Silicon Phosphorus Analogies. Fluoride Activation of Nucleophilic Displacement at the Tetrahedral Phosphorus: An Example of Nucleophilic Assistance to Nucleophilic Substitution.[1] 3

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Abstract: We report a mechanistic study of the activation of alcoholysis of the P–X bond (X = Cl, F) by F^-. Cis and trans isomers of 2-halogeno-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes, **1** and **2**, or their 2-thio analogues, **3** and **4**, and epimeric 2-halogeno-2-oxo-5,6-tetramethylene-1,3,2-dioxaphosphorinanes, **5** and **6**, were treated with alcohols or phenols in the presence of CsF. The first step is substitution of the P–Cl bond with formation of the P–F bond, followed by fast epimerization in the presence of CsF. Alcohols or phenols do not react alone with the fluoro compounds. These nucleophiles substitute only in the presence of CsF, giving an epimeric ratio of phosphates, not really depending on the nature of the nucleophile. In all cases, this ratio is different from the thermodynamic ratio. It does not depend on the stereochemistry of the starting material (cis or trans **1–4** or epimeric **5** and **6**). The results are best interpreted by a two-step mechanism involving the transient formation of quasi-symmetric *trans*-difluorophosphorane oxide anion. The reactions offer another example of nucleophilic activation for a nucleophilic substitution at phosphorus, a mechanism well documented in silicon chemistry.

As part of a general comparison between silicon and phosphorus chemistry, we have been recently engaged in stereochemical studies of nucleophilic substitution at phosphorus. Two aspects have been already investigated: (i) the influence of the different factors that affect the stereochemistry of nucleophilic displacement at Si and P (ii) the possible assistance to racemization and/or nucleophilic displacement at the tetrahedral species.

Both, $S_N2(P)$ and $S_N2(Si)$ are stereoselective reactions. In the two elements, it is possible to observe a stereochemical dependence upon the nature of the nucleophilic and the leaving group.[2,3] The ability to displace the leaving group with inversion follows the order Br > Cl > F. Furthermore, for a given leaving group, the change in stereochemistry is a function of the electronic character of the nucleophile: strong nucleophiles promote retention, whereas weak nucleophiles, presenting a delocalized negative charge, lead to more inversion. *The evidence of similar factors affecting the stereochemistry at Si and P allowed us to propose a similar interpretation for the S_N2 mechanism.*

The second project concerned nucleophilic catalysis in the process of racemization and hydrolysis of both halosilanes, R_3SiCl, and halophosphonates, $R_1(R_2O)P(O)Cl$. The kinetic data agree with a two-step process (eq 1 and 2) governed by entropy ($\Delta S \simeq -50$ eu).[5-8]

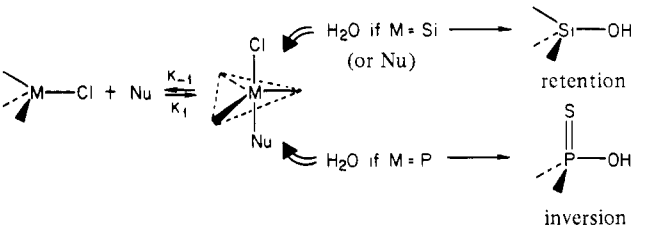
$$v_{rac} = k_{rac}[MCl][Nu]^2 \quad (1)$$

$$v_{H_2O} = k_{H_2O}[MCl][Nu][H_2O] \quad (2)$$

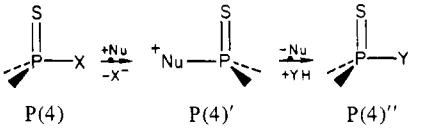
M = Si, Ge, P, and Sn. The proposed mechanism involves the formation of a pentacoordinated species in a preequilibrium reaction, followed by a nucleophilic attack in the rate-determining step (it is not actually possible to decide if whether the displacement of the chloride ion is a concerted process with formation of a five-coordinate cation species or involves a six-coordinate intermediate) (Scheme I). *The new essential feature, observed at P, was overall inversion in the case of nucleophilic activated hydrolysis of chlorothiophosphonates.* That stereochemistry allowed us to dismiss the possibility of a double displacement mechanism, for which overall retention at P is speculated.

Phosphoryl group transfer reactions, catalyzed by nucleophiles are widely accepted to involve a double substitution scheme.[9-11]

