1.614M	0.160	0.98×10^{-3}	1.0×10^{-3}

polarimetry are consistent (Table 2).

(b) *Hydrolysis.* Preliminary experiments showed that no reaction occurs between **1a** or **2** (10^{-2}M) and small amounts of water (10^{-3} to 10^{-1}M), in aprotic solvents. Addition of ten equivalents of DMF, DMA or HMPT initiates slow formation of phosphonic acids **3** and **4**.

In the case of **1a**, ^{31}P NMR data, which will be discussed hereafter, show that **1a** is not racemized during the hydrolysis process. Since **3** is achiral, the difference between the optical activity at a certain time and at the end of the reaction is a quantitative measurement of [**1a**]



1a X = O R = Men
2 X = S R = Et
3 X = O R = Men
4 X = S R = Et

not yet hydrolysed. The optical rotation value of 4 is sufficiently low compared with that of 2 to permit kinetic determinations by polarimetry (Experimental). The rate-law can be expressed by eqn (4).

$$v^{P}_{H_2O} = k^{P}_{H_2O}[R(R'O)\overset{\overset{O}{\|}}{P}Cl][H_2O][Nu] \qquad (4)$$

As for racemization, the order of nucleophilic reactivity found in the silicon serie applies to phosphorus (Table 3).

$$HMPT > DMF > DMA$$

Table 3. Rate-constants for hydrolysis of **1a**, at 23°C

Nu	k $mol^{-2}l^2s^{-1}$
DMA	1.45×10^{-3}
DMF	2.76×10^{-3}
HMPT	10.6×10^{-3}

Activation parameters have been determined (Table 1) in the case of **1a**. The catalysed hydrolysis process is characterized by a relatively low activation energy, combined with a large activation entropy, a remark which has been already mentioned for the racemization scheme.

As for racemization, activated hydrolysis of **1a** and **2** have been also followed by ^{31}P NMR. Kinetic results are in agreement with the values found by polarimetry (Table 4).

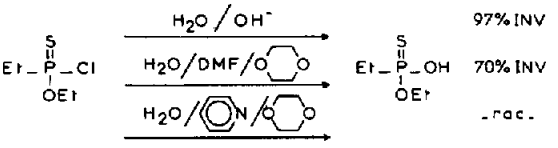
Two observations can be drawn from ^{31}P NMR data.

(1) The compound **1a** is not racemized by DMF, DMA or HMPT during the hydrolysis process. This is consistent with hydrolysis being faster than racemization by a factor 100.

(2) The hydrolysis is selective.† Phosphonic acids are obtained in good yield, whatever the nucleophile. As an example, the reaction of **2** with H_2O (5eq) in HMPT shows the unique formation of acid **4**.

Stereochemistry

Stereochemical changes in solvolysis of phosphonic chlorides catalysed by DMF, have been reported by Mikolajczyk.[9a]



(a) *Methanolysis of Menthyl-chloro(phenyl)phosphonate* **1a**. Stereochemistries are checked by ^{31}P NMR 82% inversion is obtained in methanolysis of **1a** in CCl_4, catalysed by DMF (5%), instead of 96% inversion in reaction without nucleophilic agent. As observed for hydrolysis of **1a**, the chlorophorphonate is not racemized along methanolysis. So, we have to conclude that the decrease of stereoselectivity is inherent in the catalytic process.

(b) *Hydrolysis of O-ethylchloro(phenyl)thiophosphonate* **2**. Catalysed hydrolysis of **2** in CCl_4 in the presence of DMF or HMPT are followed by polarimetry and quenched at various times. Optical purity of the starting material is determined by chemical correlation (Scheme 2) with the hypothesis that basic hydrolysis of **2** proceeds with 97% INV.[9a]

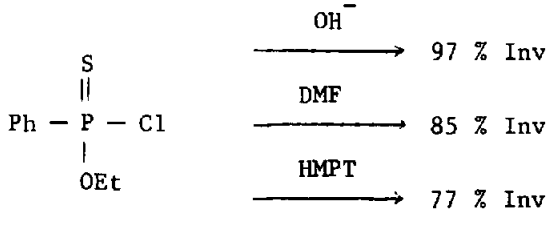


Table 4.

Ph(MenO)P(O)Cl	mol·l⁻¹ Nu	mol·l⁻¹ H_2O	Vomol l⁻¹mn⁻¹ NMR ^{31}P	Vomol l⁻¹mn⁻¹ polarimetry
	DMF			
0.02976	1.72	0.063	5.46×10^{-4}	5.72×10^{-4}
mol·l⁻¹	DMA			
	1.34	0.083	2.29×10^{-4}	2.48×10^{-4}

†Two side reactions have been characterized by ^{31}P NMR, with a degree not exceeding 15% yield.

When very low concentrations of water (≤1eq) were used relative to **1a** or **2**, menthylphenylpyrophosphonate **5**, and ethylphenyldithio-pyrophosphonate **6** were also characterized as minor reaction products. This aspect of side phosphorylation will be discussed in a forthcoming paper.[11]

Additional formation of ethyl(phenyl)phosphonic acid **7** (10% yield) in DMF catalysed hydrolysis of **2**, which gives normally ethylphenyl thiophosphonic acid **4** (90% yield), probably involves double-bonded oxygen-sulfur exchange in that medium.[12] That secondary reaction was not further studied.

