# Stereochemistry of Substitution at Trico-ordinate Phosphorus

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

A series of reactions of ring-substituted 1,3,2-dioxaphospholanes, 1,3,2-oxazaphospholanes, 1,2-oxaphospholes, and phosphetanes bearing the leaving groups Cl, OR, or $NR_2$ on phosphorus, with the nucleophiles HCl, $MeO^-$, MeOH, PhOH, $Me_2NH$, $Et_2NH$, and $[CH_2]_5NH$ have been studied. N.m.r. signals ($^1H$ and $^{31}P$) from reactant and product diastereoisomers have been assigned, and the stereochemistry of the substitution reactions have been determined by $^{31}P$ n.m.r. monitoring. The outcome varies from complete inversion to complete lack of stereoselectivity. During the initial stages many of the non-selective reactions proceed with predominant inversion, and most of the results may be interpreted by assuming that the actual substitution step occurs with inversion, and that the lack of stereoselectivity is due to competing isomerizations of products or reactants. Exceptions are certain reactions where the leaving group is Cl; these appear to involve a non-selective substitution step.

Trico-ordinate phosphorus compounds are often prepared from other trico-ordinate phosphorus compounds (notably $PCl_3$) by nucleophilic substitution of appropriate leaving groups [equation (i)].[1] A good leaving group like Cl is very

$$>P\text{-}L + Nu \longrightarrow >P\text{-}Nu + L \quad \text{(i)}$$

L = Cl, OR, SR, $NR_2$, or Ph
Nu = HCl, $F^-$, $Br^-$, $I^-$, ROH, $RO^-$, $RS^-$, $R_2NH$, $R_2N^-$, or $R^-$

easily displaced but weaker leaving groups (OR or $NR_2$) are also substituted relatively fast, in comparison with substitutions at phosphoric or carboxylic acid centres. The large rate enhancements of substitutions at trico-ordinate as compared with tetraco-ordinate phosphorus have been exploited in oligonucleotide syntheses: 'phosphite' methods [2,3] are attractive alternatives to 'phosphotriester' methods.[4]

The mechanism of substitution at tetraco-ordinate phosphorus has been studied extensively, and much is now known about kinetics, catalysis, intermediates, and stereochemistry.[5] In contrast, little is known about the mechanism of substitution at trico-ordinate phosphorus. Without such knowledge it is difficult to select optimum conditions for the reactions, and this has often been detrimental to yields and purity of products.

We have initiated a study of the mechanism of substitutions at trico-ordinate phosphorus, and present here our results concerning the stereochemistry. Stereochemical studies have been performed previously in a few cases. Kyba [6] has shown that alkyl-lithium reagents substitute aryl groups in phosphines with complete inversion. Mikolajczyk [7] has found that RLi or $Me_2NLi$ replaces OR in phosphinites with a high degree of inversion. Reactions of nucleophiles with chloro- or amino-phosphines have been described with diverse stereochemical results, *e.g.* predominant inversion,[8] production of equilibrium mixtures of diastereoisomers,[9] and retention.[10]

Horner [11] has recently studied reactions of an optically active aminophosphine with a series of nucleophiles [equation (ii)]. Racemic products were obtained in most cases, and this

$$Ph(Et)P\text{-}NEt_2 + HX \longrightarrow Ph(Et)P\text{-}X$$
$$HX = HCl, ROH, RSH, RCO_2H, \textit{etc.} \quad \text{(ii)}$$

was explained by a mechanism in which substitution with inversion was followed by fast racemization of the products. Reactions with two trifluoracetic acid esters or with *p*-cresol gave products with some degree of retention [equation (iii)]. In these cases a four-centre transition state with electrophilic attack on nitrogen was postulated.

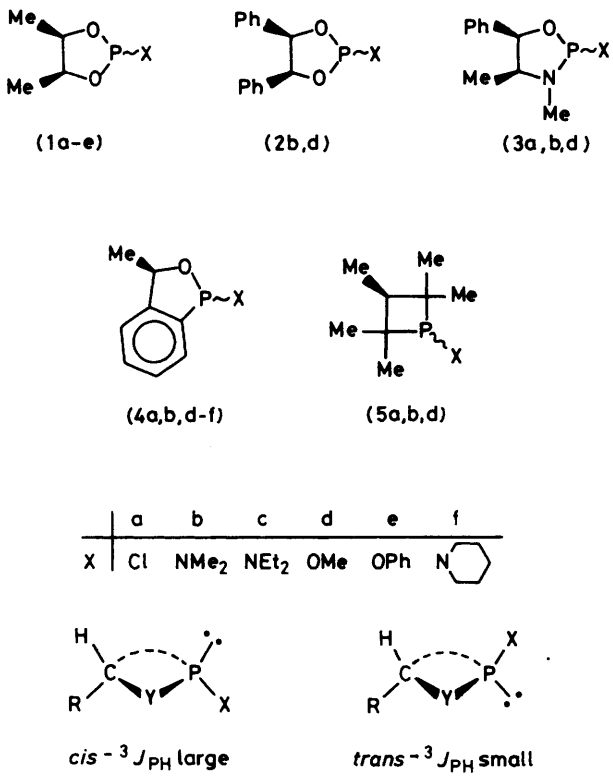
$$Ph(Et)P\text{-}NEt_2 + CF_3CO_2R \longrightarrow Ph(Et)P\text{-}OR + CF_3CONEt_2 \quad \text{(iii)}$$

Horner monitored some of the reactions by optical rotation measurements, but all the other stereochemical inferences were based solely on analyses of the end products.