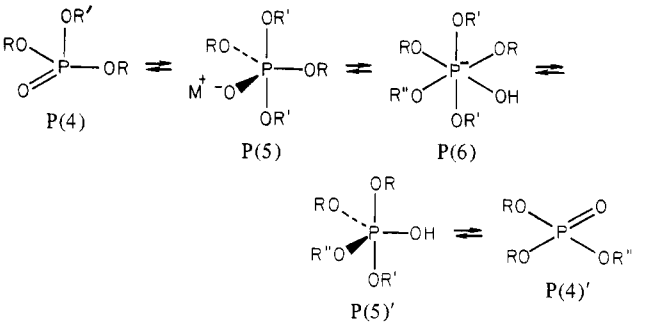
Scheme I



Scheme II



Scheme III



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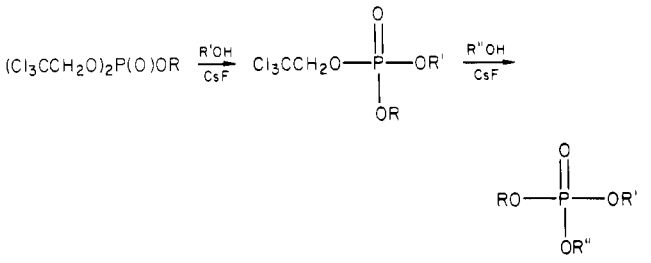
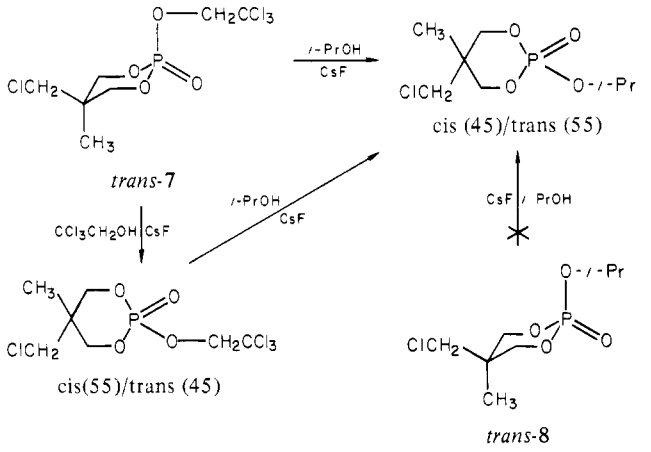
Scheme IV



Scheme V



The driving force of this process[12] *is the formation of a more reactive P(4) species* (Scheme II). The stereochemical consequence to be expected is overall retention at phosphorus (≡two inversions).[13] Overall inversion at phosphorus via a double-displacement mechanism in the case of chlorothiophosphonates would require the *unlikely prospect that the displacement of either the positively charged leaving group or the P–Cl bond occurs with retention* at phosphorus.[14]

Furthermore, in a previous work, Ramirez and al. have evidenced[15] another possibility of nucleophilic catalysis for the phosphorylation of alcohols, in aprotic solvents (Scheme III). At that time, they were the first to propose a process involving an extension of coordination at phosphorus for explaining the nucleophilic activation scheme. The key finding of this process, implicates a nucleophilic displacement reaction on a penta-coordinated activated phosphorus species through a hexa-coordinated one. Analogous P(6) compounds made from stable phosphorane P(5) derivatives have been characterized,[16] including

Table I. Exchange Reaction[a] of 5[b] with CsF (3 equiv)

			isomeric ratio[c]	
t	**5**	**6**	eq	ax
0 min	100			
2 min	95	5	60	40
7 min	85	15	57	43
10 min	73	27	55	45
15 min	70	30	53	47
30 min	60	40	52	48
60 min	46	54	50	50
90 min	38	62	46	54
120 min	32	68	41	59
240 min	16	84	35	65
480 min	10	90	20	80
900 min	4	96	12	88
3 days		100		100

[a] Reaction monitored by ^{31}P NMR spectroscopy: (**5**) δ −4.3; (6-eq) δ −16.1 (J_{PF} = 986 Hz); (6-ax) δ −16.9 (J_{PF} = 1001 Hz). [b] Initial concentration, 1 M, in THF. [c] ±5%.

X-ray diffraction structure studies.[17] Trippett has shown that the formation of six-coordinate anions from some spirophosphoranes and nucleophiles can be kinetically controlled, giving initially the less stable trans isomers.[18]

The analogies found in nucleophilic-assisted substitutions at silicon and phosphorus prompted us to extend the comparison. The present study concerns nucleophilic substitutions of halogenophosphates, catalyzed by F^-,[11] especially with reference to similar activation processes at silicon.[19] Ogilvie previously noted the catalytic effect of CsF to prepare mixed trialkyl phosphates (Scheme IV). The reaction is remarkably versatile and applies to nucleotides.[20]

Results

First of all, we have examined the stereochemistry of the activated process, described by Ogilvie, on a close model[21a] (Scheme V). Reactants and products have been prepared independently and fully analyzed. When the *trans*-2-(2,2,2-trichloroethoxy)-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane, **7**, is refluxed in 2-propanol containing CsF, for 50 h, the exchange reaction is not stereoselective. We obtain a 45/55 cis/trans mixture of the *O*-isopropyl cyclic phosphate, **8**. This ratio is constant with time, but different from the 68/32 (cis/trans) thermodynamic value. (This ratio is obtained by acid- or base-catalyzed solvolysis of the *trans-O*-isopropyl ester, **8**.) In the presence of CsF and 2,2,2-trichloroethanol, the *trans*-2,2,2-trichloroethoxy phosphate, **7**, slowly changes to a 55/45 cis/trans ratio, different from the fully equilibrated cis/trans mixture (63/37).

