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PHOSPHORUS STEREOCHEMISTRY
MECHANISTIC IMPLICATIONS OF THE OBSERVED STEREOCHEMISTRY OF BOND FORMING AND BREAKING PROCESSES AT PHOSPHORUS IN SOME 5- AND 6-MEMBERED CYCLIC PHOSPHORUS ESTERS

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CONTENTS

Abstract—The stereochemistry of endocyclic and exocyclic bond forming and breaking processes in 5- and 6-membered cyclic phosphorus esters is summarised and comparisons are made with analogous reactions in acyclic phosphorus esters. The factors that determine which bonds are broken and whether reactions occur with inversion or retention of configuration at phosphorus are complex and usually have more obvious effects for reactions in cyclic than in acyclic phosphorus esters; in particular conformational effects may be important. The stereochemistry of migration of phosphorus ester groups across 1,3-diols is also described. It is suggested that nucleophilic substitutions at phosphorus are inherently stereospecific in the sense that trigonal bipyramidal reaction intermediates break down either directly or following a single Berry Pseudorotation or Turnstile rotation process. Multiple Turnstile rotations which would lead to racemisation, and which apparently do occur in stable phosphoranes, are insignificant for reactions involving trigonal bipyramidal intermediates.

1. INTRODUCTION

Nucleophilic displacement reactions at phosphorus in tetracoordinate pentacovalent phosphorus esters and related compounds are often highly stereoselective occurring with essentially complete inversion or retention of configuration. In other instances the reactions show only marginal stereoselectivity, the relative importance of the reaction pathways leading to products with inversion or retention of configuration being very much a function of the nucleophile, leaving group and the reaction conditions.[1-3]

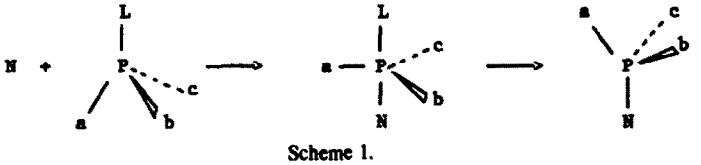
It is customary to consider that reactions with inversion of configuration occur by a S_N2P mechanism or through trigonal bipyramidal intermediates (TBP's) which are formed by attack of the nucleophile opposite the leaving group, so that nucleophile and leaving group are immediately in apical positions in the TBP, with subsequent departure of the leaving group from the apical position before any ligand reorganisations have taken place (Scheme 1). It is not easy to make a clear distinction between these two mechanisms. The difference is conceptual rather than practical and perhaps should be regarded as simply the two extremes of the same mechanism depending very much on the degree of bond formation before bond breaking and the lifetime of any intermediate species.

The importance of the TBP concept[4-7] is that it permits an explanation for nucleophilic displacement reactions at phosphorus that occur with retention of configuration. It is considered that nucleophilic attack occurs at phosphorus in an apical position opposite a ligand that is not the leaving group (Scheme 2). The leaving group attains the apical position from which it departs following ligand reorganisation by a Berry Pseudorotation (BPR)[8] or Turnstile Rotation (TR)[6] process. Whatever the precise mechanism of the ligand reorganisation, the outcome is that exchange of ligands occurs so that the nucleophile occupies a basal position in the TBP and the leaving group occupies an apical position.

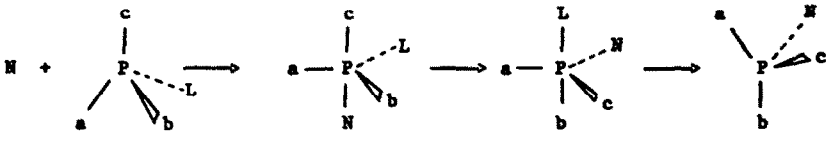
Although this mechanism allows that some reactions can occur with retention of configuration, while at the same time accommodating the principle that bond breaking and bond forming processes can only occur at apical positions in TBP's, it provides no reasons why some reactions occur with retention whereas others occur with inversion of configuration. To account for this various assumptions have to be made. For example, initial nucleophilic attack occurs at phosphorus opposite the most apicophilic group[9-12] (i.e. the group which most favours an apical position in the TBP). If the apicophilic group is also the best leaving group, a reaction with inversion of configuration will occur; if not, ligand reorganisation may precede ligand departure, probably by a single Berry Pseudorotation or equivalent Turnstile process (Scheme 2) and the reaction may take place with retention of configuration. The problem at present is to firmly establish what factors determine the apicophilicity and leaving group ability of ligands attached to phosphorus. This problem is particularly evident where phosphorus is part of a ring system which itself may introduce constraints to ligand reorganisation processes or affect the strength of bonds to phosphorus relative to corresponding bonds in acyclic systems.[7,13]

Although most discussion of the stereochemistry of reactions at phosphorus has been in terms of apical entry of nucleophiles into TBP's with apical departure of the leaving group before or after ligand reorganisation, consideration must also be given to situations where apical entry is followed by basal departure and vice versa, or basal entry is followed by basal departure; these processes allow retention of configuration without ligand reorganisation. Consideration must also be given to the possibility that the intermediate is not strictly a TBP but rather the closely related square basal pyramid (SBP). There is X-ray evidence to support such structures,[14-16] and in certain cases there are energetic advantages over TBP's and again there exists the possibility for displacements with retention of configuration without ligand reorganisation.[17]

It is not, however, the purpose of this paper to review in detail the theoretical and experimental data which seems to favour the TBP concept with apical entry and departure of groups for this subject has been dealt with in many excellent articles.[1,2,4-7] Rather it is the purpose of this paper to summarise recent stereochemical studies of endocyclic and exocyclic bond breaking and forming processes in 5- and



Scheme 1.



Scheme 2.

6-membered ring tetracoordinate pentacovalent phosphorus esters and related compounds, making comparisons with acyclic analogues where possible, to try to establish whether the results from these studies can be accommodated within, distinguish between, or require modification of, the possible mechanistic concepts.

With regard to ring forming and ring breaking processes in 6-membered rings most of the stereochemical studies have been carried out in this laboratory using cyclic phosphorus esters derived from carbohydrates. Although the possibility that the carbohydrate portion of the molecule exerts some influence on the reactions observed at phosphorus may not be discounted it is probable that these effects are slight and that the stereochemical effects at phosphorus are a function primarily of the phosphorus containing ring and not of the carbohydrate. In some cases it has been shown that reactions of cyclic esters derived from butan-1,3-diol are similar to those observed with the corresponding cyclic esters from methyl-2,3-di-O-methyl-α-D-glucopyranoside.

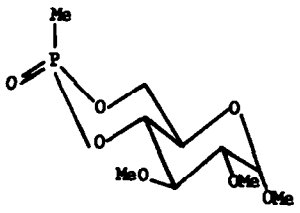
2. STEREOCHEMISTRY OF FORMATION OF 6-MEMBERED CYCLIC PHOSPHORUS ESTERS

1,3,2-Dioxaphosphorinan-2-ones and 1,3,2-dioxaphosphorinan-2-thiones are formed easily by treatment of 1,3-diols with $POCl_3$ and $PSCl_3$ respectively.[18,19] Alternative ring forming procedures have been used particularly for cyclic nucleotides (e.g. cyclic 3',5',-adenosine monophosphate and cyclic 3',5',-guanosine monophosphate) and related compounds.[20–22] The synthetic procedures are usually straightforward and are well documented. Also the conformational preferences of 2-substituents in the 1,3,2-dioxaphosphorinan-2-one system have been extensively studied with the general conclusions that electronegative substituents prefer an axial orientation and that P–Me and P–NR_2 groups prefer an equatorial orientation.[23–25] The interplay of conformational and electronic effects in monocyclic phosphorus esters has been discussed in detail.[26]

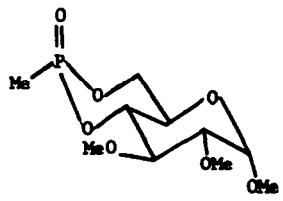
Although the above synthetic and conformational studies have been extensive there has been little discussion of the stereochemical requirements for ring closure. It is therefore pertinent to speculate on the mechanistic significance of some observations about the stereochemical course of ring closing reactions made in this laboratory[27] and elsewhere.[28]