In the present study we have examined substitution reactions of cyclic compounds containing a second asymmetric centre in addition to the phosphorus centre.[12] Products from such compounds which undergo substitution at phosphorus with inversion or retention are diastereoisomers and therefore can be differentiated by $^1H$ and $^{31}P$ n.m.r. Analysis of the n.m.r. spectra gives the stereochemical result of the substitution provided that an assignment of signals to each diastereoisomer can be made. Another advantage of these diastereoisomeric systems is that any configurational change in products or reactants can be observed during the reactions. This is of importance in understanding the variable stereochemical results obtained from simple product studies (see later).

The phosphorus compounds used in this study were the 1,3,2-dioxaphospholanes (1) and (2), the 1,3,2-oxazaphospholanes (3), the 3*H*-2,1-benzoxaphospholes (4), and the phosphetanes (5). The stereochemistry of nineteen substitution reactions has been studied: compounds (1)—(5) with leaving groups Cl, $NR_2$, or OR, and the nucleophiles HCl, $RO^-$, ROH, and $R_2NH$ (Table 2). The reactants (1)—(5) were mixtures of (racemic) diastereomers with one isomer predominant. As shown later, the predominant isomer is the *trans* [X *trans* to the ring substituent(s) on the asymmetric carbon(s)].

*Assignment of Configuration to Compounds* (1)—(5).—A large body of evidence has accumulated which allows assignment of relative configuration to diastereoisomeric cyclic phosphorus compounds.[13] This includes evidence from the relative amounts of isomers at thermodynamic equilibrium (more of the least sterically hindered *trans*-isomer), from $^{31}P$ and $^1H$ n.m.r. chemical shift differences, and from coupling constant variations. For trico-ordinate phosphorus compounds such as (1)—(5), we find that the most reliable parameter is the magnitude of $^3J_{PH}$, the three-bond coupling constant between phosphorus and hydrogen situated at a ring carbon. In four- and five-membered rings $^3J_{PH}$ has been found




Scheme 1.

to be markedly different for hydrogen atoms *cis* and *trans* to the phosphorus lone pair,[14-17] and the assignments (made from various pieces of evidence) consistently identified the *cis*-isomer as the one with the larger $^3J_{PH}$ value. We agree with this assignment (Scheme 1), which has been proven by *X*-ray structure determinations on pure isomers in several cases. These include *trans*-(2d),[18] the *P*-sulphide of *trans*-(4b),[19] the *P*-sulphide of *cis*-(5b),[20] and the *P*-methiodide of *cis*-(5; X = Ph).[21] The three derivatives last mentioned are formed in stereospecific reactions (retention [22,23]) and these results therefore provide proof of the configuration of the trico-ordinate compounds.

The assignments of *cis*- or *trans*-configuration to all reactants and products (1)—(5) in this work were made from the magnitude of $^3J_{PH}$ in accord with Scheme 1. The data are given in Table 1. Additional evidence for the assignments follows from the data in Table 1. (i) When thermodynamic equilibrium is attained the *trans*-isomer is more abundant than the *cis*-isomer for all compounds (1)—(5). (ii) Phosphorus chemical shifts show systematic variations; the *trans*-isomer resonates at higher field than the *cis*-isomer for all compounds (1)—(4); the opposite is the case for all compounds (5). (iii) Chemical shifts of the ring protons and the ring methyl protons vary in a systematic way with configuration. The ring proton of the *trans*-isomer resonates at lower field than that of the *cis*-isomer for all compounds (1)—(5); the opposite is the case for the ring methyl groups.

*Configurational Stability of Compounds* (1)—(5).—Tertiary phosphines have high inversion barriers ($\Delta G^{\ddagger}_{130}$ 29—36 kcal mol$^{-1}$) [24] and are configurationally stable at room temperature. There is no reason to expect trico-ordinate phosphorus compounds with electronegative substituents to have lower inversion barriers, although few data exist on such compounds. Horner has found that pure samples of (−)-(*R*)-EtPhPNEt$_2$ are epimerized only when heated above 100 °C,[25] and Mikolajczyk has isolated (+)-(*R*)-Bu$^t$PhPOMe 85% optically pure after distillation.[26] We observed that pure samples of non-equilibrium diastereoisomeric mixtures of (2b), (4b), (5b), and (5d) could be kept for several months at 25 °C without any change in the isomer ratios. In case of (4b), only a small change was observed after heating to 100 °C for 6 h (the *trans* content diminished from 97 to 90%); no change occurred during 3 days in dry $CDCl_3$ at 25 °C.

These results contrast with several reports on $R^1R^2PL$ systems as configurationally labile compounds. A clue to the cause of this apparent lability is the fact that isomerization is accelerated by nucleophilic impurities (water, alcohols, amines, *etc.*) and often catalysed by acids.[26] In the case of (4b), addition of $Me_2NH$ and a small amount of $Me_2NH_2^+Cl^-$ to a solution in $CDCl_3$ at 25 °C gave the equilibrium mixture (58% *trans*) after a few hours. Small amounts of water (from wet solvents or air) also caused isomerization, probably by the action of $Me_2NH$ generated from (4b) and water. Reactive species $R^1R^2PL$ isomerize faster than simple alkoxy- and amino-phosphines, and all chlorophosphines isomerize very fast, probably owing to the unavoidable presence of minute

