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DIASTEREOMERIC 2-FLUORO-4-METHYL-1,3,2-DIOXAPHOSPHORINAN-2-THIONES. RETENTION STEREOCHEMISTRY IN NUCLEOPHILIC SUBSTITUTION AT THIOPHOSPHORYL PHOSPHORUS[1]

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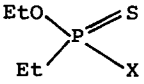
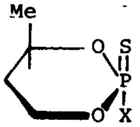
In the course of our studies on nucleophilic substitution at the thiophosphoryl centre we have shown that optically active O-ethyl ethylphosphonohalogenothionates (1) undergo alkaline hydrolysis and other displacement reactions with almost complete inversion of configuration at phosphorus[2]. The same stereochemical course has recently been demonstrated for nucleophilic substitutions at phosphorus in cyclic halogenides: trans-2-chloro- and trans-2-bromo-4-methyl-1,3,2-dioxaphosphorinan-2-thione (2) and (3)[3].



(1), X = Cl,Br,F



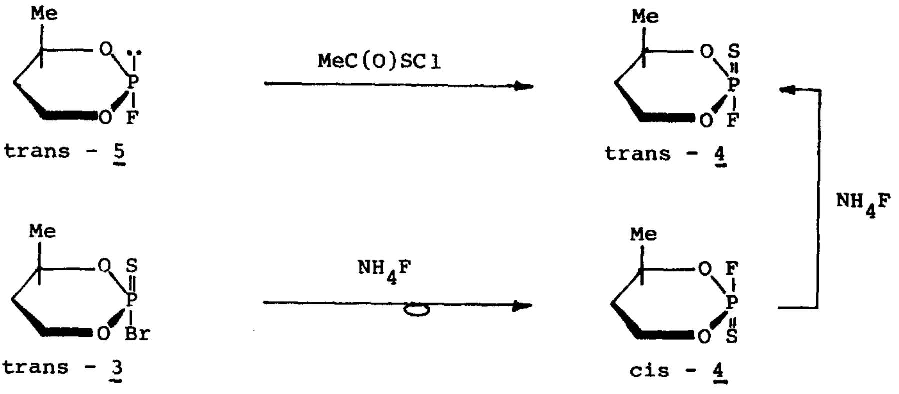
(2), X = Cl
(3), X = Br
(4), X = F

It is now reported that, in contrast to the above mentioned reactions, trans-2-fluoro-4-methyl-1,3,2-dioxaphosphorinan-2-thione (4) reacts with nucleophiles with preponderant retention of configuration. This result provides a new, clear-cut evidence that the leaving group has an influence on the stereochemical course of the S_N-P reaction and this effect is more pronounced in a cyclic phosphorus systems[4].

Diastereomerically pure trans-fluoride (4) was synthesized similarly as trans-chloride (2)[3] by treatment of trans-2-fluoro-4-methyl-1,3,2-dioxaphosphorinan (5)[7] with acetylsulphenyl chloride [trans-4: 80% yield, b.p. 61°/0.1 mm, m.p. 33-34°C (light petroleum), δ_{CH_3} 1.46 ppm ($CDCl_3$, at 80 MHz), $^3J_{H-CH_3}$ 6.2 Hz, $^4J_{P-CH_3}$ 2.6 Hz, $\delta_{^{31}P}$ - 54 ppm (CH_3CN, 85% H_3PO_4), $^1J_{P-F}$ 1086 Hz, $\delta_{^{19}F}$ - 81.4 ppm (CH_3CN, C_6F_6 ext.)] .

The second isomer was obtained from trans-bromide (3) and ammonium fluoride by the halogen exchange reaction carried out in acetonitrile solution at 40°C. After 8 hr it afforded cis-fluoride (4) as a 84% diastereomerically pure sample from which the pure cis-4 can be isolated by preparative gas chromatography [cis-4: δ_{CH_3} 1.48 ppm ($CDCl_3$, at 80 MHz), $^3J_{H-CH_3}$ 6.5 Hz, $^4J_{P-CH_3}$ 0.9 Hz, $^5J_{F-CH_3}$ 0.9 Hz, $\delta_{^{31}P}$ - 55 ppm (CH_3CN, 85% H_3PO_4), $^1J_{P-F}$ 1094 Hz, $\delta_{^{19}F}$ - 100.4 ppm (CH_3CN, C_6F_6 ext.)] . Continuation of the reaction resulted in the slow isomerization of the cis-fluoride (4) first formed to the theromodynamically more stable trans-isomer (after 50 hr a 83:17 mixture of trans-4 and cis-4 is obtained).