The thioacid **4** is isolated as dicyclohexylammonium salt (DCHA). Results are presented in Table 5. The stereoselectivity is constant along the reaction process.

Moreover, in the case of DMF catalysed hydrolysis, we have been able to isolate residual starting chlorophosphonate. As observed in activated methanolysis of **1a**, the starting compound **2** is not racemized. Thus, stereoselectivities must be considered as characteristic data of catalysed reactions.

DISCUSSION

Catalysed hydrolysis and racemization of chloro-

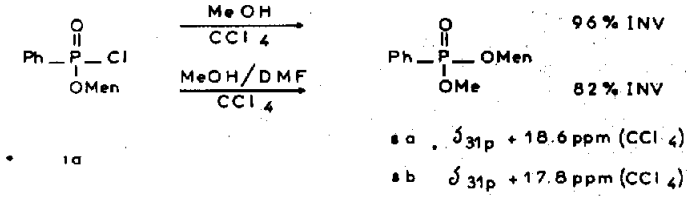
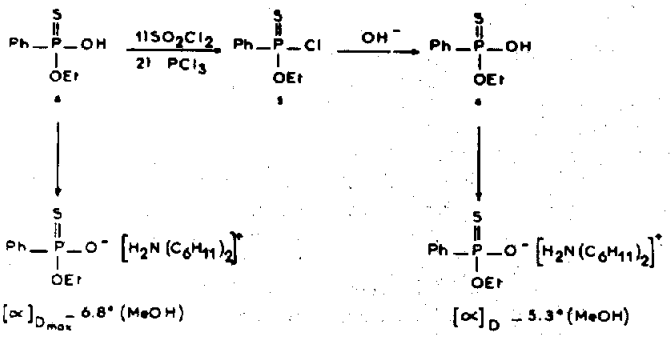


Table 5. DMF catalysed hydrolysis of 2

Nucleophile/ CCl_4	$[\alpha]_D(CCl_4)$ 2	t	$[\alpha]_D$(MeOH) DCHA	%INV
DMF	−73.8°	t1/2	−3.84	84.1
20%	(e.e83%)	t^∞	−3.94	84.9
HMPT	+62.3°	t1/2	+2.63	77.6
20%	(e.e70%)	t^∞	+2.54	76.7



Scheme 2.

phosphono compounds exhibit very great similarities with the rate-laws obtained at silicon.

$$\text{eqn (1)} \quad v^{Si}_{rac} = k^{Si}_{rac}[SiCl][Nu]^2$$

$$\text{eqn (3)} \quad v^{P}_{rac} = k^{P}_{rac}[PCl][Nu]^2$$

$$\text{eqn (2)} \quad v^{Si}_{H_2O} = k^{Si}_{H_2O}[SiCl][H_2O][Nu]$$

$$\text{eqn (4)} \quad v^{P}_{H_2O} = k^{P}_{H_2O}[PCl][H_2O][Nu].$$

Nucleophilic reactivity is in the same order DMA < DMF < HMPT. In both cases, the activation parameters are essentially characterized by highly negative activation entropic factors (Table 1). Only, the enthalpy factors are markedly different for Si and P ($\Delta H^{\neq}_{Si} \simeq 0$; $\Delta H^{\neq}_{P} \simeq 7$).

Furthermore, complete change of stereochemistry (retention instead of inversion) observed in the activated hydrolysis of chlorosilanes is not so evidenced in the case of halogenophosphorus derivatives, for which only a general decrease of stereoselectivity is observed.

These results and the dramatical changes of stereochemistry at silicon were interpreted in terms of nucleophilic assistance to nucleophilic substitution. Similar kinetic data on germanium and tin derivatives showed the generality of that phenomenon in the serie.[2,3] The present kinetic studies at phosphorus support the idea of possible analogies.

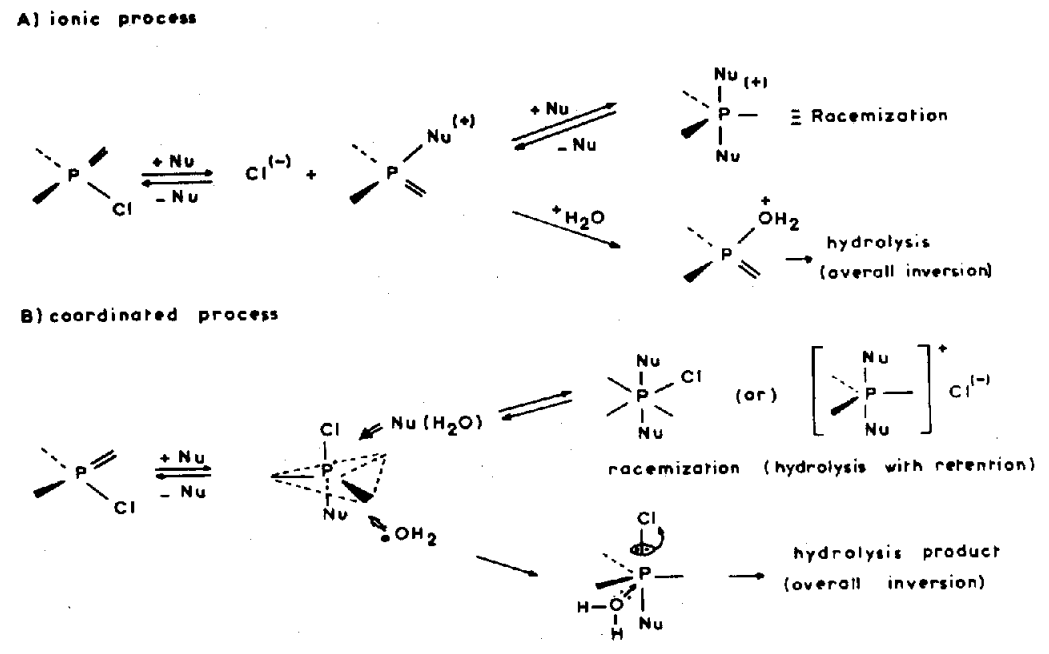
The mechanistic aspect of nucleophilic assistance to nucleophilic substitution at phosphorus is of particular interest. Indeed, activation processes of nucleophilic substitution at the four-coordinate P atom are well-documented,[7-10] and hexacoordinated species have been postulated as reaction intermediates.[10b,13,14]

