Tetrahedron Letters,Vo.26,No.36,pp 4379-4382,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain 

# STEREOCHEMICAL ASPECTS OF THE REACTION OF DIALKYL PHOSPHATES WITH AMINE IN THE PRESENCE OF TRIPHENYLPHOSPHINE AND CARBON TETRACHLORIDE

*Janina Baraniak and Wojciech J. Stec* *

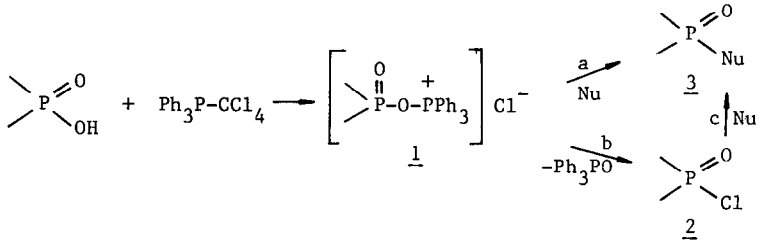
*Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Department of Bioorganic Chemistry, 90-362 Łódź, Boczna 5, Poland*

Abstract: Activation of P-chiral dialkyl phosphates with triphenylphosphine-carbon tetrachloride involves intermediate phosphonium salt 1 which undergoes nucleophilic attack by aniline or pyridine with inversion of configuration at the chiral phosphorus atom.

It has been reported from this Laboratory that application of the Appel Reaction[1] to nucleoside cyclic 3',5'-phosphates enables their conversion to the mixture of diastereoisomers of nucleoside cyclic 3',5'-phosphoranilidates, which after separation can be stereospecifically converted into nucleoside cyclic 3',5'-(Rp)- and (Sp)-phosphorothioates [2] and $|^{18}O|$phosphates [3].

In this communication we wish to describe our results concerning the stereochemistry of the Appel Reaction which sheds some light on the so far obscure mechanism of this process. According to the literature sources [4], the reaction of dialkyl phosphate with triphenylphosphine-carbon tetrachloride involves the formation of intermediate phosphonium salt 1.

SCHEME 1.



This salt (1) may undergo direct attack by nucleophile, like aniline, with formation of phosphoranilidate 3 (*route a*). As an alternative route, the collapse of 1 with the formation of phosphorochloridate 2 has been considered (*route b*). Subsequent reaction of phosphorochloridate 2 with nucleophile leads to desired 3 (*route c*). If the rate of the reaction of 1 or 2 with nucleophile is comparable with that for the reaction of 1 or 2 with unactivated dialkyl phosphate, as the side product tetraalkylpyrophosphates are formed. Above analysis clearly indicates that *route a* involves the single act of nucleophilic substitution at phosphorus atom while *route b* and *c* have to involve two sequential acts of nucleophilic substitutions. Because it is generally accepted (with few exceptions [5]) that single nucleophilic substitution at phosphorus atom, which is not incorporated within a small ring system and where the attacking nucleophile may approach phosphorus opposite the leaving group (*in-line* mechanism), is accompanied by inversion of configuration [6], our stereochemical approach to the Appel Reaction should enable differentiation between *routes a* and *b-c*.

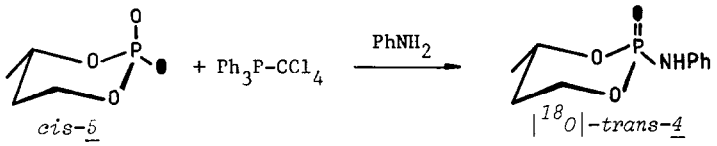
As a model system we applied diastereoisotopomeric dialkyl $|^{16}O, {}^{18}O|$phosphates, *cis*- and *trans*-5 [7], which were obtained according to the procedure involving the stereospecific reaction of *cis*- and *trans*-2-phenylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (4) with

sodium hydride-|$^{18}$O|benzaldehyde [8].

The isotope enrichment and the distribution of oxygen-18 between axial and equatorial P-exocyclic positions were assigned as described elsewhere [3] (see Table 1).