**Table 1.** N.m.r. parameters for *cis*- and *trans*-isomers of compounds (1)—(5), in $CDCl_3$ at *ca.* 30 °C unless otherwise specified

| Compound | | $\delta_P$ | % [a] | $\delta_H$ (ring CH) | $^3J_{PXCH}$ | $\delta_H$ (ring $CH_3$) |
|---|---|---|---|---|---|---|
| (1a) | *trans* | 167.5 | 92 | 4.81 | 2.1 | 1.28 |
| | *cis* | 172.2 | 5 | | | |
| (1b) | *trans* | 139.9 | 91 | 4.48 | 3.7 | 1.16 |
| | *cis* | 147.4 | 6 | 4.18 | 7.6 | 1.25 |
| (1c) | *trans* | 142.2 | 90 | 4.45 | 3.8 | 1.16 |
| | *cis* | 150.3 | 7 | 4.19 | 7.7 | 1.24 |
| (1d) | *trans* | 135.5 | 87 | 4.55 | 2.1 | 1.19 |
| | *cis* | 147.8 | 10 | 4.36 | 8.1 | 1.33 |
| (1e) | *trans* | 129.5 | 87 | 4.53 | 2.0 | 1.18 |
| | *cis* | 138.2 | 10 | 4.43 | 8.3 | 1.38 |
| (2b) | *trans* | 142.8 | 91 | 5.67 | 3.2 | |
| | *cis* | 148.0 | 9 | 5.42 | 6.6 | |
| (2d) | *trans* | 138.4 | 99 | 5.67 | 2.0 | |
| | *cis* | 151.3 | 1 | | | |
| (3a) | *trans* | 169.1 [b] | 92 [b] | 5.91 [b,c] | 1.1 [b,c] | 0.70 [b] |
| | *cis* | 170.3 [b] | 8 [b] | 5.54 [b,c] | 3.9 [b,c] | 1.13 [b] |
| (3b) | *trans* | 130.4 | 97 | 5.51 [c] | <1 [c] | 0.60 |
| | *cis* | 143.9 | 3 | | | |
| (3d) | *trans* | 138.9 | 89 | 5.64 [c] | <1 [c] | 0.59 |
| | *cis* | 148.1 | 11 | 5.41 [c] | 2.5 [c] | 0.73 |
| (4a) | *trans* | 169.6 | 62 | 5.90 | 6.7 | 1.63 |
| | *cis* | 172.3 | 38 | 5.75 | 18.5 | 1.71 |
| (4b) | *trans* | 131.2 | 58 | 5.64 | <1 | 1.52 |
| | *cis* | 132.6 | 42 | 5.28 | 14.2 | 1.56 |
| (4d) | *trans* | 158.2 | 64 | 5.81 | <1 | 1.56 |
| | *cis* | 162.7 | 36 | 5.50 | 14.0 | 1.63 |
| (4e) | *trans* | 157.2 | 62 | 5.76 | 1.7 | 1.56 |
| | *cis* | 160.2 | 38 | 5.60 | 15.0 | 1.63 |
| (4f) | *trans* | 127.3 | 61 | 5.61 | <1 | 1.51 |
| | *cis* | 129.2 | 39 | 5.27 | 14.5 | 1.53 |
| (5a) | *trans* | 169.2 | 71 | 2.81 | 1.3 | 0.77 |
| | *cis* | 149.0 | 29 | 2.17 | 2.4 | 0.89 |
| (5b) | *trans* | 127.5 | 70 | 2.65 | <0.5 | 0.73 |
| | *cis* | 99.6 | 30 | 1.64 | 3.4 | 0.82 |
| (5d) | *trans* | 186.6 | 64 | 2.60 | 0.6 | 0.72 |
| | *cis* | 169.5 | 36 | 1.84 | 2.2 | 0.81 |

[a] Equilibrium values from $^{31}P$ n.m.r. integrals. Remaining % is (±)-isomer from (±)-butane-2,3-diol. [b] In [$^2H_8$]toluene at −50 °C. One signal ($\delta_P$ 169.2) at 30 °C in [$^2H_8$]toluene, one signal ($\delta_P$ 171.1) at 30 °C in $CDCl_3$; no splitting to −60 °C. [c] Ring CH next to oxygen.

**Table 2.** Stereochemical results of substitution reactions [a] on compounds (1)—(5)

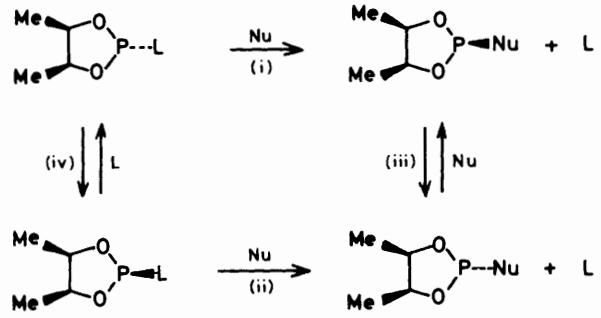
| No. | Reactant | *trans* : *cis* | Nucleophile | *trans* : *cis* Product | *trans* : *cis* Initial [b] | *trans* : *cis* Equilibrium [c] | $t_{5\%}$ [d] |
|---|---|---|---|---|---|---|---|
| 1 | (1a) | 95 : 5 | $MeO^-$ [e,f] | (1d) | 90 : 10 | 90 : 10 | ≪1 min |
| 2 | (1a) | 95 : 5 | MeOH + $Et_3N$ | (1d) | 90 : 10 | 90 : 10 | ≪1 min |
| 3 | (1a) | 95 : 5 | $Et_2NH$ [g] | (1c) | 94 : 6 | 94 : 6 | ≪1 min |
| 4 | (1b) | 94 : 6 | MeOH | (1d) | 6 : 94 | 90 : 10 | <1 min |
| 5 | (1b) | 94 : 6 | PhOH | (1e) | 23 : 77 | 90 : 10 | <1 min |
| 6 | (1c) | 93 : 7 | $Me_2NH$ [g] | (1b) | *ca.* 60 : 40 | 94 : 6 | 50 min |
| 7 | (1d) | 90 : 10 | PhOH | (1e) | *ca.* 70 : 30 | 90 : 10 | 80 h |
| 8 | (1e) | 90 : 10 | MeOH | (1d) | *ca.* 90 : 10 | 90 : 10 | 55 h |
| 9 | (2b) | 99 : 1 | MeOH | (2d) | 8 : 92 | 99 : 1 | 10 min |
| 10 | (3a) | 92 : 8 [h] | MeOH + $Et_3N$ | (3d) | 56 : 44 [i] | 89 : 11 | ≪1 min |
| 11 | (3a) | 92 : 8 [h] | $Me_2NH$ [g] | (3b) | 97 : 3 | 97 : 3 | ≪1 min |
| 12 | (3b) | 97 : 3 | MeOH | (3d) | 45 : 55 [i] | 89 : 11 | <1 min |
| 13 | (4b) | 97 : 3 | HCl [f,g] | (4a) | 62 : 38 | 62 : 38 | ≪1 min |
| 14 | (4b) | 97 : 3 | MeOH [f] | (4d) | 15 : 85 | 64 : 36 | 2 h |
| 15 | (4b) | 97 : 3 | PhOH [f] | (4e) | 16 : 84 | 62 : 38 | 1 min |
| 16 | (4b) | 97 : 3 | $[CH_2]_5NH$ [f] | (4f) | 16 : 84 | 61 : 39 | 6 h |
| 17 | (5a) | 71 : 29 | $MeO^-$ [e,f] | (5d) | 29 : 71 | 64 : 36 | ≪1 min |
| 18 | (5a) | 71 : 29 | $Me_2NH$ [g] | (5b) | 13 : 87 | 70 : 30 | ≪1 min |
| 19 | (5b) | 5 : 95 [j] | MeOH | (5d) | *ca.* 65 : 35 [j] | 64 : 36 | 17 h |