Rate-laws and energetic data we have found are consistent with the participation of both nucleophile and water in the hydrolysis process. Moreover, on the basis of experimental results, we have to make the reasonable assumption of a similar mechanism for both explaining racemization and hydrolysis at phosphorus. Such hypothesis must be emphasized in the light of the forthcoming discussion.

Two processes can be reasonably invoked (a) a two-consecutive steps mechanism implying nucleophilic substitution by the nucleophile, followed by rate-determining nucleophilic attack on the positively charged leaving group (Scheme 3-A), or (b) an associative mechanism corresponding to nucleophilic assistance of the nucleophile to rate-determining attack on a penta-coordinate species (Scheme 3-B).

The two proposed mechanisms have to be consistent with the seterochemistries observed therein:

In the process A, invoking two consecutive substitutions at phosphorus, it is known that nucleophilic substitution on chlorophosphono compounds generally proceeds with inversion.[15] That means in the second step, nucleophilic attack of water has to proceed with



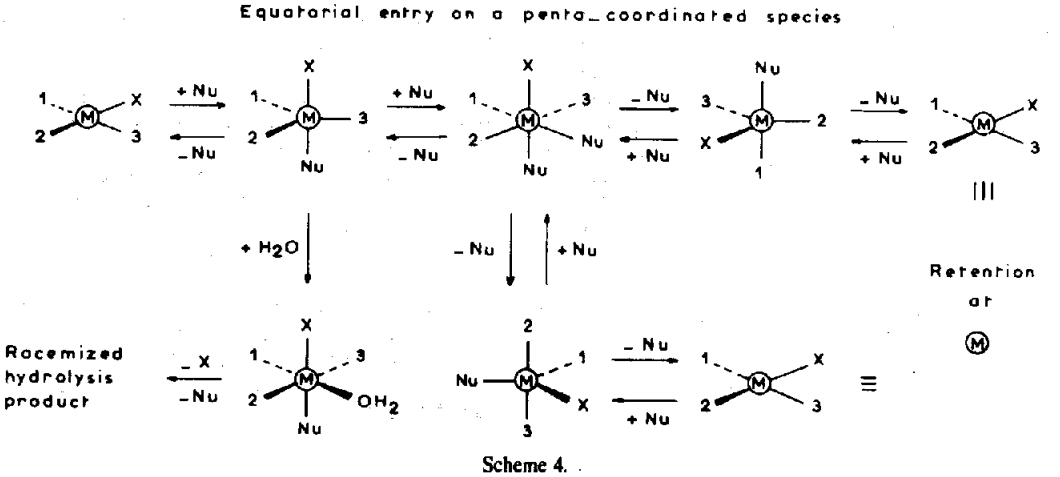
Scheme 3.

preponderant retention to give an overall inversion pathway. At the opposite, the racemization scheme necessarily implies displacement of the positively charged leaving group with inversion.†

In the process B, attack of the nucleophilic agent opposite to the halogen atom gives the more stable trigonal bipyramidal (tbp) intermediate. Rate-determining attack of the second nucleophilic molecule or water can proceed from both sides of the equatorial plane. Back-side attack of water relative to Cl gives the expected hydrolysis product with overall inversion. On the other hand, only front-side attack of water or Nu, relative to Cl, can both explain the low content of hydrolysis with retention or the racemization scheme.

Apart, little is known about the stereochemistry of the formation of octahedral hexacoordinate species from trigonal bipyramid (tbp), or their decomposition.[13] Hitherto, the generally accepted view supposes that attack of a nucleophile on a tbp proceeds in the equatorial plane to give three possible hexacoordinate geometries. However, the experimental results on Si and P compounds cannot be explained by such processes. For example, concerning the racemization scheme, formation and decomposition of hexacoordinate species (Scheme 4) give only retention of configuration of the four-coordinated molecule. The only way for explaining the observed racemization is an approach of the second solvent molecule out of the equatorial plane and opposite to the first coordinated nucleophile.[2a] Moreover, stereoselectivity noted in the nucleophilic activated solvolysis of chlorosilanes or chlorophosphonates is not in accord with a process involving equatorial attack on a

†Different stereochemistries for H_2O or Nu involved in the second step are not incompatible with the proposed common mechanism: racemization is only obtained if the second attack of Nu proceeds with inversion. The attack with retention leads to starting configuration, and cannot be accounted in the racemization process. In accord, hydrolysis is 100 times faster than racemization.