With $MePOCl_2$ or $MePOF_2$ and triethylamine in dichloromethane, methyl 2,3-di-O-methyl-α-D-glucopyranoside afforded a mixture of the (*R*)- and (*S*)-4,6-methylphosphonates (**1ax** and **1eq**). Whether (**1ax**) or (**1eq**) was preponderant in the reaction mixture was a function of reaction time, since (**1ax**) was the kinetically favoured product, (**1eq**) was the thermodynamically favoured product and isomerisation of **1ax** to **1eq** occurred in the reaction mixture. This result was substantiated when it was shown that in the presence of triethylamine in dichloromethane ring closure of methyl 2,3-di-O-methyl-α-D-glucopyranoside 6-(*RS*)-methylphosphonofluoridate (**2**) gave first (**1ax**) which then isomerised to (**1eq**). This mechanism requires that one of the isomers of **2**, epimeric at phosphorus, ring closes more readily than the other. This could not be confirmed since the isomers of **2** are in rapid equilibrium and apparently disappeared from the reaction mixture at equal rates. Similar behaviour was observed when **1ax** and **1eq** were formed by ring closure of methyl 2,3-di-O-methyl-α-D-glucopyranoside 4-(*RS*)-methylphosphonofluoridate (**3**). This type of observation for methylphosphonates is quite general and occurred for example when methyl 6-methylamino-2,3-di-O-methyl-α-D-glucopyranoside was treated with $MePOCl_2$ and when methyl 2,3-di-O-methyl-α-D-galactopyranoside was treated with $MePOCl_2$. In the latter case the 1,3,2-dioxaphosphorinane ring is *cis*-fused to the sugar rather than *trans*-fused as with glucose.

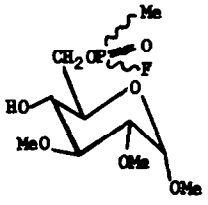
The question raised by these observations is why the thermodynamically favoured product, e.g. **1eq**, should not also be the kinetically favoured product since for example for ring closure of **2** to **1ax** and **1eq** the transition intermediate (**4**) might be expected to be much more favoured than **5** where there appears to be strong steric crowding between H-4 and the P–Me substituent. Such a ring closure assumes a TBP and a chair conformation for the 1,3,2-dioxaphosphorinan-2-one ring. It is clearly reasonable, particularly with regard to results elsewhere in this paper, to accept the assumption of a TBP. It is however not necessary to postulate that ring forming reactions will take place through intermediates in the same conformation as the final product since there is no evidence on this point. In fact the results obtained may be conveniently rationalised on the assumption that the TBP leading to the formation of **1ax** is in a ring with a twist-ring conformation (**6**) with the P–Me group occupying a sterically unhindered pseudoequatorial orientation (*cf* **7**, where P–Me is pseudoaxial). If it is further postulated that once the 1,3,2-dioxaphosphorinan-2-one ring is formed the conformational preference is for a chair rather than a



1ax



1eq



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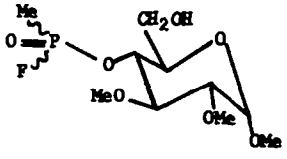

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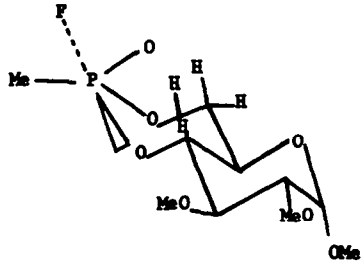

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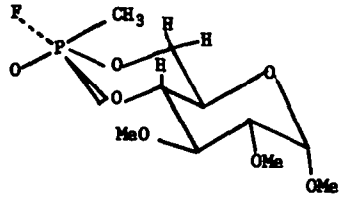

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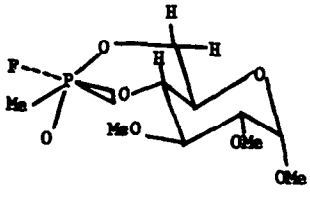

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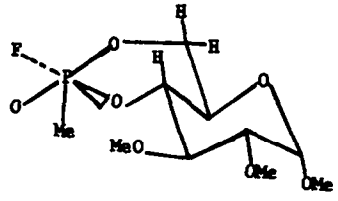

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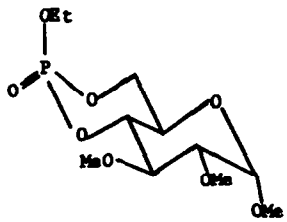
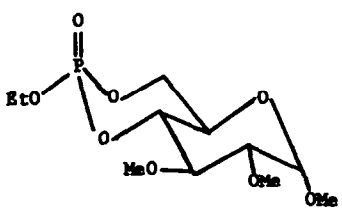
twist-ring or boat form (and NMR evidence is consistent with this) it is reasonable that **1eq** should be thermodynamically favoured over **1ax** where 2,4-diaxial interactions are a destabilising influence.

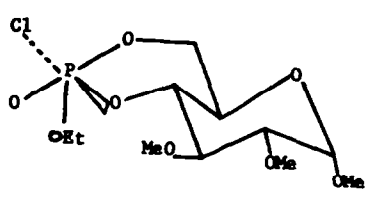
The twist-ring intermediate hypothesis also accounts for the observation that when methyl 2,3-di-O-methyl-α-D-glucopyranoside was treated with ethyl phosphorodichloridate and triethylamine the isomer with the equatorial P–OEt group (**8eq**) preponderated initially but rearranged in the reaction mixture to give an excess of the more stable isomer (**8ax**). The rapid formation of **8eq** is consistent with the well recognised axial preference of electronegative substituents in 1,3,2-dioxaphosphorinan-2-ones (the "gauche" effect or anomeric effect in carbohydrate chemistry) only if an intermediate of non-chair conformation such as **9** is invoked and the subsequent conversion of **8eq** into **8ax** is also consistent with this stereochemical preference in the chair conformation finally adopted.



8ax



8eq



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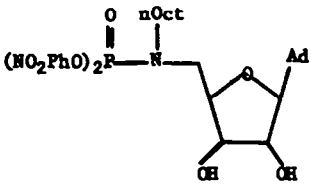

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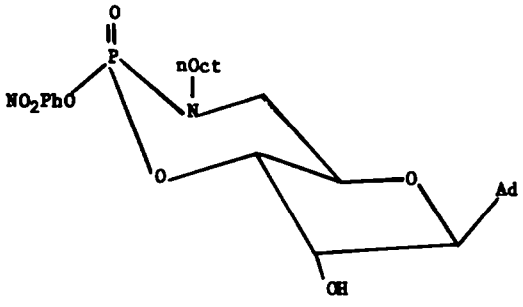
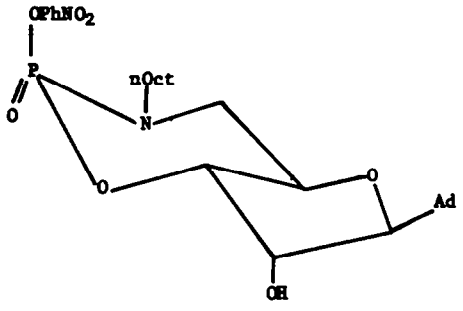
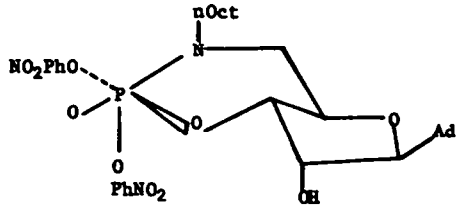


11eq



11ax

A similar observation has been reported by Murayama *et al.*[28] Ring closure of the adenosine derivative (**10**) in the presence of base afforded the equatorial isomer (**11eq**) with a high degree of stereoselectivity. On treatment of **11eq** with an excess of sodium nitrophenoxide, equilibration with the axial isomer (**11ax**) occurred, resulting in a 1:1 mixture. The kinetic preference for **11eq** was interpreted as resulting from unfavourable steric interactions between a nitrophenyl group and the ribose residue in the ring forming chair transition intermediate which would have led to **11ax**. The possible alternative explanation that ring formation occurs through a twist-ring intermediate such as **12** was not considered but fits the facts equally well. It is then necessary to postulate that the interactions between the nitrophenyl group and the ribose ring determine the thermodynamic equilibrium because unlike in glucose derivatives where electronegative groups including nitrophenyl take up almost exclusively axial orientations there is no such clear preference in **11**.