[a] *ca.* 1M-Solutions in $CDCl_3$ at *ca.* 30 °C catalysed by $Me_2NH_2^+Cl^-$ (*ca.* 0.1M), unless otherwise stated. [b] After *ca.* 5% had reacted, or after 5 min for fast reactions. [c] From Table 1. [d] Approximate times for 5% product to appear; ≪1 min signifies reactions which are over in 5 min. [e] In MeOH at 0 °C. [f] No catalyst added. [g] 2M. [h] Measured in $[^2H_8]$toluene at −50 °C. [i] *ca.* 10% Ring-opened product formed. [j] (5b) Isomerizes to a 70 : 30 mixture before any product is observed.

amounts of HCl. The isomerization may be fast enough to cause coalescence of the $^{31}P$ n.m.r. signals. Thus, (3a) gave one $^{31}P$ n.m.r. signal in $CDCl_3$ or $[^2H_8]$toluene at 30 °C, and only in the latter solvent were separate signals from *cis*- and *trans*-(3a) seen upon cooling (Table 1). In case of (1a) the signals from *cis*- and *trans*-(1a) collapsed to one signal on addition of an equimolar amount of $Et_3N$ in $CDCl_3$ at 30 °C.

The foregoing results strongly suggest that all trico-ordinate phosphorus compounds have high inversion barriers, like the tertiary phosphines. The ease of isomerization found for many $R^1R^2PL$ systems is due to the presence of impurities; these probably cause isomerization by initiating a substitution process. The same conclusion was drawn by Mikolajczyk.[26] However, since we have found that at least in one case [(5b) + MeOH] isomerization of starting material proceeds much faster than any observable substitution, there may be several mechanisms operating for the catalysed isomerization of $R^1R^2PL$ systems. A more detailed study must await results from kinetic studies on substitution reactions in general.

*Results.*—The stereochemical results of the reactions of compounds (1)—(5) with a series of nucleophiles are given in Table 2. The reactions were run in $CDCl_3$ at *ca.* 30 °C in most cases, and $Me_2NH_2^+Cl^-$ (catalyst [27,28]) was added for L = $NR_2$ or OR. The reactions were followed by $^{31}P$ n.m.r. until no further change in signal intensities was observed. Reaction times varied from less than 5 min to several days. The initial product *trans* : *cis* ratios were determined by integration of the $^{31}P$ n.m.r. signals after *ca.* 5% had reacted or after 5 min for fast reactions. From these initial product ratios it is seen that the reactions in many cases occurred with predominant (Nos. 5, 9, 14, 15, and 16) or complete (Nos. 4 and 17) inversion. In one case (No. 18) the product contained more *cis*-isomer than corresponding to 100% inversion. Except for the phosphetane products (5b) and (5d), which isomerized very slowly, all products isomerized during the reactions, and the stereoselectivity was gradually lost. For a number of the reactions (Nos. 1, 2, 3, 7, 8, 11, 13, and 19) the initial product ratios were the equilibrium ratios, *i.e.* no stereoselectivity was found; a few cases (Nos. 6, 10, and 12) showed poor selectivity.




**Scheme 2.**

The majority of these results may be rationalized by assuming that the substitution reactions occur with complete inversion, and that loss of stereoselectivity is caused by parallel substitution reactions on the products or the reactants resulting in isomerization. The various possibilities are illustrated for compounds (1) in Scheme 2. For such a system clean inversion will be observed when the substitution steps (i) and (ii) are much faster that the isomerization steps (iii) and (iv). Loss of selectivity can arise from fast isomerization of products [(iii) fast], or from fast isomerization of reactants [(iv) fast] if the reactants are not equilibrium *cis*–*trans* mixtures or if the rates of the substitution steps (i) and (ii) are different. An exact analysis of a system like this would require a knowledge of all relative rate constants; this was not attempted in the present study. Nevertheless we will show in the following that most of the results of Table 2 may be rationalized by using this scheme combined with estimates of the magnitudes of the relative rates.