Scheme 4.

tbp. In the transient hexacoordinate species, the two leaving groups X and Nu are at the opposite relative to the plane defined by the other four ligands. Consecutive departure of Cl and Nu would lead to epimerized mixture.

Now, concerning the process (A), since a number of substitutions at phosphorus are known to proceed with retention[1,16] "stricto sensu", it is impossible to rule out such possibility of two consecutive substitutions at phosphorus from the only stereochemical considerations.

However, simple substitutions of chlorophosphono derivatives generally proceed with inversion at phosphorus.[15-17] And meantime, the displacement with retention of the positively charged leaving group appears also unlikely: as examples, chlorination by PCl_5[18] or acidic solvolysis of phosphonamidates[16b] show the positively charged leaving groups being always displaced with inversion in S_N2 processes.

Furthermore two types of experimental data can be argued against the ionic mechanism (A).

(1) *Conductivity method.* Determination of conductivity of **1** and **2** in presence of nucleophiles (HMPT, DMF, etc) showed the observed conductance lower than the value which could be due to HCl formed by hydrolysis with residual water in organic solvents.[19] No ionic species are evidenced, contrary to the mixture $OPCl_3$, HMPT, for example.

(2) *^{31}P NMR data.* ^{31}P NMR chemical shift values of **1** and **2** in CCl_4 or PhH, remain constant when nucleophilic agents HMPT, DMF or NMI are added. Displacement of the ^{31}P chemical shift had been argued in the case of $OPCl_3$, DMF.[20] The Vilsmeier-type ionic complex shifted of at least 9.5 ppm towards high field relative to $OPCl_3$, at similar concentration in the same solvent.

So, from conductivity and NMR data, no ionic species can be characterized.

Seen as a whole, such results afford little if any evidence in support of a two consecutive substitution process. Of themselves, they give us better confidence in our view that direct substitution on a preformed pentacoordinate complex or extension of coordination to give an hexacoordinate intermediate or transition state is more in accord with kinetic and stereochemical data. We can note than Ramirez *et al.* found that solvolysis of a number of cyclic phosphates derivatives catalysed by nucleophilic agents could be similarly rationalized if the reactions proceed through hexacoordinate species.[10]

CONCLUSION

The main future of the present work has been the comparison of nucleophilic substitution of chlorosilicon and chlorophosphorus compounds, activated by external nucleophiles, in non polar aprotic solvents. Similar rate-laws and activation parameters for racemization and hydrolysis at phosphorus emphasize the importance of coordinating properties of activating agents on the central atom.

EXPERIMENTAL

Reactions were carried out in Schlenk tubes under dry N_2. ^1H NMR spectra were recorded on a VARIAN EM 390 instrument, with TMS as internal reference; ^{31}P NMR spectra were measured at 40.295 MHz on a Fourier Transform JEOL JNM PS 100. Positive chemical shifts are downfield relative to external 85% H_3PO_4 diluted in D_2O (lock signal). IR spectra were obtained with a Perkin-Elmer 257.

Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Concentrations for specific rotations are given in g/100 ml M.ps are uncorrected. Mass spectra were recorded on a Jeol JMS D 100 mass spectrometer. Satisfactory analytical data were obtained for all new compounds.

Menthylchloro(phenyl)phosphonate, **1**. According to Aaron,[21] 10.02 g (0.0358 mole) of menthylphenylphosphinate,[22] $[\alpha]_D - 20.1°$, in 100 ml CCl_4, were added dropwise to 4.78 g (0.0358 mole) N-chlorosuccinimide with 100 ml CCl_4, at ambient temp. The mixture was then cooled to −15°, and filtered. The solvent was removed *in vacuo*, yielding 10.85 g (0.0345 mole) of menthylchloro(phenyl)phosphonate; $[\alpha]_D - 80.4°$: (c,1.16 in CCl_4). (CCl_4) NMR ^{31}P: **1a** $(S)_P + 26$ ppm; **1b**$(R)_P + 25.6$ ppm. (Found: C, 60.80; H, 7.61; P, 9.75; Cl, 10.82 $C_{16}H_{24}PO_2Cl$ requires: C, 61.05; H, 7.63; P, 9.85; Cl, 11.28%).

(−) Menthol (39.82 g), plus pyridine (20.86 ml) in 300 ml benzene were added dropwise to dichlorophenylphosphonate (49.78 g) in 200 ml benzene. The mixture was filtered and concentrated ($[\alpha]_D - 51.7°$, CCl_4 c, 1.5). Crystallization at −78° of a soln in n-hexane afforded 3.84 g of **1a** (yield 4.8%) ($[\alpha]_D - 79.8°$ CCl_4 c, 1.2).