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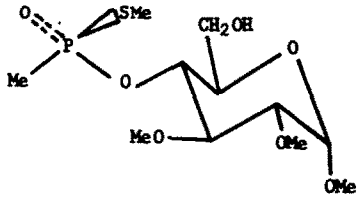
The above experiments provide no direct evidence that ring closures occur with inversion of configuration at phosphorus. However, all available data on the stereochemistry of displacement of chloride, fluoride or nitrophenoxide in acyclic phosphorus derivatives show that the reactions occur with inversion (Section 4). Further it has recently been shown[29] that ring closure of **13** occurs highly stereoselectively with inversion of configuration to give **1eq**. This result may be compared with displacements of SMe in analogous acyclic phosphorus derivatives which usually show a high ratio of inversion to retention products (for discussion on P–S bond breaking see Section 3.4).

Direct evidence that 6-membered rings in phosphoranes may adopt a non-chair conformation has been provided by Trippett *et al.*[30] who showed that the 6-membered ring in **14** is not in a chair conformation. It will be of interest to discover when more X-ray or other physical information is available whether non-chair forms are common in 6-membered rings which are part of phosphoranes. The above discussion assumes that the 1,3,2-dioxaphosphorinanes have chair conformations. Although this is almost certainly true for **1ax**, **1eq**, **8ax** and **8eq**, it need not always be the case and there is increasing evidence that some 1,3,2-oxazaphosphorinanes as solids[31] and in solution[32] and some 1,3,2-dithiaphosphorinanes[33] have twist-ring conformations.



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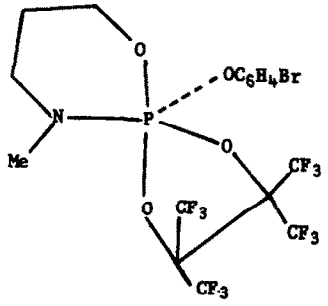

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The experiments described in this Section which imply that bond breaking and forming processes may occur in ring conformations that are not easily defined make it extremely difficult to analyse relative bond stabilities in terms of orbital overlap (Section 10).

3. RING OPENING REACTIONS OF 6-MEMBERED CYCLIC PHOSPHORUS ESTERS

Ring opening of 1,3,2-dioxaphosphorinan-2-ones (thiones), 1,3,2-oxothiaphosphorinan-2-ones (thiones) and 1,3,2-oxazaphosphorinan-2-ones (thiones) has been studied with reagents such as sodium hydroxide, sodium alkoxides, Grignard reagents and alkyllithiums. In many cases it has been possible unequivocally to establish whether ring opening occurs with inversion or retention at phosphorus whereas in other cases only tentative identification of the overall stereochemistry of the reactions has been possible. In some reactions the situation is further complicated by the fact that the kinetically favoured bond-breaking process between phosphorus and the heteroatom does not give the thermodynamically preferred product, with the consequence that subsequent migration of the phosphorus group occurs. In most reactions studied rates of ring opening were very much faster than subsequent rearrangements (where such rearrangements occurred) which in turn were much faster than any intermolecular reactions of the acyclic products. It was thus possible to control the experimental conditions to study the desired phase of the reaction sequence. The rate of ring opening reactions may be estimated to be at least ten times greater than for reactions of comparable acyclic molecules to

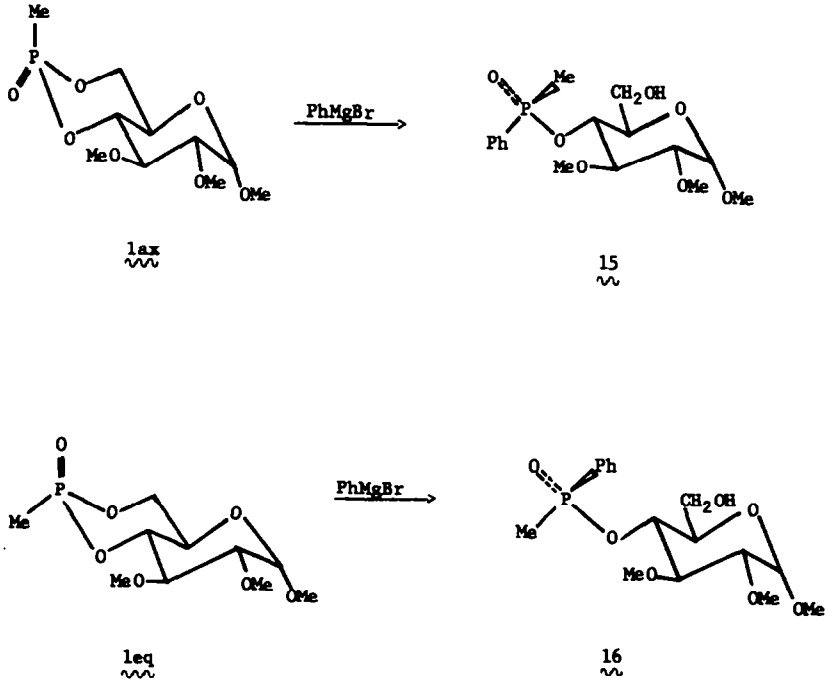
account for this fact. In this Section the available evidence will be summarised and then appropriate comments made about the mechanistic significance of the experimental observations that have been reported.

Since reactions with Grignard reagents and alkyllithiums give products which do not appear to rearrange these will be described first.

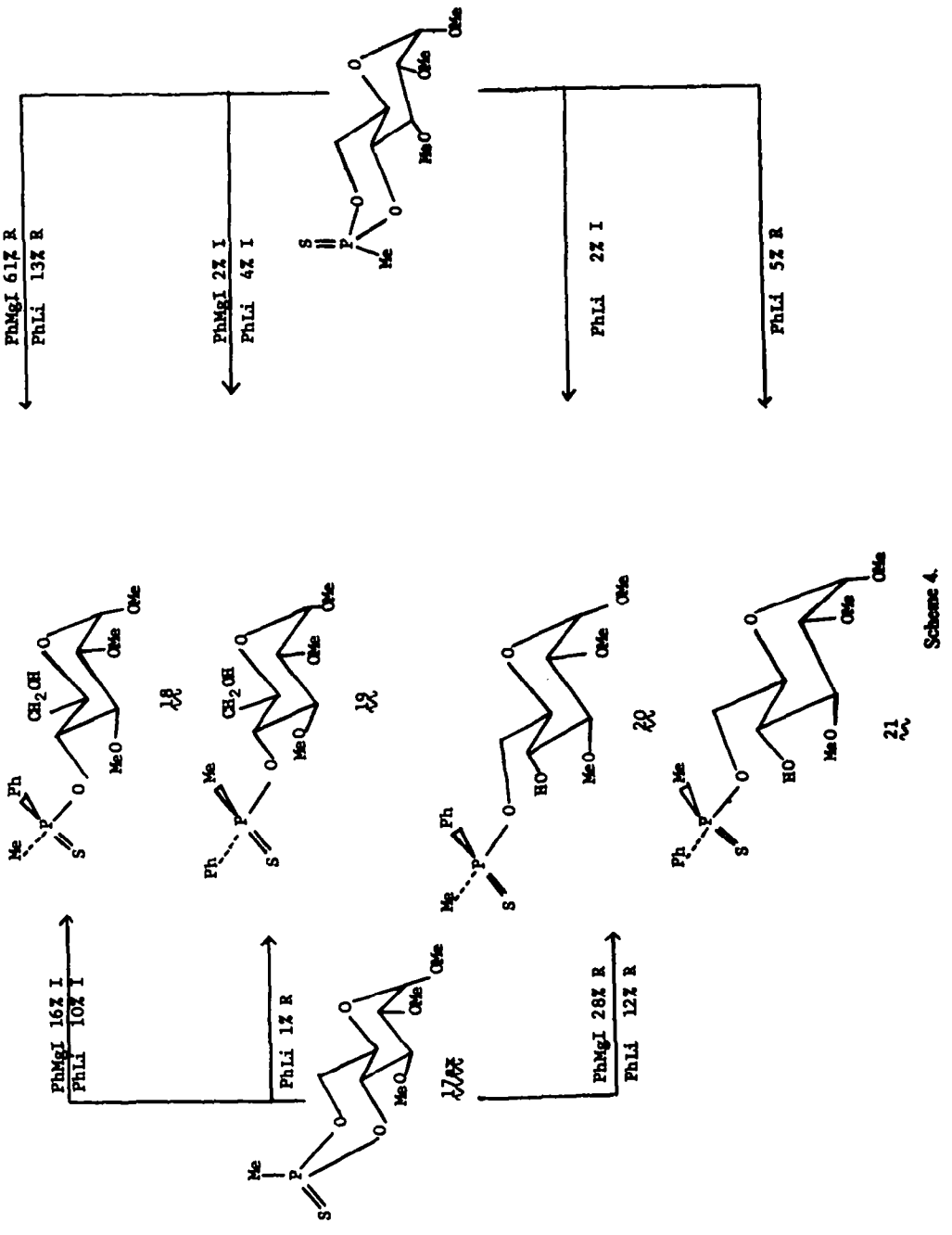
3.1 2-*Alky*(*aryl*)-1,3,2-*dioxaphosphorinan*-2-*ones* (*thiones*) *with Grignard reagents and alkyllithiums*