We will first consider the reactions 4—8 (Table 2). Substitution of $NMe_2$ in (1b) with OMe or OPh is relatively fast when catalysed by $Me_2NH_2^+Cl^-$ (Nos. 4 and 5). Substitution

of OR in (1d) or (1e) with another OR group is much slower (Nos. 7 and 8). If reactions 7 and 8 can be considered models for the isomerization of products in reactions 4 and 5, then isomerization should be slower than substitution and the reactions 4 and 5 should be quite stereoselective. This is observed. Another consequence of the reaction scheme is that the stereoselectivity should fall if the substitution reaction were slowed relative to product isomerization. This is probably what happened when the catalyst concentration in reaction 4 or 5 was drastically reduced, since the more basic reactant (1b) is expected to respond more strongly to acid catalysis than the product (1d) or (1e). The result is a fall in stereoselectivity, from 6% *trans* in reaction 4 to 20% *trans* without added catalyst, and from 23% *trans* in reaction 5 to 55% *trans* without added catalyst. In reaction 6, where leaving group and nucleophile are alike, substitution and isomerization rates should be similar, and a low stereoselectivity is expected and observed. For the very slow reactions 7 and 8, where OMe and OPh are interchanged, substitution and isomerization rates are probably also similar and a low stereoselectivity is observed.

The reactants (1) in the foregoing reactions are initially equilibrium mixtures of *cis*- and *trans*-isomers. No significant changes in the reactant *cis* : *trans* ratios were seen during the reactions, which indicates that the rates of the substitution steps (i) and (ii) (Scheme 2) are not very different. The observed change in stereoselectivity with catalyst concentration found for reactions 4 and 5 also argues against the alternative pathway of Scheme 2 for loss of stereoselectivity, namely fast isomerization of reactants and different substitution rates for the two isomers. The rates involved in this pathway should respond equally to a change in catalyst concentration because the same leaving group is involved, and therefore no change in stereoselectivity should occur.

Most of the other results listed in Table 2 may be similarly rationalized. A high selectivity is found for reactions 9 and 17; for both reactions the substitution reaction is likely to be much faster than isomerization. A somewhat lower selectivity is observed for reactions 14—16; these reactions were run without added catalyst and this should make the product isomerization reactions more competitive and lower the selectivity, as observed. A still lower selectivity found for reaction 12 could be the result of reversible ring opening because of the presence of the NMe group in the ring of (3d). About 10% of a ring-opened product was seen after 5 min, and the signal increased to 32% after 1 h and then decreased slowly. Reaction 13 gave immediately the equilibrium product mixture, no doubt because of fast isomerization of the *P*-chloro product (4a); when less than the equivalent amount of HCl was used, the remaining (4b) was observed to isomerize much more slowly than the product.

An unexpected result was obtained in one case (No. 18); the product (5b) was richer in *cis*-isomer than expected for 100% inversion. This was even more pronounced when the reaction was run in pentane, in which case (5b) was isolated as a 5 : 95 *trans* : *cis* mixture after distillation. Since the *trans*-isomer in this case is also the more stable isomer (Table 1) the result is explained by different rates of reaction for *cis*- and *trans*-(5a) with $Me_2NH$. The rate of isomerization of the *P*-chloro compound (5a) is probably greater than the substitution rate, and if *trans*-(5a) reacts faster than *cis*-(5a) with $Me_2NH$, then substitution with complete inversion will give more *cis*-(5b) than corresponding to the *trans*-(5a) content, as observed. By inspection of models of *cis*- and *trans*-(5a) in their most probable conformations [29] it can be seen that a nucleophile which attacks phosphorus opposite to Cl is likely to experience less steric hindrance in the *trans*-isomer, as required for the above explanation. A similar increase in the amount of *cis*-product was not found in reaction 17, probably because $MeO^-$ reacts much faster than $Me_2NH$ with (5a); if substitution is fast enough, the starting material will have no time to isomerize.

The *P*-chloro compound (1a) reacted very fast with $MeO^-$, MeOH + $Et_3N$, or $Et_2NH$ (Nos. 1—3) and gave immediately the equilibrium product mixtures. These results are not in accord with the model depicted in Scheme 2. Product isomerizations are unlikely to be much faster than those of reaction 4 or 6 where stereoselectivity was observed. The very high substitution rates of reactions 1—3 should, according to Scheme 2, enhance the degree of stereoselectivity, because isomerization reactions should be unable to compete, but the result is complete loss of selectivity. The alternative isomerization route of Scheme 2, fast isomerization of (1a) combined with different rates of substitution steps (i) and (ii), is also unlikely. The rates of substitution steps (i) and (ii) were not very different for reactions 4—8, so there is no reason for them to be very different for reactions 1—3. Besides, product ratios governed by different substitution rates would not be expected to equal the equilibrium product ratios for all three reactions. We therefore conclude that for reactions 1—3 the actual substitution steps are non-stereoselective. The same conclusion is drawn for reaction 11; surprisingly, reaction 10 retains some selectivity.

Finally, from the result of reaction 19 nothing can be inferred about the stereochemistry of the slow substitution step, since both product and reactant isomerize quickly under the reaction conditions.

*Conclusion.*—The results of this and previous studies indicate that nucleophilic substitution reactions at trico-ordinate phosphorus centres in most cases proceed with complete inversion. When the reactants and products are configurationally stable under the reaction conditions the overall result is inverted products, as found for the limited number of reactions studied by Kyba [6] and Mikolajczyk,[7] as well as for one of the reactions in this study (No. 17). However, since trico-ordinate phosphorus compounds with good leaving groups like Cl, OR, or $NR_2$ normally are configurationally unstable under the conditions of their formation, the overall result for such reactions is substitution without stereoselectivity. This was found for most of the reactions of $EtPhPNEt_2$ studied by Horner,[11] and is the normal result in this study, although we have shown that the actual substitution step in these cases too often occurs with inversion. The model used for the substitution reactions (Scheme 2) explains the results of this and previous studies, with some exceptions. These are Horner's examples of reactions with partial retention,[11] our observations of apparently unselective substitution of the *P*-chloro compounds (1a) and (3a), and our finding of rapid isomerization of (5b) without product formation.