Menthylphenylphosphonic acid, **3**. Menthyl-chloro(phenyl)-phosphonate (6.29 g) in 10 ml dioxane were hydrolysed with 200 ml 2N NaOH. The soln was washed with petroleum ether, acidified and extracted with ethyl ether. The organic layer was dried with $MgSO_4$, filtrated and concentrated. 4.44 g of **3** were isolated (yield 75%). After recystallization in ether, m.p. 88°, $\delta_{31P} + 16.8$ ppm. (Found: C, 64.46; H, 8.61; P, 10.22. $C_{16}H_{25}O_3$ requires: C, 64.48; H, 8.44; P, 10.47%).

To 1.77 mmoles of **3** were added 1.77 mmoles of dicyclohexylamine in 10 ml anhydrous ether; 1.72 mmoles of DCHA salt were isolated (yield 97%), m.p 219–220°. Mass spectrum *m/e* M^+477.

Dimenthylphenylpyrophosphonate. **5** was prepared[24b] from **3** by action of NaH in benzene, followed[18] by coupling reaction with **2**, in dimethoxyethane (yield 96%). Mass spectrum *m/e* M^+ 574; $\delta_{31P} = +7.4$ ppm; IR $\nu_{P=O}$ 1270 cm^{-1} ν_{P-O-P} 950 cm^{-1}.

O-*Ethylphenylthiophosphonic acid* **4**. As described,[24] **4** was optically resolved by crystallization of the (+) and (−) α-phenylethylammonium salts, according to the method recorded.[25] $[\alpha]_D - 6.3°$ (MeOH *c*, 1.0); m.p. 126° (PTE salt). After hydrolysis by 2N NaOH, the basic aqueous soln was washed with petroleum ether, acidified and extracted with ether. Concentration left a residue, **4**, $\delta_{31P} + 79.7$ ppm. Mass spectrum *m/e* M^+ 202. The thio acid was identified as DCHA salt. m.p. 146° (Found: C, 62.54; H, 8.93; P, 8.10; S, 8.04; N, 3.53 $C_{20}H_{34}O_2$ PSN requires: C, 62.66; H, 8.87; P, 8.09; S, 8.35; N, 3.65%).

O-*Ethylchloro(phenyl)thiophosphonate,* **2**

PCl_5 *method.* Initially, **2** had been obtained by the method of Michalski and Mikolajczyk.[26] To 0.03 mole PCl_5 in CCl_4 were added dropwise 0.03 mole of (−) **4** ($[\alpha]_D - 3.9°$), under N_2 at 0°. The mixture was warmed to 5–10° and the solvent removed *in vacuo*. After addition of 100 ml ether, the organic layer was washed with 0.5 N NaOH, dried and concentrated. 0.0158 mole of **2** were isolated (yield 53%); $[\alpha]_D - 67.7°$ (CCl_4 *c*, 1.2). Optical rotation of **2** was not constant in successive experiments.

SO_2Cl_2–PCl_3 *method.* Proposed by the same authors this gave better results.[27] 0.0193 mole SO_2Cl_2 in PhH were added to 0.0193 mole of (−) **4** $[\alpha]_D - 3.9°$ (CCl_4 *c*, 1.0), at 0°. PCl_3 (0.0193 mole) was added dropwise. After treatment, 2.97 g (0.0135 mole) of **2** were isolated, Yield 70%, $-[\alpha]_D - 79.2°$ (CCl_4 *c*, 0.80). In another experiment (+) **4**, $[\alpha]_D + 3.14°$ gave (+) **2**, $[\alpha]_D + 83.1°$. $\delta_{31P} + 86.4$ ppm (Found: C, 43.78; H, 4.6; Cl, 16.19; P, 13.90; $C_8H_{10}POClS$ requires: C, 43.8; H, 4.5; Cl, 16.1; P, 14.06%).

The following compounds have been prepared according to known procedures.[11,26] and identified by NMR ^1H, ^{31}P, IR spectra and mass spectroscopy. O–O-diethyldithiopyrophosphonate $\delta_{31P} + 74.7$ ppm (threo), $\delta_{31P} + 75.03$ ppm (meso); O-ethylphenylphosphonic acid $\delta_{31P} + 16.8$ ppm; diethylphenylpyrophosphonate $\delta_{31P} + 8.6$ ppm.

Basic hydrolysis of O-*ethylchloro(phenyl)thiophosphonate.* To 5.05 g (0.0229 mole) of **2**, $[\alpha]_D - 73.8°$ (CCl_4, *c*, 0.97), in 5 ml dioxane were added 20 ml of 3N NaOH, at room temp. The mixture was twice washed with petroleum ether, and the aqueous

phase was acidified by HCl. Extractions by ether left an organic phase, which was dried with $MgSO_4$ and concentrated, 4.59 g (0.0227 mole) of **4** were isolated. 0.0227 mole of dicyclohexylamine in 10 ml anhydrous ether were added, precipitating 5.67 g (0.0148 mole) dicyclohexylammonium salt (DCHA) of **4**; m.p.: 141–142° $[\alpha]_D$ − 5.3° (MeOH *c*. 0.99) (yield 65%).