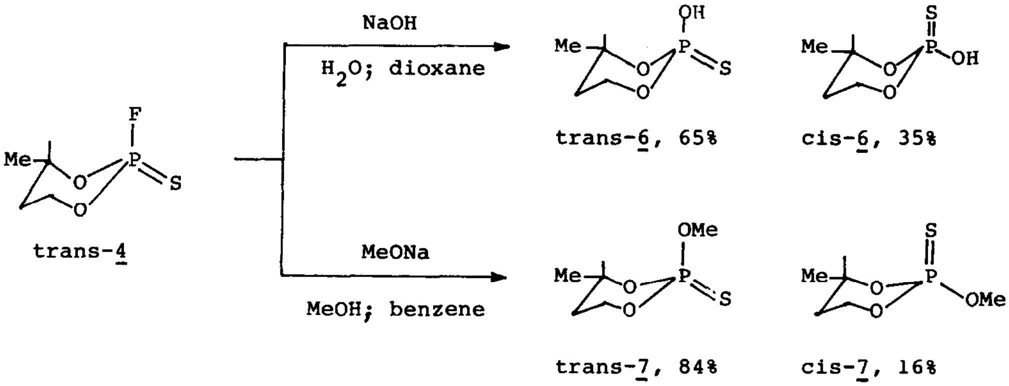
Scheme 1



The n.m.r (^1H, ^{31}P, ^{13}C, ^{19}F) data available at present are consistent with a rigid chair conformation for trans-4 in which thiophosphoryl sulphur and the C_4-methyl group occupy equatorial positions. Also cis-4 is very likely to exist in a chair conformation having opposite configuration at phosphorus. In the latter case, however, conformational equilibrium can not be excluded. This point is under current study.

We have found that alkaline hydrolysis and methanolysis of trans-fluoride(4) occur with predominant retention of configuration at the thiophosphoryl centre affording the corresponding thioacid (6)[8] and thionophosphate (7)[8] as a mixtures of diastereomers. The isomeric ratios are shown in Scheme II.

Scheme II



trans-4

trans-6, 65%

cis-6, 35%

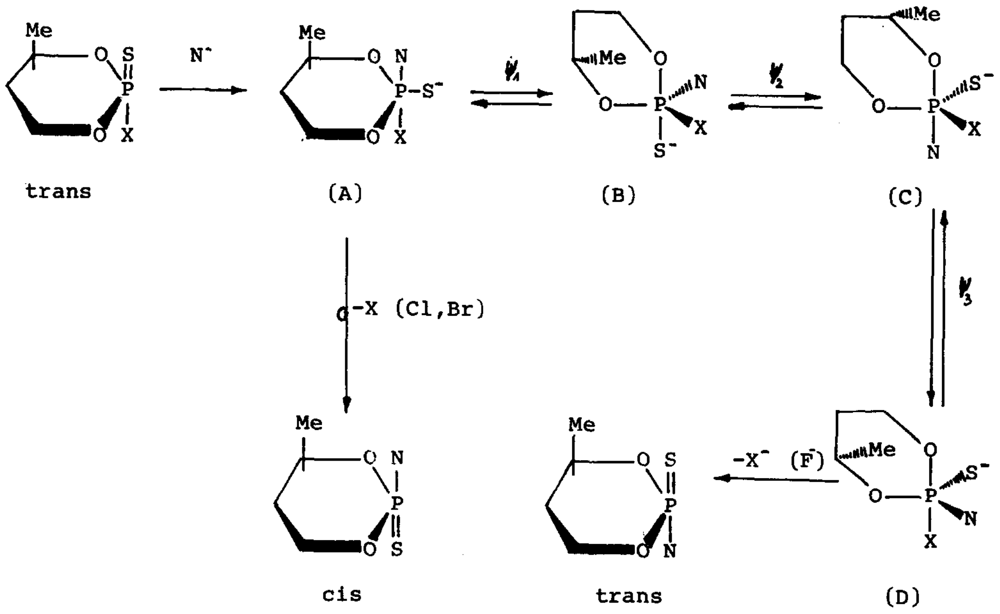
trans-7, 84%

cis-7, 16%

Since diastereomeric thioacids (6) and thionophosphates (7) are configurationally stable under the reaction conditions, the observed stereochemistry must be the consequence of the S_N-P reaction mechanism involved.

We believe that our results are best rationalized[9] by assuming the initial formation of the trigonal bipyramidal penta-coordinate phosphorus intermediate (A) in which the six-membered ring spans equatorial positions and the entering and leaving group occupy apical positions. When X is a good leaving group (Cl, Br) it decomposes quickly to give the substitution product with inversion of configuration. However, when the phosphorus atom is connected with a poor leaving group (F) stability of the intermediate adduct (A) is increased. Therefore, it has enough time to undergo permutational changes. A new trigonal bipyramid (D) formed after three consecutive pseudoratations depicted in Scheme III would lead to the retention product.

Scheme III



*conformation of the ring has been neglected

References

(1) Presented at the V-th International Conference on Organic Phosphorus Chemistry, 16-21, September 1974, Poland; Abstract Book, p. 46.
(2) M.Mikołajczyk, Tetrahedron, 1967, 23, 1543; J.Michalski, M.Mikołajczyk and B.Pliszka-Krawiecka, Angew.Chem., 1966, 78, 716; Bull.Acad.Polon.Sci., 1969, 17, 75; M.Mikołajczyk, J.Omelańczuk and M.Para, Tetrahedron, 1972, 28, 3855 and references cited therein.
(3) M.Mikołajczyk, J.Krzywański and B.Ziemnicka, Phosphorus, in press.
(4) Nucleophilic substitution at phosphorus with retention of configuration has recently been observed by Wadsworth[5] and Inch[6] in a similar cyclic systems.
(5) W.S.Wadsworth, J.Org.Chem., 1973, 38, 2921; W.S.Wadsworth and Yuh-Geng Tsay, J.Org.Chem., 1974, 39, 984.
(6) J.M.Harrison, T.D.Inch and G.J.Lewis, J.Chem.Soc., Perkin I, 1974, 1053.
(7) W.J.Stec, A.Okruszek, unpublished results.
(8) M.Mikołajczyk and J.Łuczak, Tetrahedron, 1972, 28, 5411.
(9) Other explanations will be discussed in a full paper.