Fluoride Activation of Nucleophilic Displacement at Tetrahedral Phosphorus

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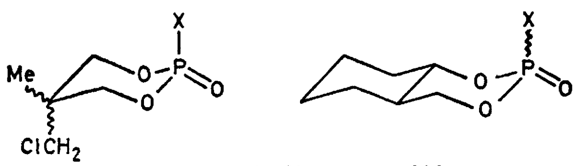
Summary Participation of fluoride anion in nucleophilic substitution at tetrahedral phosphorus implies the transient formation of *trans*-difluorophosphorane oxide.

FLUORIDES exert a reactivating action on phosphorylated cholinesterases.[1] They have been extensively studied also as catalysts in the preparation of biologically active models.[2] In 1977, Ogilvie reported a simple method for transesterification with CsF, *via* the intermediate fluorophosphates.[3] More recently, the use of CsF allowed the isolation of stable hexaco-ordinated phosphorus species.[4] Thus, the growing interest in the possibility of nucleophilic assistance at phosphorus[5] or silicon[6,7] justified a study of the solvolysis of six-membered-ring halogenophosphates, catalysed by added CsF. The stereochemical data obtained in this study are rationalized on the basis of an unexpected F^--activated process.



(1) (2)

a; X = Cl
b; X = F
c; X = OR
(R = alkyl or aryl)

In the absence of fluoride, reaction of 2-chloro-2-oxo-1,3,2-dioxaphosphorinan, (**1a**), with alcohols or phenols is very slow (*e.g.* two weeks for Pr^iOH).[8] The corresponding fluoride, (**1b**), is inactive. When CsF is added, however, the reaction is complete in several hours.

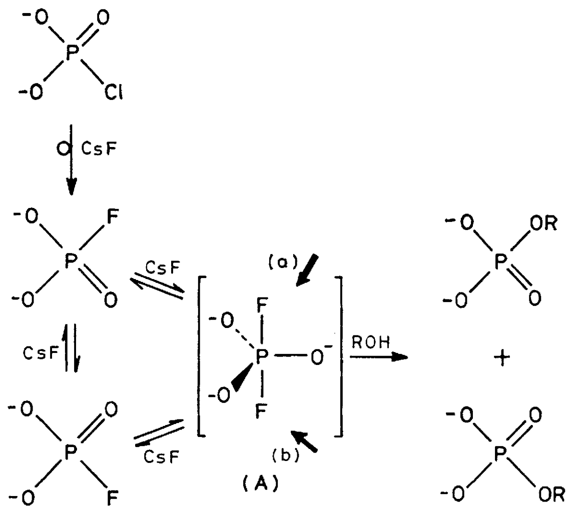
Cyclic halogenophosphates (**1**) and (**2**) were mixed with stoicheiometric amounts of alcohols or phenols in the presence of 3 equiv. of CsF. Product ratios were determined *in situ* by ^1H and/or ^{31}P n.m.r. spectroscopy, as previously described.[9]

The results are presented in the Table. In the case of (**1b**), isomerization is extremely fast relative to solvolysis and we could only characterize the thermodynamic mixture, *cis*:*trans* 73:27. On the other hand, the *trans*-fused system, (eq)-(**2b**), exchanges to the thermodynamically more stable (ax)-(**2b**) only slowly. The phosphate was always formed in the same ratio whatever the nature (chloride or fluoride) or isomeric composition of the reactant. This ratio was almost the same for all the phenols or alcohols investigated, *ca.* 50:50 for the monocyclic system (**1**) and *ca.* 85:15 (eq:ax) for the fused model, (**2**). Moreover, we noted that product ratios were (i) constant during the reaction, (ii) different from the thermodynamic ratio of the starting fluoro-derivative, and (iii) different from the thermodynamic ratio of the reaction product (Table). This was particularly noticeable for the bicylic system, for which the predominantly formed isomer

TABLE

Reactant	Isomeric ratio *cis*:*trans*	Nucleophile	Product: Kinetic ratio *cis*:*trans*	Product: Thermodynamic ratio *cis*:*trans*
(**1a**)	100:0	MeOH	54:55	71:29
,,	,,	EtOH	55:45	—
,,	,,	CCl_3CH_2OH	55:45	63:37
,,	,,	Pr^iOH	45:55	—
,,	,,	$CH_2{=}CHCH_2OH$	55:45	—
,,	,,	*p*-$MeOC_6H_4OH$	53:47	67:33
,,	,,	*p*-MeC_6H_4OH	54:46	67:33
,,	,,	PhOH	53:47	68:32
,,	,,	3,5-$(OMe)_2$-C_6H_3OH	53:47	—
,,	,,	2-Pr^i-5-Me-C_6H_3OH	53:47	—
,,	67:33[a]	*p*-MeC_6H_4OH	53:47	67:33
(**1b**)	73:27[a]	MeOH	55:45	71:29
,,	,,	CCl_3CH_2OH	55:45	63:37
,,	,,	*p*-MeC_6H_4OH	55:45	67:33
,,	0:100	Pr^iOH	45:55	—
,,	,,	*p*-MeC_6H_4OH	55:45	—
(**1c**; R = CH_2CCl_3)	20:80[b]	CCl_3CH_2OH	55:45	63:37
,,	,,	Pr^iOH	45:55	—
(**1c**; R = Pr^i)	0:100[b]	Pr^iOH	0:100	—
(**2a**)	0:100[c]	*p*-MeC_6H_4OH	85:15[c]	0:100[c]
,,	,,	PhOH	85:15[c]	0:100
,,	,,	CCl_3CH_2OH	76:24[c,d]	,,
(**2b**)	0:100[c]	*p*-MeC_6H_4OH	85:15[c]	,,
,,	20:80[c]	,,	80:20[c]	,,
,,	35:65[c]	,,	83:17[c]	,,
,,	0:100[c]	PhOH	87:13[c]	,,

[a] Thermodynamic ratio. [b] Reactions carried out at 80 °C for 60 h (ref. 3). [c] eq:ax. [d] The product is slowly isomerized under the reaction conditions.



Scheme

is the less stable one;† in other words, starting from the thermodynamic isomer of (**2b**), we obtained a kinetic product, (**2c**).

The most reasonable assumption, consistent with all the data is the formation of a pentaco-ordinated symmetric intermediate (A) with two equivalent fluorides in apical positions (Scheme).

The experimental isomer ratios would be the consequence of two competing directions of attack (a) and (b) on the activated phosphorane oxide.[10] This explanation is supported by the 55 : 45 product ratio observed in the case of nearly symmetric monocyclic derivatives, whereas for the fused bicyclic model, the energetic balance between attack (a) and (b) would be responsible for the large difference in the kinetic 85 : 15 (eq : ax) ratio.

Such participation of transient associated species in S_N2(P) reactions may be more important than hitherto recognized. They may also be relevant in biological processes.

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† The more stable *trans*-fused compounds, (ax)–(**2**), are those with the electronegative substituent in the apical position (D. Bouchu and J. Dreux, *Tetrahedron Lett.*, 1979, 3151; M. Haemers, R. Ottenger, J. Reisse, and D. Zimmermann, *ibid.*, 1971, 461; D. G. Gorenstein and R. Rowell, *J. Am. Chem. Soc.*, 1979, **101**, 4925, and references therein). The equatorial isomer, (eq)–(**2c**) (X = $-OC_6H_4Me$), gives the axial isomer after 3 days in a large excess of *p*-cresol, in the presence of CsF. In contrast, substitutions of halogenophosphates take place in a matter of hours.

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