DMF catalysed hydrolysis of **2**. 1.458 g (0.0066 mole) of **2**, $[\alpha]_D$ − 73.8°, were diluted in a wet mixture DMF-CCl_4 (1/4) containing 0.0139 mole water. The reaction course was polarimetrically checked. At time corresponding to $\alpha/4$, 25 ml of the mixture was quenched, and hydrolysed in basic medium. The aqueous phase was extracted with petroleum ether, and the organic portions dried with $MgSO_4$ and concentrated *in vacuo*. 0.64 g of **2** were isolated $[\alpha]_D$ − 74.1° (CCl_4 *c*, 1.01). The aqueous phase was acidified to give 0.21 g of **4**.

A second aliquot of 12.5 ml, quenched at $\alpha/2$, was treated as previously to give the mixture of 0.25 g of **2**, $[\alpha]_D$ − 67.8°, plus 10% of diethylphenylpyrophosphonate, identified by ^{31}P NMR spectroscopy. From the aqueous acidic phase, 0.16 g of **4** were isolated, giving 0.21 g of DCHA salt $[\alpha]_D$ − 3.84°.

After 24 h, 12 ml were hydrolysed and the basic aqueous phase three times washed with petroleum ether giving 0.15 g of diethylphenylpyrophosphonate, δ_{31P} + 8.6 ppm. From the acidic phase, 0.251 g of **4** were extracted and isolated as DCHA salt $[\alpha]_D$ − 3.94° (MeOH *c*, 1.1); m.p. 140–142°.

HMPT catalysed hydrolysis of **2**. The same procedure was followed, starting from 1.011 g (0.00456 mole) of **2** $[\alpha]_D$ + 62.35° (CCl_4 *c*, 1.08), and 50 ml of HMPT-CCl_4 (1/4 v.v) containing 0.25 ml water. At half-reaction, 25 ml were quenched and hydrolysed by 0.5N NaOH. The aqueous phase was washed with petroleum ether, acidified and extracted with ether. 0.38 g (0.00188 mole) of **4** was isolated as DCHA salt $[\alpha]_D$ + 2.63° (MeOH *c*, 0.9) m.p.: 139–142°. At the end point (t = 24 h), the thio-acid salt had a specific rotation $[\alpha]_D$ + 2.54° (MeOH *c*, 1.1), m.p. 140–142°.

Solvents for rate measurements. All were purified just prior to use. CCl_4 was distilled from P_2O_5; HMPT was first treated with Na and then redistilled over CaH; DMF "Baker Instra Analyzed, G. C. Spectrophotometric Quality" and dimethylacetamid "Fluka A. G. Purissimum" were distilled from P_2O_5, under reduced pressure. N-Methylimidazole "purum" was purchased from Fluka, and distilled. Concentrations in water were measured by titration with Karl Fischer's reagent with a Methrom E 408 A apparatus.

Kinetics

Polarimetry. Optical rotations were measured at 589 nm in thermostat cells. Mixtures of solvent + nucleophile + water, were added at once on chlorophosphorus compounds at time t_0.

Racemizations. Partial order in chlorophosphonate was

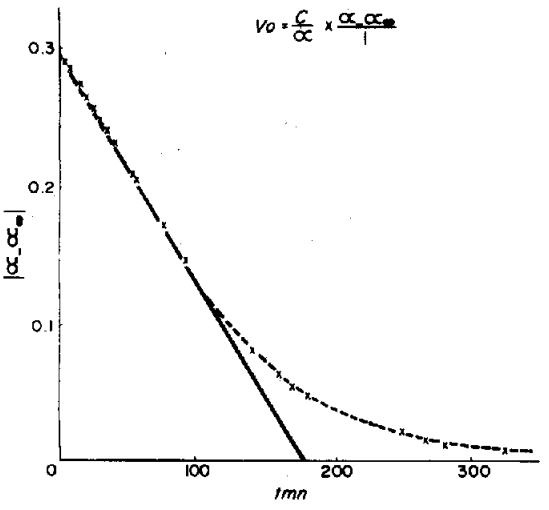


Fig. 2. V_0, initial rate constant for racemization of **1a** (0.03 M) in 8% DMF-CCl_4 (v/v), at 37°C

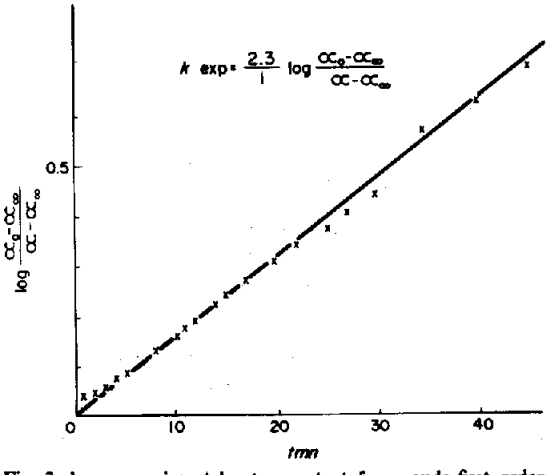


Fig. 3. k_{exp}, experimental rate constant for pseudo-first order racemization of **1a** (0.02 M), in 20% HMPT-PhH (v/v), at 26°C

Table 6. k_{exp}, experimental pseudo-first order rate constant vs, concentration in chlorophosphonate, **1a** or **2** for different nucleophiles