*Cis*-|$^{18}$O|-2-hydroxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (5, 0.6 g, 4 mmole) in acetonitrile solution was treated with triphenylphosphine (1.3 g, 4.8 mmole), carbon tetrachloride (0.4 ml, 4 mmole) and aniline (0.7 ml, 8 mmole). $^{31}$P-NMR analysis of the reaction mixture showed the presence of *trans*-2-phenylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (4, $\delta_{31P(CH_3CN)}$ -1.8 ppm) and bis-(2-oxo-4-methyl-1,3,2-dioxaphosphorinanyl)oxide ($\delta_{31P(CH_3CN)}$ -20.8 ppm) in the ratio 4:1. For the purpose of the separation of *trans*-4 the reaction mixture was chromatographed on $Al_2O_3$ with $CHCl_3$-$C_2H_5OH$ (98:2) as an eluent system and crude *trans*-4 was crystallized from ethyl acetate (yield 13.2%, Scheme 2)[9]. M.S. analysis of this compound after correction to natural abundance of oxygen-18, let us assign the content of this isotope as 55.7%.

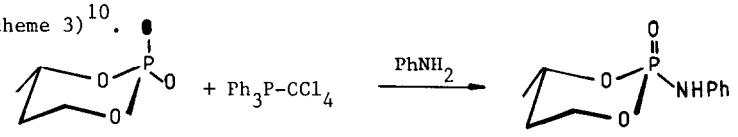
SCHEME 2.




*cis*-5 |$^{18}$O|-*trans*-4

The analogous reaction has been performed with *trans*-|$^{18}$O|-2-hydroxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (5, positional enrichment in oxygen-18 given in Table 1). In this case *trans*-4 was formed in 17% yield with 2.7% enrichment in oxygen-18 allocated to an axial position (Scheme 3)[10].

SCHEME 3.




*trans*-5 *trans*-4

Since our synthesis of cAMP-anilidates was performed in pyridine as solvent, and the ratio of Rp:Sp diastereoisomers was 2:1, we decided to repeat the reaction of *cis*-5 and *trans*-5, independently, with $Ph_3$-$CCl_4$-$PhNH_2$ using pyridine as the reaction medium. A mixture of *trans*-4 and *cis*-4 in the ratio 2:1 in 12% yield was obtained from both substrates. The distribution of oxygen-18 in above products is presented in Table 1.

Table 1. Positional incorporation of |$^{18}$O| into *cis*-4, *trans*-4, *cis*-5 *and trans*-5

| No. | Compounds | $^{18}$O enrichment measured on molecular ion (%) | Positional $^{18}$O enrichment in | |
|---|---|---|---|---|
| | | | equatorial | axial |
| 1. | *cis*-5 | 61.4 | 56.4 | 5.0 |
| 2. | *trans*-5 | 63.1 | 4.2 | 58.9 |
| 3. | *trans*-4 1a) | 55.7 | | 55.7 |
| 4. | *trans*-4 1b) | 2.7 | | 2.7 |
| 5. | *trans*-4 and *cis*-4 2a) | 54.9<br>47.4 | 47.4 | 54.9 |
| 6. | *trans*-4 and *cis*-4 2b) | 8.6<br>16.6 | 16.6 | 8.6 |

1a) - the reaction was performed on *cis*-5 in $CH_3CN$, 1b) - the reaction was performed on *trans*-5 in $CH_3CN$, 2a) - the reaction was performed on *cis*-5 in $C_5H_5N$, 2b) - the reaction was performed on *trans*-5 in $C_5H_5N$