To answer the question of possible double displacement involving the transient formation of fluorophosphate, we have considered direct activated alcoholysis of monocyclic (**1–4**) and bicyclic (**5**, **6**) halogenophosphorus esters.[21] The bicyclic model has been investigated in order to remove any ambiguous conclusion on the thermodynamic or kinetic nature of the product ratios.[27] In that

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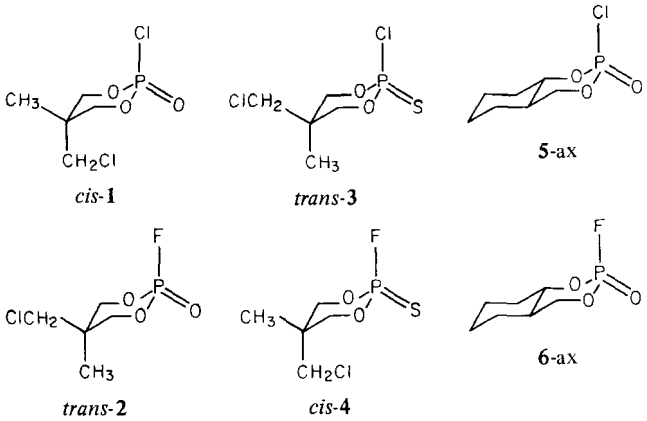
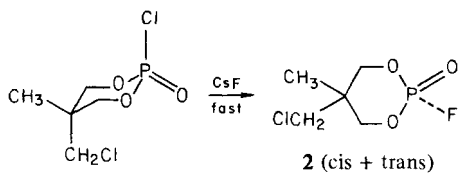


series, the isomer with an axial electronegative substituent (halogen or alkoxide) is always much more stable than the isomer with X in the equatorial position.[11b,22,27]

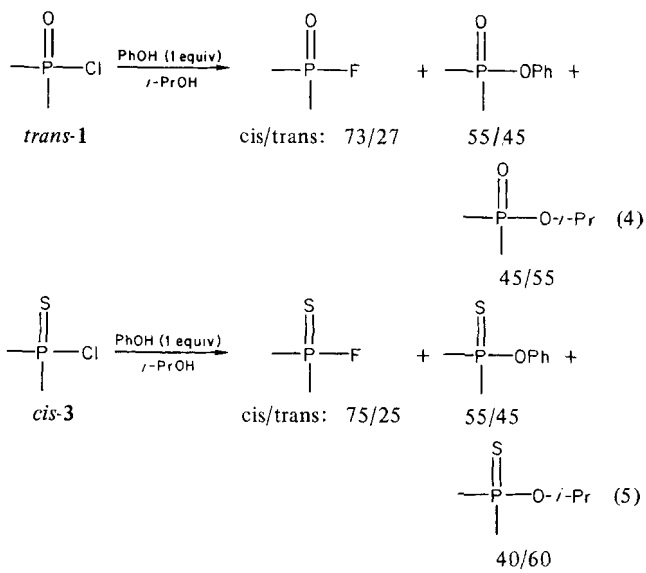
The direct alcoholysis of *cis*-2-chloro-2-oxo-1,3,2-dioxaphosphorinane, **1a**, is a very slow (2 weeks for 2-propanol[21b]) and highly stereoselective reaction, proceeding with predominant inversion. By contrast, the exchange of chlorine by fluorine with CsF is a very fast and nonselective process (eq 3). The reaction is complete



(3)

in a few minutes, giving the thermodynamic mixture of **2** (73/27, cis/trans). As a common feature for all the present reactions, the bicyclic compounds are not so reactive as the monocyclic derivatives. For example, we have not observed any substitution of the axial chlorophosphate, **5**-ax, with ethanol in 3 weeks. However, slow exchange reaction of **5**-ax with CsF can be checked by ^{31}P NMR (Table I). Substitution of the P–Cl bond by F^- gives initially the less stable equatorial fluorophosphate **6**-eq. Then, this compound is epimerised into 6-ax in the presence of excess CsF. We have studied the reactivity of the fluorophosphates: without the assistance of external fluoride anion, the fluorophosphates, **2**, **4**, or **6**, are completely unreactive in the presence of alcohols or phenols. If we add some CsF (generally 3 equiv) to the medium, we observe phosphorylation, fast in the case of the monocyclic compound, slower with the bicyclic model. Stereochemical results are reported in Table II and III. The most important fact in these results is that the *fluorophosphates react with alcohols only when they are activated by fluoride anions.* Another interesting point is the following: whatever the starting materials, chloro- or fluorophosphates of different isomeric ratios, the ratio of the product is the same. Furthermore, the cis/trans (eq/ax) ratios of the products are practically independent of the nature of the alcohols or phenols used as nucleophiles. Interestingly, these ratios, about 50/50 (cis/trans) for the monocyclic system and 85/15 (eq/ax) for the bicyclic model, differ from the thermodynamic mixtures (ca. 70/30 for the cis/trans monocyclic esters and exclusively axial for the bicyclic isomers).

Competitive reactions with mixed nucleophiles gave exactly the same ratios as when the reactants were considered separately (eq 4 and 5). In the case of the thio compounds, **3** and **4**, the isomeric ratios are somewhat dependent upon the nature of the nucleophile. Alcohols give 40/60 cis/trans mixtures, whereas the results with para-substituted phenols are more closely related to the 2-oxo



compounds (55/45 cis/trans mixtures). However, fast isomerization of the initially formed fluorothiophosphate is always observed.

These reactions also occur when KF is used in place of CsF. At room temperature, KF is only able to epimerize the fluoro derivatives **2** and **4**. Both, halogen exchange reactions (Cl, F) and activated alcoholysis need more drastic conditions. For example, the fluorothiophosphate **4** in refluxing ethanol with 3 equiv of KF (5 h) gives the same 31/69 cis/trans mixture of monocyclic ester.