Ph(RO)P(Y)Cl	Nucleophile/ solvent	t	C_0 mole $l.^{-1}$	k_{exp} min^{-1}
Y = 0	DMF 8%/CCl_4	37°C	0.02	1.22×10^{-2}
R = Menthyl	1.04 mole $l.^{-1}$		0.03	1.28×10^{-2}
			0.04	1.25×10^{-2}
			0.01	3.10×10^{-3}
Y = 0	DMA 8%/CCl_4	37°C	0.02	2.73×10^{-3}
R = Menthyl	0.861 mole $l.^{-1}$		0.03	3.02×10^{-3}
			0.04	3.15×10^{-3}
Y = 0	HMPT 16%/PhH		0.01	4.44×10^{-2}
R = Menthyl	0.909 mole $l.^{-1}$	23.5°C	0.04	4.50×10^{-2}
			0.08	4.03×10^{-2}
Y = 0	NMI/PhH	23.5°C	0.008	7.84×10^{-2}
R = Menthyl	1.26×10^{-5} mole $l.^{-1}$		0.020	7.76×10^{-2}
			0.075	7.05×10^{-2}
Y = S	HMPT 20%/PhH	23°C	0.01	2.48×10^{-3}
R = Ethyl	1.137 mole $l.^{-1}$		0.04	2.57×10^{-3}
			0.08	2.66×10^{-3}

determined independently by initial rate method (Fig. 2) and/or integrated method (Fig. 3).

For a similar concentration in nucleophile, the pseudo first-order rate constant k_{exp} kept its value (with experimental error) for various concentrations in **1a** or **2** (Table 6).

Partial order in nucleophile was obtained by the determination of k_{exp} at different concentrations, [Nu]. Linear fonction of k_{exp} with $[Nu]^2$ (see Fig. 1) was characteristic of partial second orders in nucleophiles.

Hydrolysis. Partial order one in H_2O was obtained from the slopes of the curves log V_0 = f (log C_0), Fig. 4, with V_0 as initial rate and C_0 initial concentration of water, measured by Karl-Fischer method. Partial order 1 in chlorophosphonate was obtained from the integrated equation treatment:

$$k'_{exp}t = \frac{2.3}{b-a}\log\left(\frac{a}{a-x}\cdot\frac{b-x}{b}\right)$$

$a = [R(R'O)POCl]$

$b = [H_2O]$

with

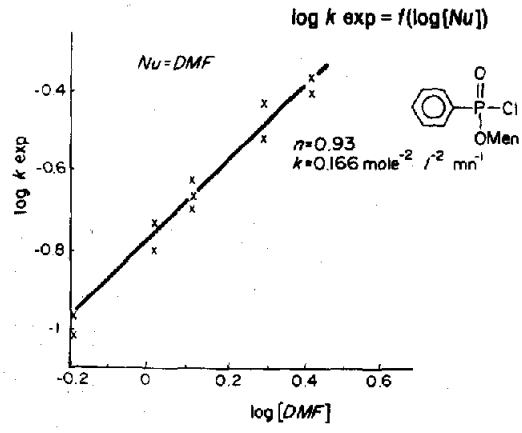
$$k'_{exp} = k'[Nu]^n$$

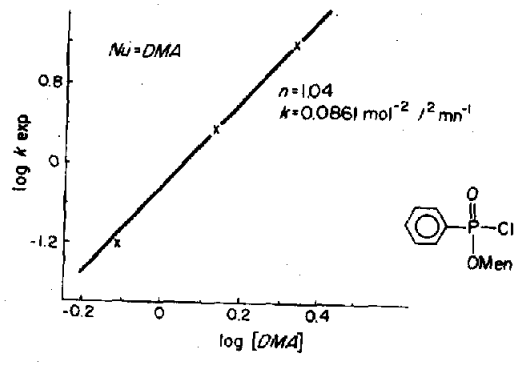
As an example, we report in Table 7 the data for the hydrolysis of **1a** (a = 0.0201M) by water (b = 0.0695M), plus DMF (1.298M) in CCl_4.

Plots of log [a(b − x)/b(a − x)] vs time were straight lines, and their slopes were linearly dependent on the concentration of nucleophiles and chlorophosphonates (Fig. 5 and Table 8).

For both racemization and hydrolysis, the activation parameters have been determined from k_{exp} or k'_{exp} at different temperatures.[27]

Fourier transform NMR ^{31}P data. Spectra were recorded at regular intervals, time being counted at half-accumulation. Peak hights were measured relative to H_3PO_4 as external standard. In





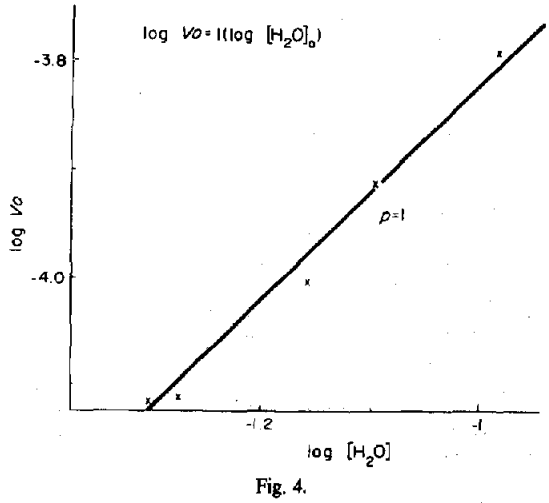


Fig. 4.