The first ring opening reactions of 1,3,2-dioxaphosphorinan-2-ones by Grignard reagents to be studied stereochemically were between the axial and equatorial methylphosphonates (**1ax** and **1eq**) and phenyl and ethylmagnesium bromides.[27] In all cases the major product isolated in about 50% yield was that formed by cleavage of the P–O6 bond with inversion of configuration at phosphorus (e.g. Scheme 3). Subsequent reactions between the related axial and equatorial Me (or phenyl) phosphonothioates and Grignard reagents showed a much more complex reaction pattern[34] which has recently been investigated in more detail.[35] Further, comparison has been made with the corresponding reactions of alkyl and aryllithiums. Thus in Scheme 4 it is shown that **17ax** with PhMgI afforded the inversion product **18** by P–O6 bond cleavage and the retention product **20** by P–O4 bond cleavage. With PhLi, **17ax** afforded the same preponderant products together with a trace of the retention product **19**. In contrast, the equatorial phenylthioate derivative (**17eq**) with PhMgI gave the product **18** by P–O6 bond cleavage in 61% yield with retention of configuration as very much the preponderant product whereas with PhLi low yields of the four possible isomers (**18**, **19**, **20** and **21**) were obtained. (Yields of products from the aryllithium reactions were low since further reactions to form phosphine sulphides were competitive with ring opening. If these reactions occur at significantly different rates with the initial products it is possible that in some cases the isolated isomer ratio may not accurately reflect the stereochemistry of ring opening. Repeat reactions gave no indication that this might be so.) The stereochemistry of the ring opened products was established by their hydrolysis to *R*(+)- or *S*(−)-methylphenylphosphinothioic acids by aqueous sodium hydroxide. The stereochemistry of the methylphenylphosphinothioic acids (isolated as their cyclohexylammonium salts) has been established unequivocally.[36]

The reactions of the axial and equatorial phenylphosphonothioates (**22ax** and **22eq**) with methylmagnesium iodide and methyllithium are shown in Scheme 5. From the equatorial isomer (**22eq**) the major product with both reagents was **19** formed by P–O6 bond cleavage with retention of configuration and in each case the only other product isolated was the product **18** formed by P–O6 bond cleavage with inversion of configuration. (It was previously reported[34] in error that the minor product had the phosphorus



Scheme 3.


PhMgI 61% R
PhLi 13% R
PhMgI 2% I
PhLi 4% I
PhLi 2% I
PhLi 5% R
PhMgI 16% I
PhLi 10% I
PhLi 1% R
PhMgI 28% R
PhLi 12% R
CH2OH
MeO
OMe
Me
Ph
S
O
P

Scheme 4.

MeMgI 45% R
MeLi 45% R
MeMgI 23% I
MeLi 6% I
MeMgI 75% I
MeLi 37% R
Ph
Me
S
O
CH2OH
OMe
MeO
HO

Scheme 5.

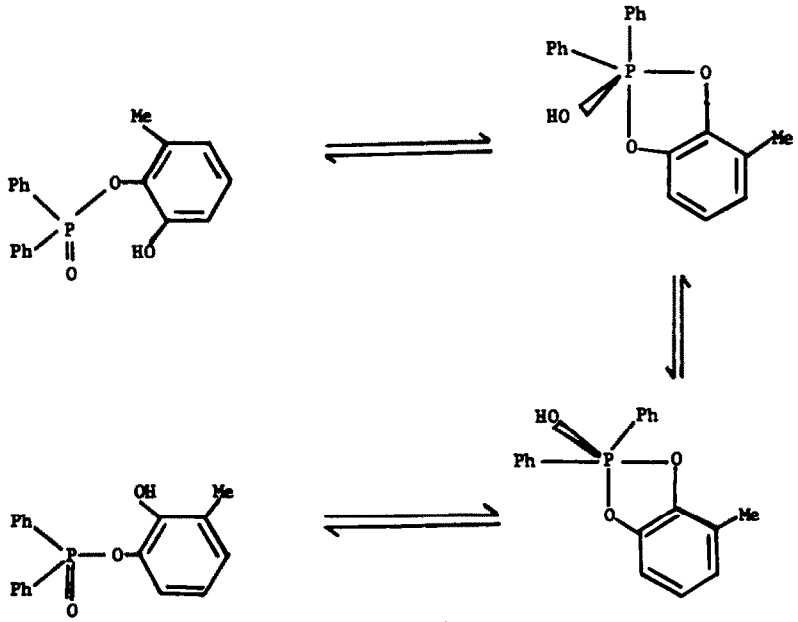
substituent on O6.) The axial isomer (**22ax**) reacted quite differently with the two reagents. Thus with MeMgI the product **19** formed by P–O6 cleavage with inversion of configuration was the only product and was isolated in high yield, whereas with MeLi the major product was **21** formed by P–O4 cleavage with retention of configuration.

One difference between the axial derivatives (**17ax** and **22ax**) and the equatorial derivatives (**17eq** and **22eq**) with Grignard reagents was that the axial derivatives as well as giving mainly products with inversion of configuration also reacted more rapidly than the equatorial derivatives which gave preponderantly products with retention of configuration.

