Tetrahedron Letters, Vol.22, No.34, pp 3281 - 3284, 1981
Printed in Great Britain

0040-4039/81/343281-04$02.00/0

STEREOCHEMISTRY OF SUBSTITUTION AT TRICOVALENT PHOSPHORUS

Otto Dahl

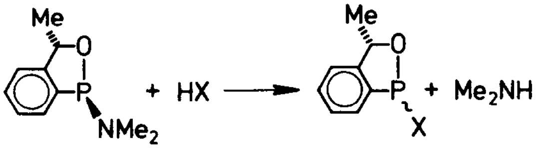
Department of General and Organic Chemistry, The H. C. Ørsted Institute,
University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen,
Denmark

Reactions of one diastereomer of a $>P\text{-}NMe_2$ *compound (1a) with alcohols, phenol and amines have been shown by NMR to proceed with initial inversion at phosphorus, but the overall reactions are not stereoselective.*

In contrast to nucleophilic substitutions at tetracovalent phosphorus, which have been extensively studied due to their importance in biochemistry, similar substitutions at tricovalent phosphorus, and particularly their stereochemistry, have been much less investigated.[1] Such substitutions, e.g. eq. 1, might be synthetically useful for obtaining optically active tricovalent phosphorus compounds which are of current interest as potential ligands for catalysts employed in asymmetric syntheses.

$$>P\text{-}NR^1_2 \; + \; R^2OH \; \rightarrow \; >P\text{-}OR^2 \; + \; R^1_2NH \qquad \text{eq. 1}$$

This paper describes preliminary results from a study of the reactions of diastereomerically pure (1a) with some alcohols, phenol and amines, eq. 2



(1a) (2)

$X = OMe, OBu^t, OPh, NMe_2, N(CH_2)_5, NHPh$ eq 2

The stereochemistry was investigated by monitoring the reactions by ^1H and ^{31}P NMR. Since the possible products are diastereomers they give rise to separate NMR signals the analysis of which gives the stereochemical results of the reactions.

The starting material 2-dimethylamino-5-methyl-5$\underline{H}$-1,2-benzoxaphospholen ($\underset{\sim}{1}$) was prepared analogous to the 5-unsubstituted compound[2] from racemic 1-phenylethanol and Me_2NPCl_2 (35% yield, b.p. 50-51° at 0.1 mmHg, ca. 60 : 40 mixture of diastereomers, δ_P 131.2 and 132.6 ($CDCl_3$)). The main diastereomer ($\underset{\sim}{1a}$) (δ_P 131.2, racemic) was obtained 97% diastereomerically pure by spinning band distillation. When ($\underset{\sim}{1a}$) was treated with HX (X = OMe, OPh, or $N(CH_2)_5$) at 25° in $CDCl_3$ there appeared two products ($\underset{\sim}{2}$), one of which was formed in great excess initially (Fig. 1). During the reactions the relative amounts of products changed, and the amount of the minor diastereomer of ($\underset{\sim}{1}$), ($\underset{\sim}{1b}$), increased. This indicates that the substitution reaction is stereoselective but that further reactions occur to give, eventually, an equilibrium mixture of diastereomers of ($\underset{\sim}{1}$) and ($\underset{\sim}{2}$). In separate experiments it has been shown that ($\underset{\sim}{2}$) exchange with HX for all X studied, i.e. ($\underset{\sim}{2}$) (and ($\underset{\sim}{1a}$)) are not configurationally stable in the presence of HX.