The stereochemistry of a reaction is one important clue to the reaction mechanism. Other indispensable information comes from kinetic studies. These are in progress for selected examples of the reactions reported here; mechanistic proposals for the substitution step of reactions which fit the model of Scheme 2, as well as for the exceptions, will be postponed until the kinetic studies are completed.

## Experimental

N.m.r. spectra ($^1H$ and $^{31}P$) were recorded with a JEOL FX 90 Q spectrometer. Chemical shifts are given relative to internal $Me_4Si$ for $^1H$ data ($\delta_H$) and relative to external 85% $H_3PO_4$ for $^{31}P$ data ($\delta_P$), and are positive for low-field shifts. N.m.r. data for all phosphorus compounds in this work are listed in Table 1. The relative amounts of isomeric compounds were

determined by integration of the $^{31}P\{^1H\}$ spectra (pulse width 30°, acquisition time 0.67 s, pulse repetition 1 s, 60 pulses). The relative amounts determined in this way corresponded well (± 3%) with $^1H$ integrals, and with the theoretical values for several known test mixtures. Elemental analyses were performed by the microanalytical department of this laboratory. All manipulations with trico-ordinate phosphorus compounds were carried out under nitrogen using dry solvents and pre-dried apparatus. $CDCl_3$ was kept over basic $Al_2O_3$ (Woelm B, Super 1).

The following compounds were prepared according to published procedures: 2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane (1a),[30] 2-dimethylamino-4,5-dimethyl-1,3,2-dioxaphospholane (1b),[31] 2-diethylamino-4,5-dimethyl-1,3,2-dioxaphospholane (1c),[32] 2-methoxy-4,5-dimethyl-1,3,2-dioxaphospholane (1d),[33] 2-methoxy-4,5-diphenyl-1,3,2-dioxaphospholane (2d),[18] 1-chloro-2,2,3,4,4-pentamethylphosphetane (5a),[8] and 1-dimethylamino-2,2,3,4,4-pentamethylphosphetane (5b).[34]

The remaining compounds are new or previously reported without preparative details.

4,5-*Dimethyl*-2-*phenoxy*-1,3,2-*dioxaphospholane* (1e).[35] A mixture of compound (1b) (0.81 g, 5 mmol) and phenol (0.51 g, 5.5 mmol) was heated with stirring to 60 °C for 0.5 h, cooled, and evacuated on a water-pump to remove $Me_2NH$. The residue was vacuum distilled to give the *product* (1e) (0.74 g, 70%), b.p. 66—67 °C at 0.1 mmHg as an 84 : 13 : 3 mixture of *trans*- and *cis*-(1e) and the (±)-isomer. After 3 days at 25 °C in $CDCl_3$ with phenol added the mixture contained 87% *trans*-, 10% *cis*-, and 3% (±)-isomer; no further change was seen (Found: C, 56.75; H, 6.25; N, 0.05. $C_{10}H_{13}O_3P$ requires C, 56.6; H, 6.15%).

2-*Dimethylamino*-4,5-*diphenyl*-1,3,2-*dioxaphospholane* (2b).[36] A mixture of *meso*-1,2-diphenylethane-1,2-diol (6.44 g, 30 mmol), $(Me_2N)_3P$ (5.04 g, 30 mmol), and a small amount of $Me_2NH_2^+Cl^-$ was heated with stirring to 110 °C for 1 h, cooled, and evacuated on a water-pump to remove $Me_2NH$. The residue was distilled to give the *product* (2b) (5.9 g, 68%), b.p. 130—134 °C at 0.1 mmHg, m.p. 77—85 °C, as a 91 : 9 mixture of *trans*- and *cis*-(2b). Recrystallization once from hexane gave pure *trans*-(2b) (> 99% *trans*, according to $^{31}P$ n.m.r.), m.p. 87—88 °C (Found: C, 66.95; H, 6.3; N, 4.85. $C_{16}H_{18}NO_2P$ requires C, 66.9; H, 6.3; N, 4.85%).

2-*Chloro*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholane* (3a).[10,37] To a stirred mixture of (−)-ephedrine hydrochloride (20.1 g, 0.10 mol) and $Et_3N$ (30.0 g, 0.30 mol) in tetrahydrofuran (THF) (250 ml), $PCl_3$ (13.7 g, 0.10 mol) was added dropwise during 0.5 h. The solids were filtered off and the solution evaporated to an oil, which was purified by distillation to give the *product* (3a) (8.10 g, 35%), b.p. 96—100 °C at 0.2 mmHg. The product was more than 95% pure according to $^1H$ and $^{31}P$ n.m.r.

2-*Dimethylamino*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholane* (3b).[38] A mixture of (−)-ephedrine hydrochloride (10.0 g, 50 mmol) and $(Me_2N)_3P$ (8.1 g, 50 mmol) in THF (50 ml) was heated with stirring to 50 °C for 1.5 h. The solids were filtered off and the solvent removed to leave an oil, which was distilled to give the *product* (3b) (5.40 g, 43%), b.p. 109—110 °C at 0.2 mmHg, m.p. 49—50 °C, > 95% pure according to $^1H$ and $^{31}P$ n.m.r., as a 97 : 3 mixture of *trans*- and *cis*-(3b). The mixture was unchanged after 3 days.