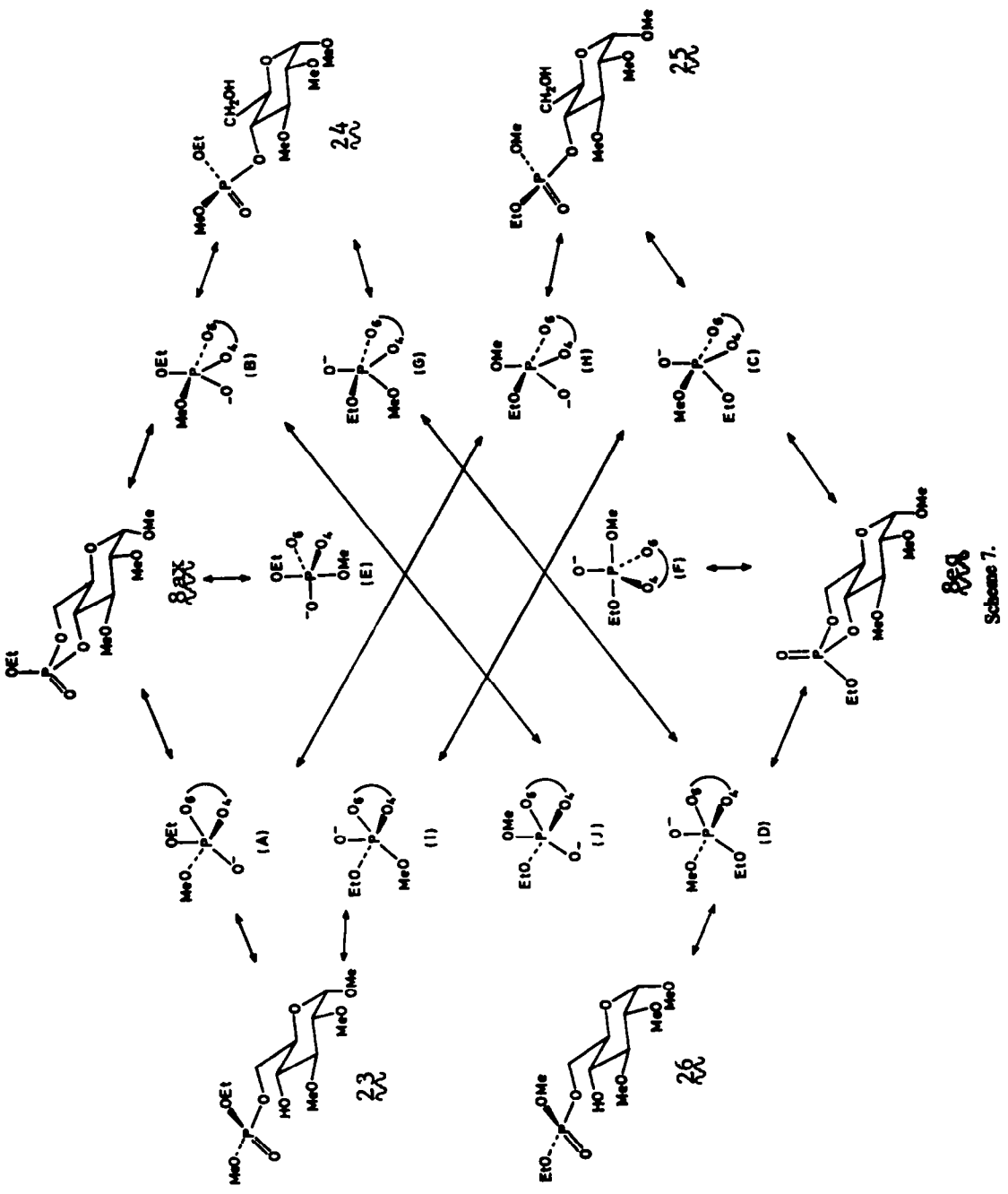
These results serve to emphasise that steric considerations not only determine which bond is broken but also whether the reaction occurs with inversion or retention of configuration at phosphorus. From a consideration of the Grignard reactions it is tempting to speculate that the axial isomers ring open rapidly and with inversion of configuration since in the transition intermediate they can readily adopt a twist-ring conformation which does not contain a pseudo-axial P-alkyl or P-phenyl group. The equatorial isomers can only achieve such a conformationally favourable intermediate following ligand reorganisation. However, if such considerations have any validity, addition suppositions are necessary, for example, to rationalise the differences between the reactions of **22ax** with methylmagnesium iodide and methyllithium. It is also necessary to compare the above results with the results for ring openings of 1,3,2-oxazaphospholidines with Grignard reagents and alkyl(aryl)lithiums which show equally bewildering variability but which are subject to quite different steric constraints (Section 6.3).

Attempts to cause migration of a methylphenylphosphinothioate substituent from O-4 to O-6 on glucose or vice versa have all been unsuccessful. Both acidic and alkaline conditions have been investigated in a variety of solvents and at different temperatures. This contrasts with alkylphosphonate or phosphate substituents where under basic conditions facile migration from O-4 to O-6 occurs (Sections 3.2 and 3.3). The results also require careful analysis in comparison with recent reports that isomerisation of O-hydroxyphenyl phosphinates[37] occurs via pentacoordinate trigonal bipyramidal intermediates (Scheme 6) suggesting that migration of a phosphinyl grouping can occur across a 1,2-diol but not across a 1,3-diol.

By appropriate choice of starting material and Grignard reagent, ring opening and subsequent hydrolysis can provide a reasonably convenient synthetic route to enantiomerically pure chiral phosphinothioic acids.[35] For example, hydrolysis of **18** prepared from **17eq** gave *R*(+)-methylphenylphosphinothioic acid and hydrolysis of **23** prepared from **22ax** gave *S*(−)-methylphenylphosphinothioic acid. It must be pointed out however that the choice of synthetic route depends on the initial cyclic ester and on the Grignard reagent, and that the optimum route in every case has to be established by experimentation and cannot be predicted. Other chiral acids prepared in this laboratory include ethylmethyl, butylmethyl, and ethylphenylphosphinothioic acids.



Scheme 6.



Scheme 7.

3.2 2-*Alkoxy* 1,3,2-*dioxaphosphorinan*-2-*ones* (*thiones*) *with sodium alkoxides* (*Scheme* 7)

The ring opening reactions of 2-alkoxy-1,3,2-dioxaphosphorinan-2-ones (cyclic phosphates) and related compounds may be most conveniently discussed by reference to the ring opening of **8ax** and **8eq**. Ring opening of both isomers occurs rapidly in <0.1 M sodium methoxide in methanol and although subsequent migration of the phosphate group across the 1,3-diol (the 4- and 6-glucose hydroxyls) occurs, stronger alkoxide (*ca.* 1M) is required to promote the migration at a comparable rate. Consequently, product analysis for the early stages of ring opening were considered to relate directly to the ring opening process and not to subsequent rearrangements.[38]

The ring opening reactions did not occur stereospecifically; **8ax** gave approximately equal amounts of the 4- and 6-(ethyl methyl phosphates) whereas **8eq** afforded a high preponderance of the 4-substituted product. Further, although the 6-derivative from **8ax** was essentially the single isomer (**23**) formed by ring opening with inversion of configuration, the 4-derivative from **8ax** was a 4:1 mixture of the inversion and retention products (**24** and **25**) respectively. The ratio of the inversion and retention products (**25** and **24**) respectively from **8eq** was 7:3.

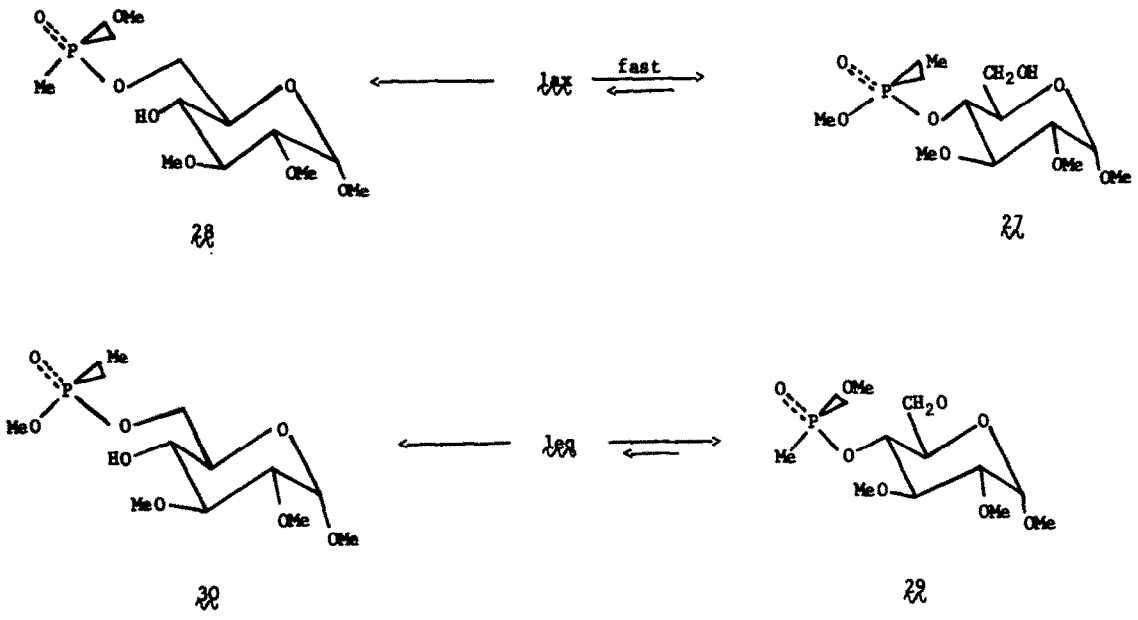
Migration from the 4- to the 6- position was shown to occur stereospecifically with retention of configuration when **23** was obtained from **25**, both isomers having been prepared previously by an independent route. The reverse migration from the 6- to the 4- position could also be induced with retention of configuration but the rate and extent of this migration were very low. The fact that migrations occur with retention of configuration is consistent with the involvement of simple reorganisation of the TBP; e.g. **25** to **23** could occur through the TBP's (H) and (A) or (C) and (I). Such a migration pathway is consistent with the observation that **25** can be converted into **23** in either sodium methoxide in methanol or sodium ethoxide in ethanol. Any route for migration which necessitates re-formation of the original cyclic esters (**8ax** and **8eq**) would result in alkyl group exchange and the significant formation of the 6-(diethyl phosphate) or 6-(dimethyl-phosphate).[34]