Discussion

The normal nucleophilic substitutions of the P–Cl bonds that we observe with alcohols are in good agreement with $S_N2(P)$ processes.[23] The reactions proceed slowly, and the stereochemical behavior is predominant inversion at phosphorus. When we add CsF in the medium, we note an increased reactivity and a completely different stereoselectivity. Obviously, some activation has to be involved, but the question is how. Three observations are pertinent. (1) The P–Cl bond exchanges to a P–F bond with added CsF faster than it phosphorylates alcohols and phenols. (2) The fluorophosphates, alone, are not reactive with the alcohols or phenols, in the absence of F^- anions. (3) An excess of fluoride gives a relatively fast epimerization of the fluorophosphate and allows the substitution by alcohols. At first, a two-step process involving initial formation of the fluorophosphate would be relevant to explain retention at phosphorus. But, as shown, this compound is even less reactive than P–Cl. Therefore, at this stage, we must suppose some activation by fluoride. Furthermore, we have to take into account the fact that isomerization of fluorophosphate is faster than exchange with alcohol.

The mechanism that we propose is a three-step process involving initial formation of the fluorophosphate, which then reacts with F^- to give a pentacoordinated phosphoranoxide anion.[24] We speculate this activated species would exist in a very low steady-state concentration and be more reactive than the P(4) species with alcohols (Scheme VI).

The more stable geometry of the intermediate involves the two fluorine atoms in apical positions (Chart I).[25,26] This symmetrical structure explains the fast epimerization of the fluorophosphate, compared to solvolysis. It also explains the lack of selectivity in the reaction with alcohols and phenols. The substitution corresponds to the displacement of one (or another) fluorine atom by an alcohol molecule. The ratios of isomers formed are independent of the nature of the nucleophile. In the case of nearly symmetric oxo (or thio) monocyclic derivatives, the two approaches would be of similar energy, explaining the approximately 1:1 product ratio. On the other hand, the fused bicyclic model is known to be more sensitive to steric and/or stereoelectronic effects.[27,28] That

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Table II. Summary of Stereochemistry for Monocyclic Derivatives **1-4** (with Added CsF)

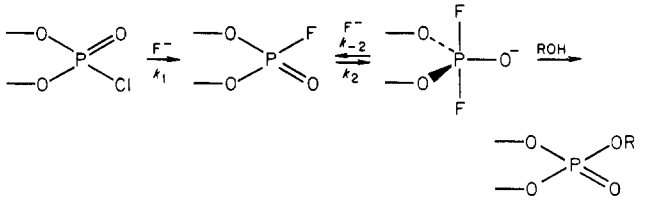
no.	reactant ratio, cis/trans	nucleophile	product ratio: kinetic cis/trans	product ratio: thermodynamic cis/trans
1	100/0	MeOH	54/46	71/29
	100/0	EtOH	55/45	
	100/0	CCl_3CH_2OH	55/45	63/37
	100/0	*i*-PrOH	45/55	
	100/0	CH_2=$CHCH_2OH$	55/45	
	100/0	3,5-$(OMe)_2C_6H_3OH$	53/47	
	100/0	*p*-$MeOC_6H_4OH$	53/47	67/33
	100/0	*p*-MeC_6H_4OH	54/46	67/33
	100/0	C_6H_5OH	53/47	68/32
	67/33	*p*-MeC_6H_4OH	53/47	
2	0/100	*i*-PrOH	45/55	
	0/100	*p*-MeC_6H_4OH	55/45	
	73/27	MeOH	55/45	
	73/27	*i*-PrOH	45/55	
	73/27	*p*-MeC_6H_4OH	55/45	
3	0/100	EtOH	34/66	
	0/100	*i*-PrOH	40/60	
	0/100	*p*-MeC_6H_4OH	47/53	
	0/100	C_6H_5OH	55/45	
4	100/0	MeOH	32/68	
	100/0	EtOH	32/68	
	100/0	CCl_3CH_2OH	40/60	62/38
	100/0	*i*-PrOH	36/64	
	100/0	*p*-MeC_6H_4OH	45/55	70/30
	72/28	EtOH	34/66	
	72/28	*p*-MeC_6H_4OH	45/55	

Table III. Summary of Stereochemistry for Bicyclic Derivatives **5** and **6** (with Added CsF)

no.	reactant ratio, eq/ax	nucleophile	product ratio: kinetic[a] eq/ax	product ratio: thermodynamic eq/ax
5	0/100	EtOH	80/20	0/100
	0/100	CCl_3CH_2OH	76/24	0/100
	0/100	*p*-MeC_6H_4OH	85/15	0/100
	0/100	C_6H_5OH	80/20	0/100
6	0/100	*p*-MeC_6H_4OH	85/15	0/100
	20/80	*p*-MeC_6H_4OH	80/20[b]	0/100
	35/65	*p*-MeC_6H_4OH	83/17	0/100
	0/100	C_6H_5OH	85/15[b]	0/100
	0/100	EtOH	82/18	0/100
	0/100	CCl_3CH_2OH	58/42	0/100

[a] Unless noted, determined to 20% completion of the reaction progress. [b] Half-reaction.

Scheme VI

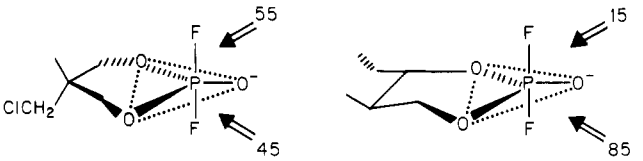


could be an explanation for the large difference in the kinetic 85/15 (eq/ax) ratio.