2-*Methoxy*-3,4-*dimethyl*-5-*phenyl*-1,3,2-*oxazaphospholane* (3d).[10] To a stirred mixture of compound (3a) (1.75 g, 7.6 mmol) and $Et_3N$ (0.85 g, 8.4 mmol) in THF (25 ml) was slowly added MeOH (0.24 g, 7.5 mmol) at −20 °C. The mixture was stirred at room temperature for 1 h, filtered, and evaporated. The residue was distilled to give the *product* (3d) (1.05 g, 61%), b.p. 90—91 °C at 0.3 mmHg, as an 89 : 11 mixture of *trans*- and *cis*-(3d), unchanged after 2 days (Found: C, 58.75; H, 7.25; N, 6.3. $C_{11}H_{16}NO_2P$ requires C, 58.65; H, 7.15; N, 6.2%).

1-*Dimethylamino*-3-*methyl*-3H-2,1-*benzoxaphosphole* (4b). BuLi in hexane (1.52M; 132 ml, 0.20 mol) was added at 20 °C to a solution of racemic 1-phenylethanol (12.2 g, 0.10 mol) and *N,N,N',N'*-tetramethylethylenediamine (30 ml, 0.2 mol) in hexane (200 ml), and the mixture was refluxed with stirring overnight (10—15 h). After dilution with hexane (150 ml) and cooling in solid $CO_2$–acetone, $Me_2NPCl_2$ (14.6 g, 0.10 mol) in hexane (50 ml) was added dropwise with stirring during 1 h. The mixture was stirred at −78 °C for 0.5 h and during warm-up to room temperature (1—2 h), and then set aside for the solids to settle. The hexane solution was decanted, the solids were washed once with hexane (100 ml), and the solvent was removed on a rotary evaporator. The red-brown oily residue was purified by Kugelrohr distillation, followed by distillation through a 15 cm Vigreux column to give a colourless *oil* (6.9 g, 35%), b.p. 62—63 °C at 0.2 mmHg, a 58 : 42 mixture of *trans*- and *cis*-(4b) (Found: C, 61.55; H, 7.35; N, 7.35. $C_{10}H_{14}NOP$ requires C, 61.55; H, 7.25; N, 7.2%).

The *trans*-diastereoisomer was isolated by distillation of the foregoing product (6 g) through an 85-cm Perkin–Elmer 251 spinning band column (reflux ratio 15 : 1). No change in b.p. was observed during distillation, but the first sample collected (2 g) was 97% diastereoisomerically pure *trans*-(4b). Later samples contained varying amounts of both isomers, probably because the high pot temperature (130—140 °C) caused some decomposition and isomerization of (4b).

1-*Chloro*-3-*methyl*-3H-2,1-*benzoxaphosphole* (4a). A solution of HCl in ether (2M; 5.5 ml, 11 mmol) was mixed with a solution of compound (4b) (0.98 g, 5 mmol) in ether (10 ml). The solids were filtered off and the solution evaporated to leave an oil which was purified by distillation through a small Claisen head; yield 0.41 g (40%), b.p. 59—60 °C at 0.2 mmHg. The *product* was a 63 : 37 mixture of *trans*- and *cis*-(4a), unchanged after 8 days (Found: C, 51.25; H, 4.4; Cl, 18.65. $C_8H_8ClOP$ requires C, 51.5; H, 4.3; Cl, 19.0%).

1-*Methoxy*-3-*methyl*-3H-2,1-*benzoxaphosphole* (4d). A mixture of compound (4b) (0.98 g, 5 mmol) and MeOH (1.0 ml, 25 mmol) was heated to reflux for 1 h. The excess of MeOH was removed *in vacuo* and the residue distilled through a small Claisen head; yield 0.62 g (68%), b.p. 48—48.5 °C at 0.1 mmHg. The *product* was a 59 : 41 mixture of *trans*- and *cis*-(4d), which had changed to 64 : 36 2 days after addition of MeOH (Found: C, 59.65; H, 6.1. $C_9H_{11}O_2P$ requires C, 59.35; H, 6.1%).

3-*Methyl*-1-*phenoxy*-3H-2,1-*benzoxaphosphole* (4e). A mixture of compound (4b) (0.98 g, 5 mmol) and PhOH (0.56 g, 6 mmol) was heated to 60 °C for 1 h, cooled, and evacuated on a water pump to remove $Me_2NH$. The residue was distilled through a small Claisen head to give the *product* (4e) (0.92 g, 75%), b.p. 111—112 °C at 0.1 mmHg, as a 62 : 38 mixture of *trans*- and *cis*-(4e), which had not changed 1 month after addition of PhOH (Found: C, 68.75; H, 5.4. $C_{14}H_{13}O_2P$ requires C, 68.85; H, 5.35%).

3-*Methyl*-1-*piperidino*-3H-2,1-*benzoxaphosphole* (4f). A mixture of compound (4b) (0.98 g, 5 mmol) and $[CH_2]_5NH$ (1.72 g, 20 mmol) was refluxed for 2 h. The excess of $[CH_2]_5NH$ was removed *in vacuo* and the residue distilled through a small Claisen head to give the *product* (4f) (0.88 g, 75%), b.p. 104—105 °C at 0.2 mmHg, as a 61 : 39 mixture of *trans*- and *cis*-(4f), which had not changed 1 month after addition of $[CH_2]_5NH$ (Found: C, 66.2; H, 7.85; N, 5.95. $C_{13}H_{18}NOP$ requires C, 66.35; H, 7.7; N, 5.95%).