Since the involvement of TBP's in the migration reactions is well demonstrated, the results of the ring opening may be interpreted in the following way. Attack by methoxide on the cyclic ethylphosphate (**8ax**) occurred opposite O-4 and O-6. When methoxide attack was opposite 0-4 the TBP (A) was formed which broke down without ligand reorganisation to give the 6-phosphate (**23**) with inversion of configuration at phosphorus, or after ligand reorganisation through (H) to give the 4-phosphate (**25**) with retention of configuration. When attack by methoxide was opposite O-6 the 4-phosphate (**24**) was formed with inversion of configuration, probably through the TBP (B). Similar arguments apply to the ring opening of **8eq**.

It must be emphasised that the ring opening and migration pathways described are not the only ones possible but under the experimental conditions used do appear to be the major ones. In other solvents and under other reaction conditions some evidence was obtained to show that some reformation of the cyclic esters could occur, albeit to a very small extent, and presumably contribute to the migration procedure. It is unlikely that the TBP's (E) and (F) contribute significantly since these would result in direct alkoxyl group exchange which is not observed. Similar ring opening and migration experiments with 1,3,2-dioxaphosphorinan-2-thiones showed essentially the same preponderant features.[34]

3.3 2-*Alkyl*-1,3,2-*dioxaphosphorinan*-2-*ones* (*thiones*) *with sodium alkoxides* (*Scheme* 8)

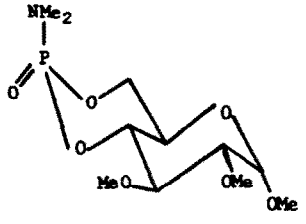
2-Alkyl-1,3,2-dioxaphosphorinanes (cyclic phosphonates) undergo ring opening with alkoxides at room temperature with preponderant if not exclusive inversion of configuration.[34,38] For example, the axial phosphonate (**1ax**) with sodium methoxide in methanol gave the 4-methylphosphonate (**27**) as the only 4-isomer and very much the preponderant product compared with the 6-methylphosphonate (**28**). In sodium methoxide/methanol the 4-methylphosphonate (**27**) was converted into the 6-methylphosphonate (**28**) so that on storage overnight only the 6-isomer was present. No significant epimerisation at phosphorus occurred during the migration. In contrast, the equatorial methylphosphonate (**1eq**) afforded with sodium methoxide similar amounts of the 4- and 6-methylphosphonates (**29** and **30**) respectively. Also in contrast with the ring opening of **1ax** where both 4- and 6-methylphosphonates (**27** and **28**) may be regarded as being formed stereospecifically with inversion of configuration, in some cases the preponderant inversion products (**29** and **30**) from **1eq** were contaminated with trace amounts of the isomers (**27** and **28**) as detected by ^{31}P NMR (*cf* alkaline aqueous hydrolysis of **32ax** and **32eq**; see Section 3.4). A similar variation in the direction of initial ring opening was observed with cyclic methylphosphonothioates, phenylphosphonates and phenylphosphonothioates, with the axial products favouring initial ring opening to the 4-isomers although in all cases the 6-isomers were the final products.



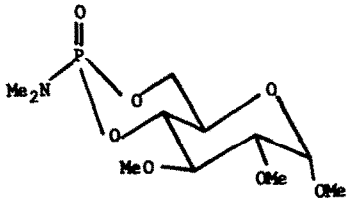
Scheme 8.

The migration mechanism is almost certainly one which involves re-formation of the starting cyclic derivative and re-opening of the ring until only the thermodynamically favoured 6-isomers are present. The observed stereochemistry favours this mechanism, cyclic products may be detected when pure 4-isomers are treated with methoxide, and when a 4-(methyl methylphosphonate) is treated with sodium ethoxide exchange of the methyl group for ethyl occurs and a 6-(ethyl methylphosphonate) results.

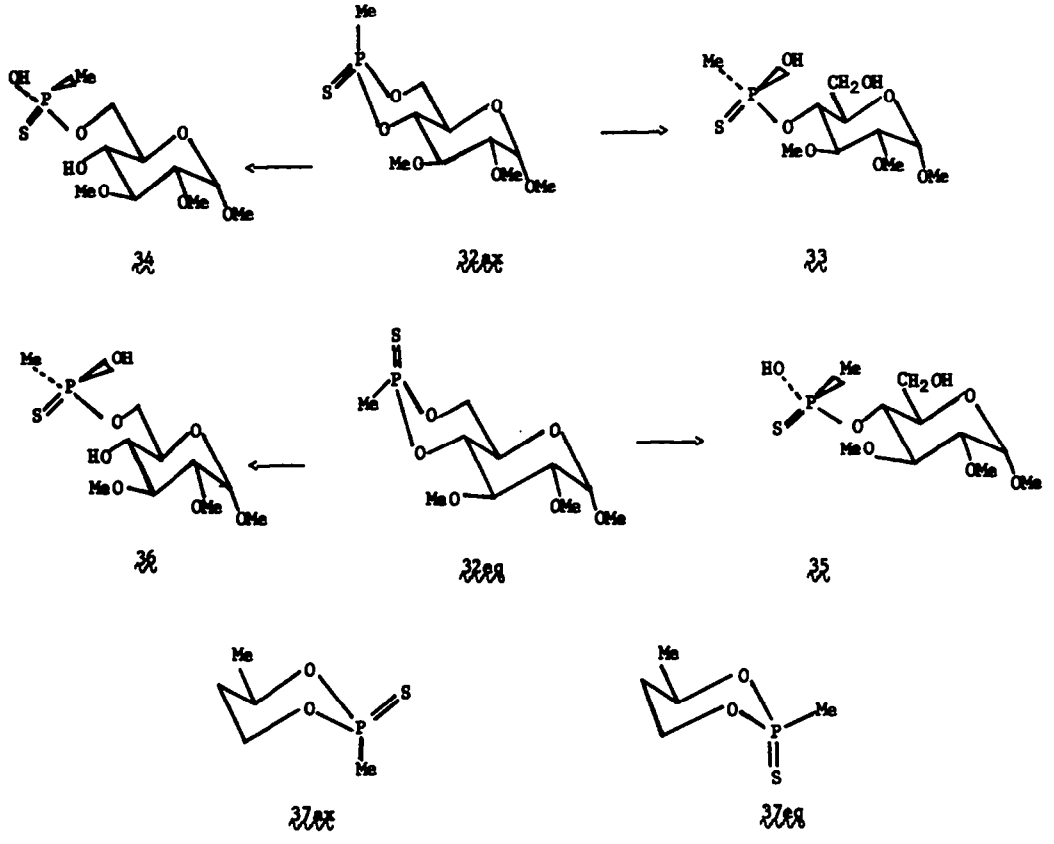
Exocyclic amidates, e.g. **31ax** and **31eq** react with alkoxides in similar fashion to the cyclic phosphonates, ring opening occurring with inversion of configuration.[39] Ring opening of the axial isomer (**31ax**) occurred more rapidly than the equatorial isomer (**31eq**). However, unlike the ring opening of the cyclic phosphonates which occur at room temperature the amidates reacted at reasonable rate only when heated under reflux. Under these conditions it was not possible to distinguish migration reactions from less specific general decomposition processes.



31ax



31eq



Scheme 9.