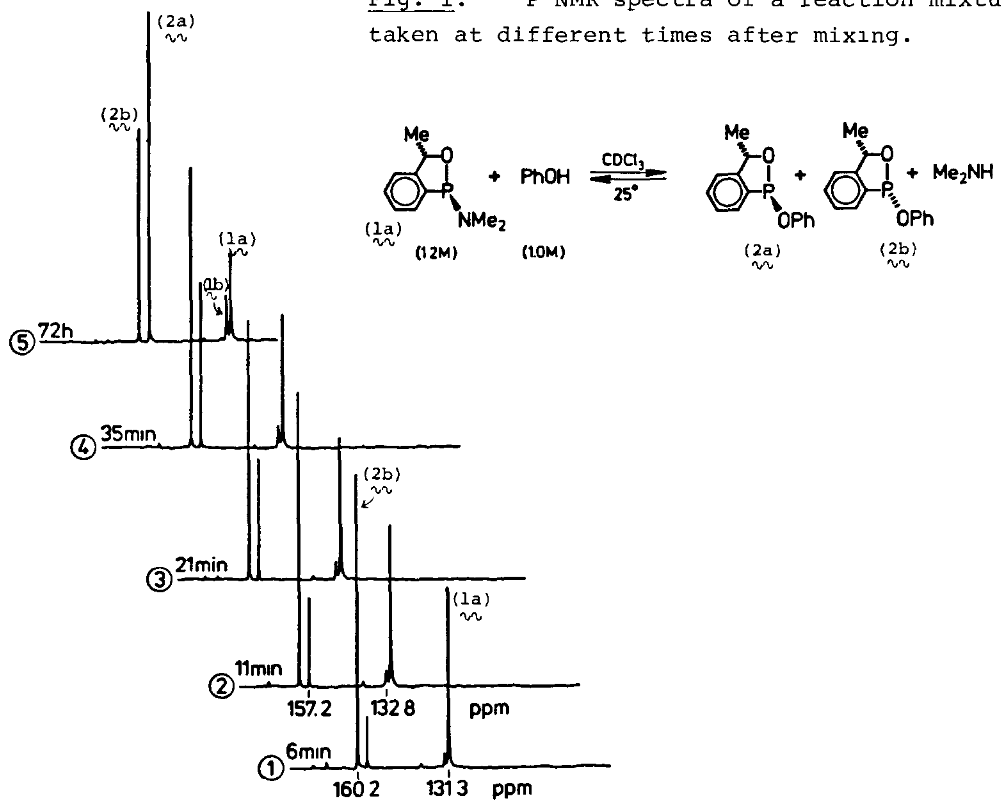
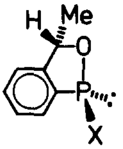


Fig. 1. ^{31}P NMR spectra of a reaction mixture taken at different times after mixing.

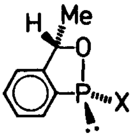
Evidence for the stereochemistry of the reactions, i.e. the configuration of the compounds, has been obtained as follows.

In the ^1H NMR spectra all compounds (**2**) showed a broadened quartet (**2a**) or a doublet of quartets (**2b**) due to the 5-hydrogen atom. This shows that $^3J_{POCH}$ is small (<2 Hz) for (**2a**) and large (>14 Hz) for (**2b**). The same large difference in coupling constants was found for the two nonequivalent 5-hydrogen atoms of the 5-unsubstituted compounds.[2] Since the five-membered ring is probably planar or undergoes fast ring inversion at 25° this difference in coupling constants is taken to signal a difference in orientation of the 5-hydrogen atom relative to the lone pair on phosphorus. The compounds with the small coupling constants $^3J_{POCH}$ are tentatively[3] assigned the configuration with the *P*-substituent *trans* to the 5-methyl group, (**2a**):



$^3J_{POCH} < 2Hz$

(**2a**)

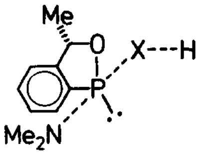


$^3J_{POCH} > 14Hz$

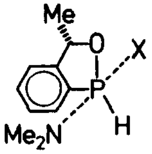
(**2b**)

The product from (**1a**) was initially largely (**2b**) for X = OMe, OPh, and $N(CH_2)_5$, i.e. the reactions proceed with predominant *inversion at phosphorus*. For X = OBu^t and NHPh the reactions at 25° were too slow to follow, but (**1a**) was slowly isomerized; at higher temperatures equilibrium mixtures of (**2a**) and (**2b**) were formed.