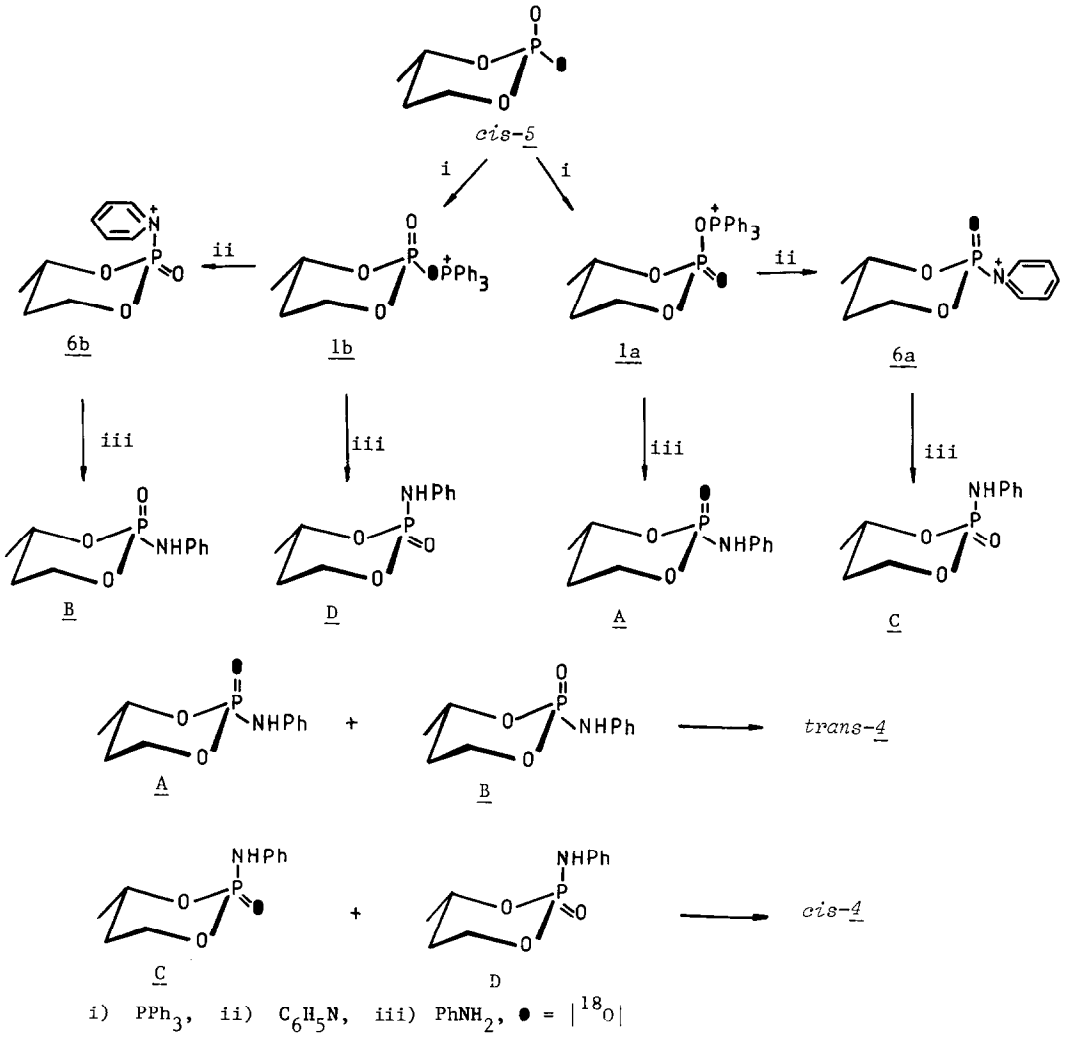
Assuming that an isotope effect is negligible, analysis of the data allows us to draw

1) An axial oxygen atom undergoes preponderant activation by $Ph_3P$-$CCl_4$ leading to intermediate 1. For the reaction performed in $CH_3CN$ we could estimate that activation of 66 molecules of 5 at axial oxygen is accompanied by a single activation at equatorial oxygen.

2) The nucleophilic reagent attacks the phosphorus atom of 1 with departure of $Ph_3PO$ and formation of a covalent bond to phosphorus. If the reaction is performed in acetonitrile solution the overall process proceeds with inversion of configuration and, due to major activation of axial oxygen, the resulting anilidate has the *trans*-geometry. The comparison of isotopic enrichments in the products resulting from *cis*-5 and *trans*-5 (Table 1) strongly supports the mechanism involving direct attack of aniline on 1 without intermediacy of phosphorochloridate 2.