3.4 2-*Alkyl*-1,3,2-*dioxaphosphorinan*-2-*thione with sodium hydroxide* (*Scheme* 9)

In ring opening reactions of glucose cyclic 4,6-phosphates it is well known that aqueous alkaline hydrolysis affords 4-phosphates in preference to 6-phosphates and that this pattern holds independently of the starting sugar since galactose derivatives follow the same pattern.[39]

The same overall effect is shown in the alkaline hydrolysis of methyl 2,3-di-O-methyl-α-D-glucopyranoside 4,6-(methylphosphonothioate) (**32ax**) which opened preponderantly with inversion of configuration to give the 4-hydrogen methylphosphonothioate (**33**) with just a trace (<5%) of the 6-hydrogen methylphosphonothioate (**34**). In contrast, under essentially the same conditions the equatorial isomer (**32eq**) ring opened to give an approximately equal mixture of the inversion products (**35** and **36**), but both contained small amounts (approx. 10%) of the retention products (**33** and **34**) respectively. These results are consistent with those from similar ring opening reactions with alkoxides but are not complicated by migration effects since under the reaction conditions migration of the 4-phosphonothioate groups in **33** and **35** to the 6-position did not take place. Under the same reaction conditions a similar pattern of ring opening was observed for the monocyclic derivatives (**37ax** and **37eq**).

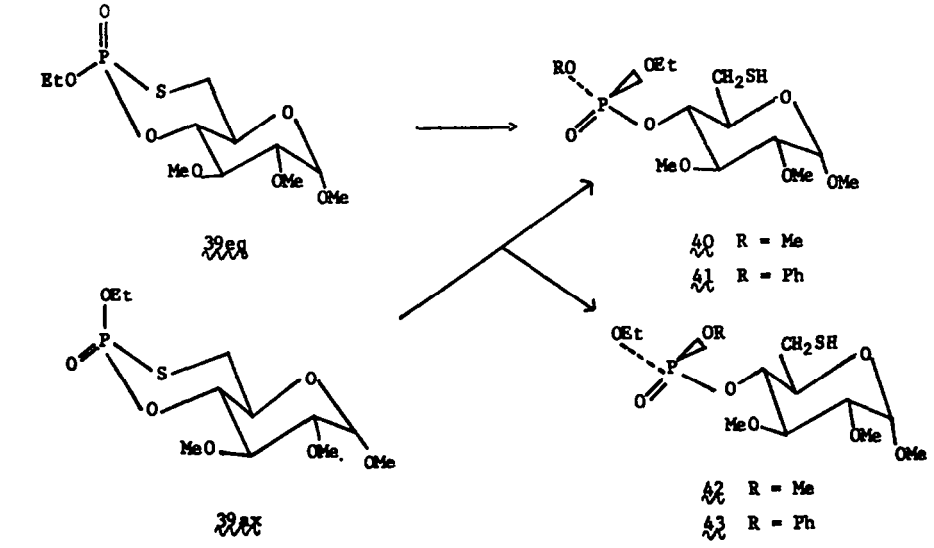
For ring opening reactions of 1,3,2-dioxaphosphorinan-2-ones (thiones) with alkoxides and hydroxide the implication of the results to date is that the cyclic isomers that are kinetically preferred in their formation, e.g. **1ax** and **32ax** are the isomers that are ring opened more cleanly with regard to whether the P–O6 bond is broken preponderantly and with regard to whether or not ring opening occurs with preponderant inversion of configuration at phosphorus. It is clearly tempting to apply to these results arguments similar to those used for the ring forming reactions which relate to the ease with which a 6-membered ring can adopt the conformation most favourable for ring opening reactions. There is no obvious stereochemical explanation for the kinetic preference for P–O6 bond cleavage. The conclusion from previous hydrolysis experiments with dialkyl alkylphosphonates was that hydrolysis rates were dependent on the size rather than the pK_a of the leaving group[40] allowing a general trend for primary alcohols to be hydrolysed faster than secondary alcohols. Unfortunately no mixed esters were studied and it is therefore difficult to relate the studies of the acyclic and cyclic esters.

3.5 2-*Alkyl(alkoxy)*-1,3,2-*oxathiaphosphorinan*-2-*ones with alkoxides*

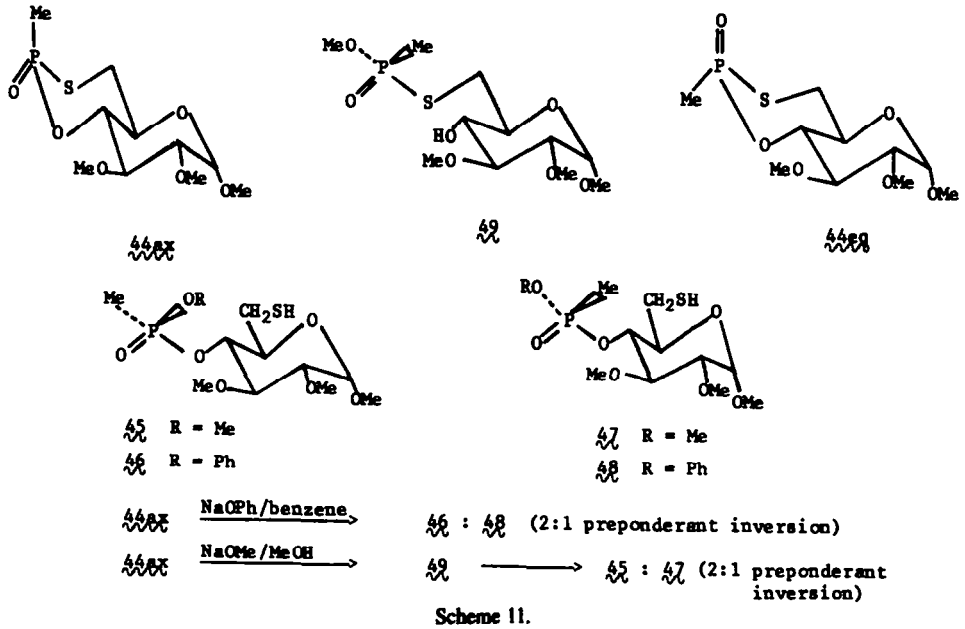
In this series only a few preliminary experiments have been reported.[34]

The equatorial ethoxy derivative (**39eq**) on treatment with sodium methoxide in methanol or sodium phenoxide in benzene undergoes P–S bond cleavage with retention of configuration to give **40** and **41** respectively. The axial ethoxy derivative (**39ax**) also undergoes P–S bond cleavage but in this case as well as the isomers (**42** and **43**) formed with retention of configuration a significant amount of **40** and **41** formed from **39ax** with inversion of configuration were also detected (Scheme 10).

With the methylphosphonothioate derivatives (**44ax** and **44eq**) ring opening of both isomers with sodium phenoxide in benzene occurred by P–S bond cleavage to give a mixture of products with inverted and retained configurations in the ratio 2:1 (i.e. **44ax** gave **46** and **48**, and **44eq** gave **48** and **46**). With sodium methoxide in methanol the initial reaction of **44ax** and **44eq** was P–O bond cleavage, probably with inversion of configuration although there is little evidence on this point. Certainly the reaction was stereospecific. However on storage in sodium methoxide in methanol the initially formed products rearranged to give the 4-(alkylmethylphosphonates) with preponderant overall inversion of configuration as related to the initial cyclic derivatives but the ratio of inverted product to product with retained configuration was approximately 2:1. For example, **44ax** gave initially **49** which then rearranged to **45** and **47** (Scheme 11).



Scheme 10.



Scheme 11.

The results from the ring opening of 1,3,2-oxathiaphosphorinan-2-ones make interesting comparison with those reported for nucleophilic displacement reactions in *S*-alkyl dialkyl phosphorothioates and *S*-alkyl alkyl alkylphosphonothioates. There are a number of reports[41,42] which show that in alkylphosphonothioates, *S*-alkyl is displaced with preponderant inversion of configuration and indeed the mechanism of such displacements has been discussed in the context of detailed kinetic analysis.[42] However, the situation is not straightforward for in certain cases P–O bond cleavage, which also takes place with inversion of configuration, becomes competitive with P–S bond cleavage.[11,43] Although the influence of solvent on such displacements in acyclic systems has not been reported (but compare reactions with phosphonium salt hydrolysis)[1] it appears that the type of results obtained for acyclic and cyclic phosphonothioates are sufficiently similar to make any specific effects of the ring system difficult to detect, if indeed such effects are present.