Concurrent S_N2 reaction of F^- with the P–F bond would explain only racemization but not the activation scheme. However, the lower efficiency of KF to promote activated alcoholysis[29] emphasizes the importance of the F^- anion as the reactive species. Meanwhile, the fact that similar isomer ratios are obtained with cesium fluoride and potassium fluoride conforts the hypothesis of symmetrical structure in the intermediate (implying no specific catalysis by the associated cation). The symmetrical structure also explains the higher reactivity of the pentacoordinated species relative to that of the starting material: the negative charge is delocalized on the two F atoms, and the two apical bond lengths are longer than in the tetrahedral species. In other words, the fluoride ion coordination stretchs and weakens the trans-apical P–F bond. A similar effect is used in silicon chemistry for enhancing the chemical reactivity of Si–H, Si–O, and Si–N bonds.[19,30]

Finally, it appears not necessary to invoke the possibility of pseudorotation at the stage of the P(5) species, since all the different systems give kinetic products, and since the two apical fluorines are in the proper energetically favorable position.

Chart I. Possible Geometries for *trans*-Difluorophosphorane Oxide Anions



Conclusion

Fluoride anions, which are known to activate nucleophilic substitution at silicon ($SN_{NA}Si$), also enter the mechanism of nucleophilic activated process at phosphorus. Nucleophilic attack on a pentacoordinated species is a well-documented scheme in silicon chemistry and was demonstrated in activated hydrolysis of chlorophosphonates. We have shown that nucleophilic activation by fluoride anion, in the substitution of the P–F, also implies the initial formation of a near symmetric *trans*-difluorophosphorane oxide anion, which then reacts with the nucleophile.

Our conclusions confort the recent proposition of Ramirez concerning the process of nucleophilic catalysis at phosphorus in aprotic solvents. Instead of being considered a double-displacement [two $S_N2(P)$], nucleophilic catalysis can be viewed as a two-step process, involving nucleophilic attack on a pentacoordinated species, initially formed by equilibrated coordination of the catalyst at phosphorus.

Many activated substitutions would be relevant. For example, we could mention the reactivating properties of fluoride anions on phosphorylated cholinesterases.[31] NaF has been widely used as antidote of Sarin.[32] Enhanced catalyzed hydrolysis with fluoride anion could be the proper mode of deactivation of the phosphoryl species, instead of blocking the esterasing site.[33] As a matter of fact, nucleophilic activation could be more common than hitherto recognized.

Experimental Section

Tetrahydrofuran (THF) was distilled under nitrogen from calcium hydride just prior to use. KF and CsF (Merck) were dried in vacuo over phosphorus pentoxide. Methanol and ethanol were distilled under magnesium and activated iodine. Other alcohols were purified by ordinary procedures. Phenols were used as commercial products.

All reactions were carried out under an atmosphere of nitrogen, with the rigid exclusion of moisture from reagents and glassware. Proton nuclear magnetic resonance spectra were recorded on a Varian Associates Model EM 390. Chemical shifts are reported in parts per million (ppm)

(29) As noted earlier,[11b,20] $(n\text{-}Bu)_4N^+F^-$ is also an efficient catalyst. However the reactions are not selective. We observe concurrent hydrolysis and formation of pyrophosphate, along with ring cleavage, probably due to water or acidic impurities in commercial TBAF. Production of pure, anhydrous tetraalkylammonium fluoride is rather unlikely. Fry, J. L., personal communication.

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Table IV. ^1H and ^{31}P NMR Spectral Parameters for 2-Alkoxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes

R		^{31}P	δH_{CH_3}	δH_{CH_2Cl}
$-CH_3$	cis	−8.17	1.01	3.89
	trans	−6.63	1.32	3.61
$-CH_2CH_3$	cis	−8.11	0.97	3.85
	trans	−6.06	1.30	3.57
$-CH(CH_3)_2$	cis	−8.23	0.95	3.83
	trans	−6.68	1.36	3.60
$-CH_2CCl_3$	cis	−9.88	0.97	3.80
	trans	−6.97	1.31	3.47
$-CH_2CH=CH_2$	cis	8.15	0.93	3.80
	trans	6.47	1.22	3.50

on the δ scale relative to internal Me_4Si. ^{31}P NMR spectra (positive values at low field) were recorded on a Bruker WP-80 spectrometer, at 32.37 MHz. Chemical shifts in ppm are referenced to external 85% H_3PO_4 in D_2O. Elemental analyses were performed by the Service Central de Microanalyse de Villeurbanne (France).

The preparations of monocyclic functional halogenophosphorus derivatives have been reported: **1**;[21a] **2**;[3a] **3**;[21c] **4**.[3a]

2-Chloro-2-oxo-5,6-tetramethylene-1,3,2-dioxaphosphorinane (5-ax). A solution of 41.5 g (0.27 mol) of phosphorus oxychloride in 100 mL of ether was added dropwise to a solution of 35.1 g (0.27 mol) of *trans*-2-hydroxymethyl)-**1**-cyclohexanol[34] and 77 mL (0.54 mol) of triethylamine in 100 mL of ether. The mixture was stirred for 3 h at 25 °C and filtered. The product, concentrated in vacuo, was purified by passage through silica gel column, with ether as the eluent. The axial isomer, **5**-ax,[27b] was recrystallized (36%) from hexane/ether at −78 °C (mp 75–76 °C): ^{31}P NMR (THF) δ −4.34. Anal. Calcd for $C_7H_{12}O_3PCl$: C, 39.8; H, 5.7; P, 14.7; Cl, 16.8. Found: C, 40.1; H, 5.8; P, 14.6; Cl, 16.6.