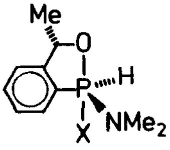
The mechanism of nucleophilic substitution at tricovalent phosphorus is often assumed to be $S_N2(P)$.[1a,4] Such a mechanism however seems unlikely in the case of (**1a**) because the transition state (**A**) or (**B**) with the ring diequatorial would experience severe ring strain.[5] More likely phosphorane intermediates (**C**) are involved. The stereochemical result of the reaction would then depend on which pseudorotation of (**C**) (necessary to place NMe_2 in an axial position for leaving) would have the lower energy barrier. The possible pseudorotations (with the exclusion of phosphoranes with the ring dieq.) are given in the Scheme. It follows that the mechanism is in accord with predominant inversion if H is more apicophilic[5] than NMe_2. This is known to be the case for similar phosphoranes.[2] The isomerization of (**1a**) which occurred for X = OBu^t



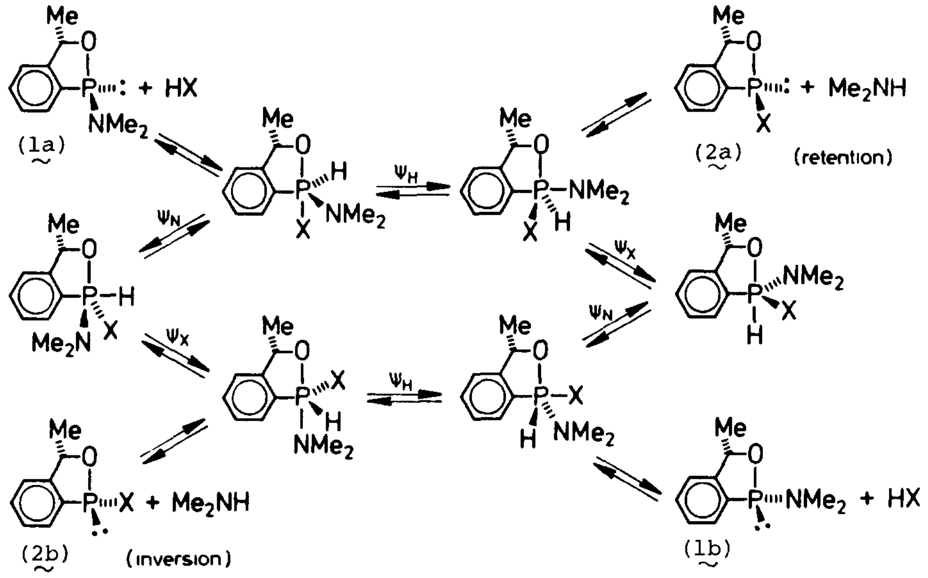
(**A**)



(**B**)



(**C**)



Scheme

and NHPh without discernible product formation may likewise be explained by the proposed mechanism if the equilibria are strongly displaced towards (1). This was shown to be true for X = NHPh. Small amounts of water, however, may be responsible for the isomerization, via reaction of (1a) with the Me$_2$NH formed by hydrolysis of (1a).

The proposed mechanism fits the results for substitutions at (1a) as we. as Horner's results for substitutions at acyclic aminophosphines.^{1a} However, true nucleophilic substitutions at tricovalent phosphorus, with X$^-$ nucleophiles, are stereoselective with a high degree of inversion^{1c} and may follow another mechanism. Further work is in progress to determine the role of the nucleophile (HX versus X$^-$) with regard to the stereochemistry of these substitution reactions.

References

1. a. L. Horner and M. Jordan, Phosphorus and Sulfur, 1980, 8, 235; M. Mikolajczyk, J. Omelanczuk and W. Perlikowska, Tetrahedron, 1979, 35, 1531; c. M. Mikolajczyk, Pure Appl. Chem., 1980, 52, 959, and references cited therein.
2. B. M. Dahl, O. Dahl and S. Trippett, J.C.S. Perkin I, 1981, in press.
3. An X-ray structure on the sulphide of (1a) is under way to prove the assignment.
4. J. A. Mosbo, Phosphorus and Sulfur, 1978, 4, 273.
5. S. Trippett, Phosphorus and Sulfur, 1976, 1, 89.

(Received in UK 27 May 1981)