3) The formation of isotopically labelled *cis*-4 in pyridine solution (isomer C, Scheme 4) can be explained by assuming that phosphonium salt 1a undergoes competitive nucleophilic attack by aniline and by pyridine, leading to anilidate A and N-phosphopyridinium salt 6a respectively. Subsequent nucleophilic attack of aniline on the salt 6a results in the formation of isomer C with reverse configuration with respect to that of isomer A.

SCHEME 4.



4) The use of pyridine as solvent changes the relative populations of 1a and 1b towards a higher contribution from intermediates with activated equatorial oxygen of 5 (salt 1b, Scheme 4)[11]. This last compound undergoes competitive reactions with pyridine and aniline, leading to 6b and D respectively. Reaction of 6b with aniline gives anilidate B. An increased population of 1b observed for reaction carried out in pyridine is responsible for reduction of isotopic enrichment of *cis*-4 and *trans*-4 caused by the formation of unlabelled anilidates D and B. If *trans*-5 was used as a substrate in pyridine solution the relative increase of isotopic enrichment in the resulting anilidates 4 (Table 1, entry 6 ) is also explained by an increased population of intermediate 1 with activated equatorial oxygen atom.

5) The analysis of isotopic enrichments and yields of *cis*- and *trans*-anilidates, resulting from isomers 5, allows us to estimate that in pyridine solution activation of axial vs equatorial oxygens in 5 with $Ph_3P$-$CCl_4$ occurs in the ratio 10:1 and differs from that observed in experiments carried out in $CH_3CN$ medium.

6) In pyridine as solvent the reaction of intermediate 1 with aniline occurs 1.5 - 2 times more rapidly than that with pyridine followed by aniline.

Although the complexity of the reaction of dialkyl phosphates with aniline in the presence of $Ph_3P$-$CCl_4$ has been enhanced by the behaviour of our model 4-methyl-1,3,2-dioxaphosphorinanyl ring system and its stereodifferentiated reactivity of phosphoryl oxygen atoms, the presented data broaden our knowledge about the course of events in the Appel Reaction and the role of nucleophilic solvent, such as pyridine, which as in many other reactions activates the phosphorylation process.

Acknowledgment: This work was financially assisted by the Polish Academy of Sciences, Grant no. MR-I-12 and, in part, by the National Cancer Programme PR-6.

References and Notes

1. R.Appel, Angew.Chem., Int.Edn.Engl., 14, 801 (1975)
2. J.Baraniak, R.W.Kinas, K.Lesiak, W.J.Stec, J.Chem.Soc., Chem.Commun., 1979, 940
3. J.Baraniak, K.Lesiak, M.Sochacki, W.J.Stec, J.Am.Chem.Soc., 102, 4534 (1980)
4. R.Ramage in "Organophosphorus Reagents in Organic Synthesis", J.I.G.Cadogan, Ed., A.P.London, N.Y., 528 (1979)
5. J.Donohue, N.Mandel, W.B.Farnham, R.K.Murray, K.Mislow, H.P.Benschop, J.Am.Chem.Soc., 93, 3792 (1971); P.M.Cullis, Tetrahedron Lett., 24, 5677 (1983)
6. F.H.Westheimer, Acc.Chem.Res., 1, 70 (1968); P.Gillespie, F.Ramirez, I.Ugi, D.Marquarding, Angew.Chem., Int.End.Engl., 12, 91 (1973)
7. The term *cis* refers to diequatorial positions of 4-methyl and the senior exocyclic group on phosphorus, as determined by the sequence rule, while *trans* refers to equatorial-axial relationship between these two groups: J.Org.Chem., 35, 2849 (1970)
8. $|^{18}O|$Benzaldehyde (65.1% enriched in oxygen-18) was obtained by hydrolysis of benzylideneaniline in $|^{18}O|H_2O$ (70% of oxygen-18).
9. From mother-liquor ca. 2 mg of *cis*-4 (yield 0.2%) containing 6.2% of oxygen-18 was isolated.
10. A minute amount (yield ca. 0.2%) of *cis*-4 containing 58.1% of oxygen-18 was isolated.
11. Axial versus equatorial phosphorus oxygen basicity in a six-membered ring phosphate anion was discussed by Verkade et al., A.P.Hong, J.B.Lee, J.G.Verkade, J.A.Chem.Soc., 98, 6547 (1976)