2-Fluoro-2-oxo-5,6-tetramethylene-1,3,2-dioxaphosphorinane (6-ax). A solution of 8.4 g (40 mmol) of the phosphorochloridate, **5**-ax, and 6 g (0.16 mol) of ammonium fluoride in 50 mL of dry acetonitrile was heated to 70–80 °C. The reaction was monitored by ^{19}F NMR. When only one doublet was observed[27] (J_{P-F} = 1003 Hz), the solution was filtered and concentrated in vacuo. The product, separated on a silica gel column with benzene/ether (1/1) as the eluent (90% yield) was recrystallized from hexane (mp 70 °C): ^{31}P NMR (THF) δ −17.2; ^{19}F NMR ($CFCl_3$) δ 86.0. Anal. Calcd for $C_7H_{12}O_3PF$: C, 43.3; H, 6.23; P, 15.95; F, 9.8. Found: C, 43.5; H, 6.30; P, 16.0; F, 9.7.

2-(2,2,2-Trichloroethoxy)-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (7). Phosphorochloridate, **1**, 18.4 g (84 mmol), was dissolved in 50 mL of freshly distilled 2,2,2-trichloroethanol. Triethylamine, 8.5 g (84 mmol), was added, and the solution was allowed to stand for 2 days. After filtration, the excess of alcohol was removed under reduced pressure. The residue, which solidified upon cooling, was recrystallized from hexane, 6.7 g (27% yield), mp 79–81 °C. The ^1H NMR spectrum showed the predominantly isomer with the chloromethyl group equatorial (95% *trans*-**7**): δ 1.32 (3 H, s), 3.48 (2 H, s), 4.45 (4 H, m), 4.66 (2 H, d).

2-(Isopropyloxy)-5-(chloromethyl)-5 methyl-2-oxo-1,3,2-dioxaphosphorinane (8). A procedure similar to that described above for **7** was used to prepare the nearly pure trans isomer, **8**, from the phosphorochloridate, **1** (0.01 mol), in 2-propanol (50 mL), plus triethylamine (0.01 mol). The residue was recrystallized from hexane, 1.7 g (71% yield): mp 73–75 °C (reported 74–75 °C).[21]

Transesterifications, in the Presence of CsF. In a typical experiment, 2-(2,2,2-trichloroethoxy)phosphorus ether, *trans*-**7** (300 mg), was heated with CsF (137 mg), in 20 mL of 2-propanol for 60 h at 80 °C. After removal of excess alcohol under reduced pressure, ether was added to precipitate cesium fluoride. ^1H and ^{31}P NMR spectra showed the only product, **8** in a 45/55 cis/trans isomeric ratio. The same reaction conducted in 2,2,2-trichloroethanol allowed the isomerization of the starting material, giving a 55/45 cis/trans mixture of **7**. No reaction was observed in the absence of cesium fluoride. Thermodynamic equilibriums were obtained by addition of small amounts of *p*-toluenesulfonic acid to 2-alkoxy esters, in the appropriate alcohols.[21]

Phosphorylations of Alcohols and Phenols, with CsF. As a typical procedure, we report the coupling reaction of the phosphorochloridate *cis*-**1**, 600 mg (2.27 mmol), with 320 mg (2.27 mmol) of *p*-methoxyphenol and 900 mg (6 mmol) of cesium fluoride, in tetrahydrofuran. **1** and the phenol were dissolved in 2 mL of THF. The solution was added directly to CsF, in the ^{31}P NMR tube, and the reaction quickly monitored (at least after 150 s). The identification of the products was made by comparison with authentic samples.[3,21,27] (Tables IV–VI).

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Table V. ^{31}P NMR Spectral Parameters for 2-Alkoxy-5-(chloromethyl)-5-methyl-2-thio-1,3,2-dioxaphosphorinanes

R	δ ^{31}P(cis)	δ ^{31}P(trans)
$-CH_3$	62.3	64.4
$-CH_2CH_3$	60.3	63.5
$-CH(CH_3)_2$	59.5	63.9
$-CH_2CCl_3$	58.1	60.5
$-CH_2CH=CH_2$	60.1	63.3

Table VI. ^{31}P NMR Chemical Shifts for 2-Alkoxy-2-(aryloxy)-2-oxo-5,6-tetramethylene-1,3,2-dioxaphosphorinanes

R	δ ^{31}P(ax)	δ ^{31}P(eq)
$-CH_2CH_3$	−7.2	−5.3
$-CH_2CCl_3$	−9.7	−7.1
$-C_6H_5$	−14.5	−11.9
$-C_6H_4(CH_3)$	−13.7	−11.8

The reactions with the alcohols, generally 50/50 in THF, were made in similar conditions, the solution being prepared prior to addition to CsF.

The coupling reaction of *p*-methylphenol (300 mg) with *cis*-**1** (600 mg) plus 900 mg of CsF in 2 mL of 2-propanol gives a mixture of 2-isopropyloxy ester, **8** (10%) (55 trans/45 cis), 2-(*p*-methylphenoxy)-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (80%) (45 trans/55 cis) and 2-fluoro derivative, **2**, (7%) (27 trans/73 cis).