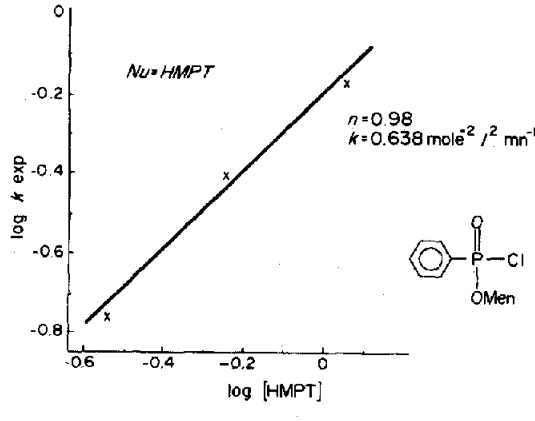


Fig. 5.

Table 7.

t_{mn}	$\frac{a-x}{a} = \frac{\alpha-\alpha_\infty}{\alpha_0-\alpha_\infty}$	$\frac{2,3}{b-a}\log\frac{a(b-x)}{b(a-x)}$	t_{mn}	$\frac{a-x}{a} = \frac{\alpha-\alpha_\infty}{\alpha_0-\alpha_\infty}$	$\frac{2,3}{b-a}\log\frac{a(b-x)}{b(a-x)}$
5	0,899	1,555	35	0,583	8,322
10	0,852	2,357	38	0,560	8,983
15	0,784	3,620	40	0,540	9,584
18	0,756	4,181	45	0,502	10,804
20	0,737	4,576	50	0,569	11,953
22	0,713	5,094	60	0,416	14,012
25	0,684	5,748	80	0,311	19,148
28	0,655	6,428			
31	0,626	7,165			

Table 8. Hydrolysis of 2, catalysed by DMF in CCl_4, at 20°C

Ph(EtO)P(S)Cl mole l^{-1}	H_2O mole l^{-1}	DMF mole l^{-1}	k'_{exp} $mole^{-1}l^{1}mn^{-1}$	k' $mole^{-2}l^{2}mn^{-1}$	k' $mole^{-2}l^{2}s^{-1}$
0,045	0,09	1,3	$5,6_{n}10^{-3}$	$4,31_{n}10^{-3}$	$7,19_{n}10^{-5}$
0,074	0,28	2,6	$11,06_{n}10^{-3}$	$4,26_{n}10^{-3}$	$7,10_{n}10^{-5}$
0,100	0,20	1,9	$8,46_{n}10^{-3}$	$4,35_{n}10^{-3}$	$7,25_{n}10^{-5}$

Table 9. Methanolysis of **1a**, in CCl_4, followed by NMR ^{31}P, with 5% DMF (top) and without nucleophile (bottom), [**1a**] = 0.10 mole $l.^{-1}$; [MeOH] = 0.38 mole $l.^{-1}$

		PhP(0)(OMen)(OMe)				
t_{mn}	Ph(MenO)P(O)Cl $\delta = +26.0$	(S) $\delta = +18.9$ ppm	(R) $\delta = +17.2$ ppm	(R) + (S)	% **1a**	% PhP(O)(OMen)(OMe)
5	162.4	11.5	0	11.5	93.5	5.0
20	133.8	55.3	9.2	64.5	77.0	27.8
31	89.5	99.6	17.9	111.7	51.5	48.25
45	59.7	124.0	25.6	149.6	34.4	64.6
57	42.1	139.9	28.2	168.1	24.2	72.6
69	28.9	154.7	33.8	188.5	16.6	81.4
81	20.8	157.2	38.6	195.8	12.0	84.6
112	10.5	170.8	40.7	211.5	6.0	91.3
∞	0	187.3	44.2	231.5	0	100
		PhP(O)(OMen)(OMe)				
t_{mn}	Ph(MenO)P(O)Cl $\delta = +26.9$	(S) $\delta = +19.3$ ppm	(R) $\delta = +18.7$ ppm	(R) + (S)	% **1a**	% PhP(O)(OMen)(OMe)
6	118.5	6.5	0	6.5	95.0	4.0
19	93.2	35.7	0	35.7	79.0	20.5
31	60.7	66.2	4.5	70.7	50.0	40.5
42	38.7	93.9	—	93.9	30.0	54.0
53	28.4	118.7	6.7	125.4	22.0	62.0
71	13.8	136.9	5.5	142.4	10.5	82.0
84	11.0	144.2	7.7	151.9	7.5	87.0
∞	0	163.9	10.2	174.1	0	100

racemization studies plots of log [1a − 1b/1a + 1b] = f(t), with [**1a**] and [**1b**] as relative concentrations in diastereoisomers, gave straight lines (Table 2) as characteristic of pseudo-first order reactions. Hydrolysis was followed by means of disparition of **1a** relative to H_3PO_4 as external standard (Table 4). Methanolysis of **1a** was also followed by NMR spectroscopy. The stereochemistry was given by the relative peak intensity of diastereoisomeric O-menthyl O-methyl phenylphosphonates (Table 9).

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