1-*Methoxy*-2,2,3,4,4-*pentamethylphosphetane* (5d). The chlorophosphetane (5a) (3.57 g, 20 mmol) was added dropwise at 0 °C to a stirred solution of MeONa in MeOH [from Na

(0.46 g, 20 mmol) in MeOH (10 ml)]. The mixture was set aside for the solids to settle, then decanted, and the solvent was removed on a rotary evaporator. Distillation of the residue through a small Claisen head gave the *product* (5d) (1.75 g, 50%), b.p. 51—51.5 °C at 9 mmHg, as a 41 : 59 mixture of *trans*- and *cis*-(5d) which had changed to 64 : 36 after 8 days with MeOH in $CDCl_3$, and showed no tendency to isomerize to 1,2,2,3,4,4-hexamethylphosphetane 1-oxide [8] (Found: C, 62.25; H, 11.25. $C_9H_{19}OP$ requires C, 62.05; H, 11.0%).

## Acknowledgements

We thank Professor Stuart Trippett, The University, Leicester, for valuable suggestions and advice, and Bayer AG, Leverkusen, West Germany, for a gift of *meso*-butane-2,3-diol.

## References

1 M. Regitz, 'Houben-Weyl, Band E1, Phosphorverbindungen I,' Thieme Verlag, Stuttgart, 1982.
2 R. L. Letsinger, E. P. Groody, and T. Tanaka, *J. Am. Chem. Soc.*, 1982, **104**, 6805.
3 M. D. Matteucci and M. H. Caruthers, *J. Am. Chem. Soc.*, 1981, **103**, 3185.
4 M. J. Gait, H. W. D. Matthes, M. Singh, and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 1982, 37.
5 J. Emsley and D. Hall, 'The Chemistry of Phosphorus,' Harper & Row, London, 1976.
6 E. P. Kyba, *J. Am. Chem. Soc.*, 1976, **98**, 4805.
7 J. Omelanczuk, W. Perlikowska, and M. Mikolajczyk, *J. Chem. Soc., Chem. Commun.*, 1980, 24; M. Mikolajczyk, J. Omelanczuk, and W. Perlikowska, *Tetrahedron*, 1979, **35**, 1531.
8 J. R. Corfield, R. K. Oram, D. J. H. Smith, and S. Trippett, *J. Chem. Soc., Perkin Trans. 1*, 1972, 713.
9 G. S. Bajwa and W. G. Bentrude, *Tetrahedron Lett.*, 1978, 421.
10 C. R. Hall and T. D. Inch, *Tetrahedron Lett.*, 1976, 3645.
11 L. Horner and M. Jordan, *Phosphorus Sulfur*, 1980, **8**, 235.
12 Preliminary report, O. Dahl, *Tetrahedron Lett.*, 1981, **22**, 3281.
13 L. D. Quin, 'The Heterocyclic Chemistry of Phosphorus: Systems Based on the Phosphorus–Carbon Bond,' Wiley, New York, 1981.
14 D. Gaignaire, J.-B. Robert, J. Verrier, and R. Wolf, *Bull. Soc. Chim. Fr.*, 1966, 3719.
15 W. G. Bentrude and H.-W. Tan, *J. Am. Chem. Soc.*, 1976, **98**, 1850.
16 B. M. Dahl, O. Dahl, and S. Trippett, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2239.
17 S. E. Cremer, F. L. Weitl, F. R. Farr, P. W. Cremer, G. A. Gray, and H.-O. Hwang, *J. Org. Chem.*, 1973, **38**, 3199.
18 M. G. Newton and B. S. Campbell, *J. Am. Chem. Soc.*, 1974, **96**, 7790.
19 O. Dahl, R. Fogh, and S. Larsen, unpublished result.
20 O. Dahl and S. Larsen, unpublished result.
21 C. Moret and L. M. Trefonas, *J. Am. Chem. Soc.*, 1969, **91**, 2255; S. E. Cremer, *J. Chem. Soc., Chem. Commun.*, 1970, 616.
22 L. Horner and H. Winkler, *Tetrahedron Lett.*, 1964, 175.
23 L. Horner, H. Fuchs, H. Winkler, and A. Rapp, *Tetrahedron Lett.*, 1963, 965.
24 R. D. Baechler and K. Mislow, *J. Am. Chem. Soc.*, 1970, **92**, 3090.
25 L. Horner and M. Jordan, *Phosphorus Sulfur*, 1980, **8**, 225.
26 M. Mikolajczyk, *Pure Appl. Chem.*, 1980, **52**, 959.
27 J. A. Mosbo, *Phosphorus Sulfur*, 1978, **4**, 273.
28 E. E. Nifant'ev and N. L. Ivanova, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1971, **41**, 2217.
29 Ref. 13, p. 295.
30 H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, 1950, **72**, 5491.
31 M. Sanchez, R. Wolf, R. Burgada, and F. Mathis, *Bull. Soc. Chim. Fr.*, 1968, 773.
32 M. Mikolajczyk and M. Witczak, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2213.
33 G. Pouchoulin, J. R. Llinas, G. Buono, and E. J. Vincent, *Org. Magn. Reson.*, 1976, **8**, 518.
34 R. K. Oram and S. Trippett, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1300.
35 S. Trippett and R. E. L. Waddling, *Tetrahedron Lett.*, 1979, 193.
36 H. Germa, M. Sanchez, R. Burgada, and R. Wolf, *Bull. Soc. Chim. Fr.*, 1970, 612.
37 C. B. Cong, G. Gence, B. Garrigues, M. Koenig, and A. Munoz, *Tetrahedron*, 1979, **35**, 1825.
38 J. Ferekh, J.-F. Brazier, A. Munoz, and R. Wolf, *C.R. Acad. Sci., Ser. C*, 1970, **270**, 865.

*Received* 10*th June* 1983; *Paper* 3/965