In the same conditions, 470 mg of *trans*-**3** with 216 mg of methylphenol and 1.52 g of cesium fluoride in 2 mL of 2-propanol give after $^1/_2$ h at room temperature a complex mixture of **4** (10%) (75 cis/25 trans), 2-(*p*-methylphenoxy)-5-(chloromethyl)-5-methyl-2-thio-1,3,2-dioxaphosphorinane (70%) (55 cis/45 trans) and 2-(isopropyloxy)-5-(chloromethyl)-5 methyl-2-thio-1,3,2-dioxaphosphorinane (20%) (40 cis/60 trans).

Attempted Phosphorylations with Other Fluoride Anions. A total of 300 mg of *cis*-**4**, allowed to stand for 2 days with 900 mg of dried potasium fluoride in 2 mL of ethanol, showed the only isomerization of the starting material, **4** (70 cis/30 trans). The mixture, refluxing for 5 h, gave 60% of 2-ethoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinane (31 cis/69 trans).

The phosphorochloridate **3** (1 M) with 5 equiv of KF in 2 mL of ethanol gave no reaction at room temperature for 2 days. After the mixture was heated for 5 h at 70 °C, 40% of the 2-ethoxy derivative was identified (33 cis/67 trans).

A total of 400 mg of **2** (73 cis/27 trans) dissolved in 2 mL of 2-propanol was also heated with 2 equiv of tetrabutylammonium fluoride (EGA, 1 M in THF). After 50 min, the ^{31}P NMR spectrum showed the predominant formation of the ammonium salt of cyclic phosphoric acid (δ −5.2) (80%), plus a nonidentified compound with P–F bond, δ −5.5 (923 Hz) (8%) and residual **2** (10%).

When 300 mg of *trans*-2-(*p*-methylphenoxy)-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane were treated with 2 equiv of tetrabutylammonium fluoride, in 2 mL of THF, the ^{31}P NMR taken after 10 min showed the partial isomerization of the starting material (65 trans/35 cis) (50%), plus 30% of the ammonium salt of phosphoric acid (δ −5.1), 10% of isomerized fluorophosphate, **2**, and 10% of the unknown P–F compound, δ −5.4 (J = 921 Hz). After 1 h, the signals corresponding to **2** have disappeared, more acidic salt is formed (70%) (δ −5.4), the starting material (20%) is in a different isomeric ratio (40 trans/60 cis), and the unknown P–F material is always present (10%). After 24 h, the mixture corresponds to 80% of acidic salt (δ −5.65), 10% of 2-(*p*-methylphenoxy) ester (15 trans/85 cis), and 10% of the P–F product, δ −5.8 (J = 923 Hz).

Registry No. *cis*-**1**, 28097-07-6; *trans*-**1**, 21071-81-8; *cis*-**1** (2-OMe derivative), 28097-12-3; *trans*-**1** (2-OMe derivative), 36912-27-3; *cis*-**1** (2-OEt derivative), 78280-52-1; *trans*-**1** (2-OEt derivative), 78280-51-0; *cis*-**1** (2-OPr-*i* derivative), 78266-89-4; *trans*-**1** (2-OPr-*i* derivative), 36912-28-4; *cis*-**1** (2-OCH_2CCl_3 derivative), 78266-88-3; *trans*-**1** (2-OCH_2CCl_3 derivative), 78266-87-2; *cis*-**1** (2-$OCH_2CH=CH_2$ derivative), 78266-91-8; *trans*-**1** (2-$OCH_2CH=CH_2$ derivative), 78266-90-7; *cis*-**1** (2-$(OC_6H_3$-3,5-$(OMe)_2)$ derivative), 78266-93-0; *trans*-**1** (2-$(OC_6H_3$-3,5-$(OMe)_2)$ derivative), 78266-92-9; *cis*-**1** (2-OC_6H_4-*p*-OMe derivative), 36912-31-9; *trans*-**1** (2-OC_6H_4-*p*-OMe derivative), 36912-32-0; *cis*-**1** (2-OC_6H_4-*p*-Me derivative), 36912-33-1; *trans*-**1** (2-OC_6H_4-*p*-Me derivative), 36912-34-2; *cis*-**1** (2-OC_6H_5 derivative),

36912-30-8; *trans*-**1** (2-OC_6H_5 derivative), 36895-18-8; *cis*-**2**, 74737-11-4; *trans*-**2**, 74737-10-3; *trans*-**3**, 50600-54-9; *cis*-**3** (2-OC_6H_4-*p*-Me derivative), 50378-57-9; *trans*-**3** (2-OC_6H_4-*p*-Me derivative), 50378-50-2; *cis*-**3** (2-OC_6H_5 derivative), 50378-58-0; *trans*-**3** (2-OC_6H_5 derivative), 50378-51-3; *cis*-**3** (2-OMe derivative), 88157-75-9; *trans*-**3** (2-OMe derivative), 88157-76-0; *cis*-**3** (2-OEt derivative), 88157-77-1; *trans*-**3** (2-OEt derivative), 88157-78-2; *cis*-**3** (2-OPr-*i* derivative), 88157-79-3; *trans*-**3** (2-OPr-*i* derivative), 88157-80-6; *cis*-**3** (2-OCH_2CCl_3 derivative), 88157-81-7; *trans*-**3** (2-OCH_2CCl_3 derivative), 88157-82-8; *cis*-**3** (2-$OCH_2CH{=}CH_2$ derivative), 88157-83-9; *trans*-**3** (2-$OCH_2CH{=}CH_2$ derivative), 88157-84-0; *cis*-**4**, 74737-12-5; *trans*-**4**, 74737-13-6; **5**-*ax*, 74410-72-3; **5**-*ax* (2-OEt derivative), 88199-18-2; **5**-*eq* (2-OEt derivative), 88199-19-3; **5**-*ax* (2-OCH_2CCl_3 derivative), 78339-64-7; **5**-*eq* (2-OCH_2CCl_3 derivative), 78266-97-4; **5**-*ax* (2-OC_6H_5 derivative), 74378-77-1; **5**-*eq* (2-OC_6H_5 derivative), 74410-66-5; **5**-*ax* (2-OC_6H_4-*p*-Me derivative), 78339-63-6; **5**-*eq* (2-OC_6H_4-*p*-Me derivative), 78266-96-3; **6**-*ax*, 78339-65-8; **6**-*eq*, 78266-98-5; *trans*-**7**, 78266-87-2; *cis*-**8**, 78266-89-4; *trans*-**8**, 36912-28-4; CsF, 13400-13-0; F^-, 16984-48-8; phosphorus oxychloride, 10025-87-3; *trans*-2-(hydroxymethyl)-1-cyclohexanol, 7429-40-5.

On the Mechanism of the Thermal Conversion of Cyclopropenyl-Substituted Oxazolinones to Pyridines

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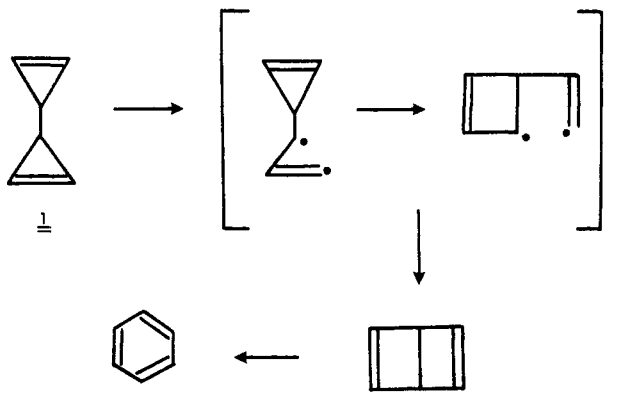
Abstract: Thermolysis or photolysis of a sample of a 3-cyclopropenyl-substituted 2*H*-azirine produced 2-methyl-3,4,5,6-tetraphenylpyridine in high yield. The reaction can best be rationalized by a mechanism involving formation of a nitrile ylide intermediate followed by intramolecular dipolar cycloaddition to give an azabenzvalene, which subsequently rearranges to the pyridine. The thermal chemistry of a series of cyclopropenyl-substituted oxazolinones was also investigated. These oxazolinones undergo a thermally induced 1,3-dipolar cycloreversion reaction with elimination of carbon dioxide to generate a nitrile ylide intermediate adjacent to the cyclopropene ring. This dipole can be trapped when the thermolysis of the oxazolinone was carried out in the presence of a reactive dipolarophile. Heating a sample of 2-phenyl-4-methyl-4-(1-methyl-2,3-diphenyl-2-cyclopropen-1-yl)-Δ^2-oxazolin-5-one at 150 °C for 24 h afforded a mixture of 2,3-dimethyltriphenylpyridine (45%), 2,4-dimethyltriphenylpyridine (20%), and 2,5-dimethyltriphenylpyridine (35%). The formation of these products is proposed to involve a stepwise cycloaddition of the initially generated nitrile ylide to produce a bicyclobutyl zwitterion which can either collapse to give an azabenzvalene or undergo rearrangement to a cyclobutenyl cation. This latter species closes to produce two different aza Dewar benzenes. Reorganization of the azabenzvalene and aza Dewar benzenes gives rise to the observed pyridines. Alternate mechanisms based on a concerted intramolecular cycloaddition reaction of the nitrile ylide do not account for the observed product ratios.

Small-ring compounds are particularly interesting species because their high energy content relative to the acyclic isomers often endows them with unusual reactivity patterns.[1-4] Studies dealing with the chemical reactions of unsaturated three-ring systems have played an important role in the development of our understanding of the mechanism by which carbon–carbon bonds may be broken and reformed.[5] During the last few years the chemistry of 3,3′-bicyclopropenyls has attracted considerable interest.[6-13] The rearrangement of these compounds to benzene derivatives is one of the most exothermic unimolecular isomerizations known (Scheme I). Its mechanism has been a source of controversy over the years. At various times the rearrangement has been postulated to proceed through Dewar benzene,[8] benzvalene,[14] prismane,[6] and diradical[11] and ionic intermediates.[8] The most recent data are consistent with a path involving initial homolytic cleavage of one of the cyclopropene rings followed by expansion of the other ring, closure to a Dewar benzene, and finally opening of the Dewar intermediate to form aromatic products.[12,13] The conversion of the closely related 3-azirinylcyclopropene system (**2**) to a pyridine derivative **5** represents a more complicated transformation since several different possibilities are available (Scheme II). One of the more attractive paths involves the initial formation of a nitrile ylide intermediate[15] **3**, followed by intramolecular dipolar cycloaddition[16] to give azabenzvalene **5** which subsequently rearranges to pyridine **4**.[17] This paper describes some of our observations in this area with particular reference to the mechanism of the rearrangement.

Scheme I



Results

Earlier work in the literature has shown that the synthesis of 2*H*-azirines based on the modified Neber reaction proceeds in high yield if the α-hydrogen is tertiary or benzylic.[18] This is probably related to the fact that the mechanism of the Neber rearrangement

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