For acyclic *S*-alkyl phosphorothioates, an observation[44] that the hydrolysis of the *S*-alkyl group in the phosphoro series was more rapid than for analogous phosphonothioates, (an anomalous result for reactions of phosphonates and phosphates) led to the discovery that P–S bonds in *S*-alkyl phosphorothioates are cleaved by alkoxides with retention of configuration.[43] This stereochemical difference could provide a possible explanation for the hydrolysis rate anomaly. The results of the ring opening of **39eq** and **39ax** where P–S bond cleavage also takes place with retention of configuration again shows the similarity of the cyclic and acyclic systems. In this case however a ring effect was demonstrated since the ring opening of **39eq** was cleaner stereochemically than with the axial isomer.

In acyclic *S*-alkyl phosphonothioates, Grignard reagents cause P–S bond cleavage with retention of configuration,[45] and P–O bond cleavage with inversion;[46] ring openings of 1,3,2-oxathiaphosphorinan-2-ones with Grignards have not been reported.

3.6 2-*Alkyl*(*alkoxy*)-1,3,2-*oxazaphosphorinan*-2-*ones* (*thiones*) *with alkoxides*

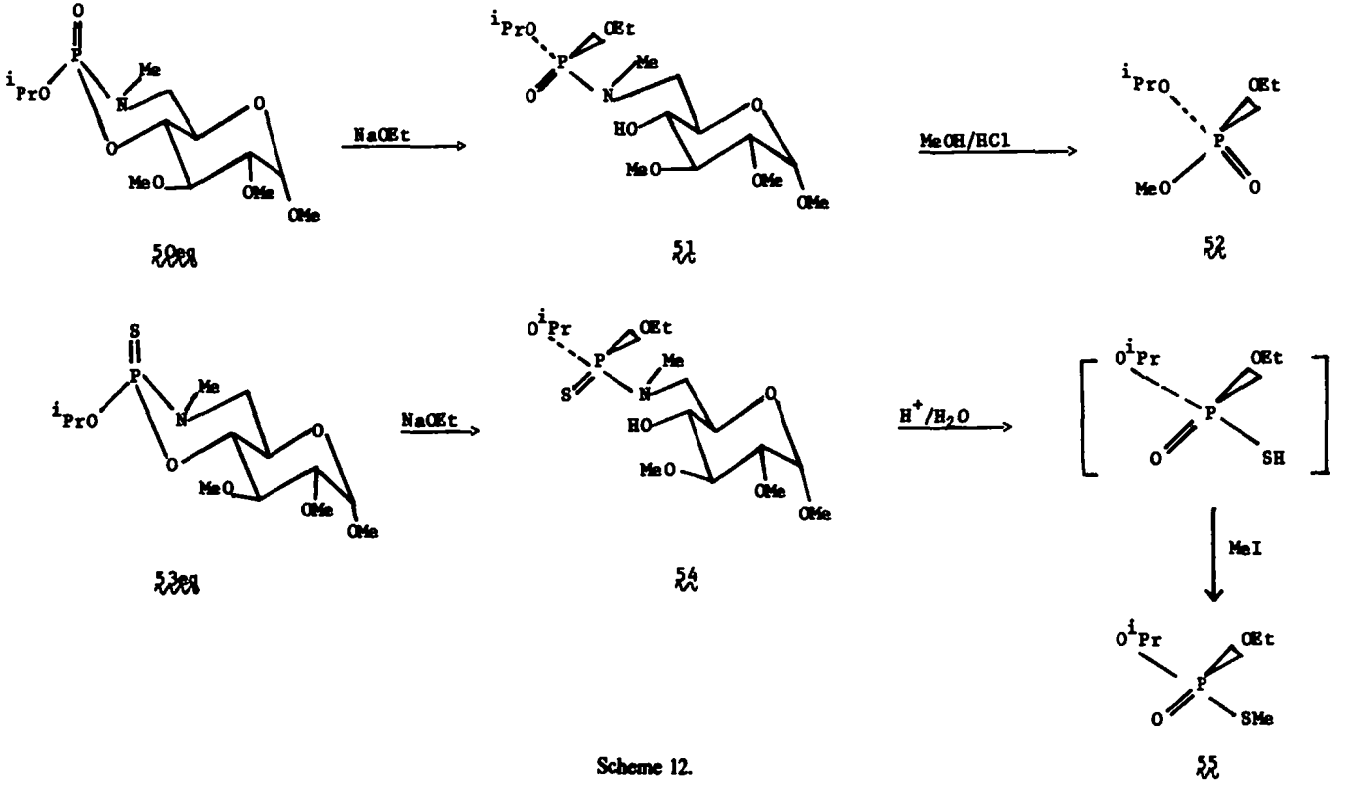
The ring opening of 1,3,2-oxazaphosphorinanes with alkoxides has been studied principally with the objective of providing a synthetic route to chiral alkylphosphates and other neutral phosphorus esters[47,48] (Scheme 12). Thus the ring opening reactions were not studied systematically from the viewpoint of investigating factors which affect the stereochemistry of ring opening. Nevertheless the following experimental results provide some indication of the problems.

Treatment of the axial and equatorial isomers of methyl 2,3-di-O-methyl-α-D-glucopyranoside 4,6-N,P-dimethylphosphoramidothioate (**56ax** and **56eq**) with alkoxides in hot alcohol resulted in preponderant (*ca.* 70%) P–O bond cleavage with inversion of configuration at phosphorus (Scheme 13). The P–N bond cleavage that occurred was also with inversion of configuration. Similar results were obtained with the phosphonamidates (**57ax** and **57eq**).

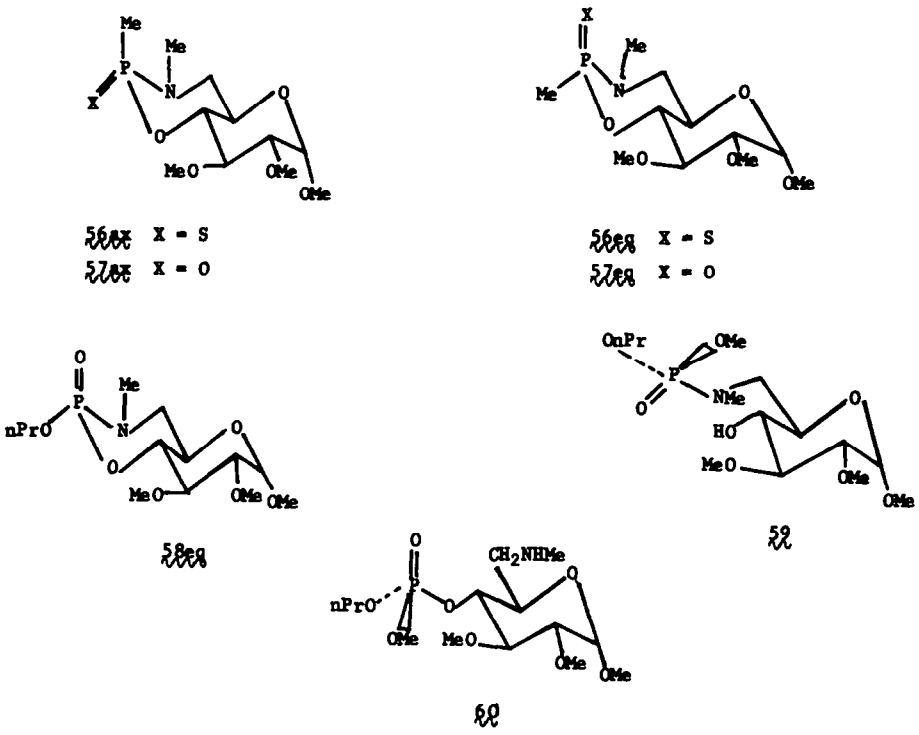
The situation for the corresponding phosphoro derivatives was less clear. In one favourable case the glucopyranoside 6-N-(methyl n-propylphosphoramidate) (**59**) was isolated from **58eq** in 45% yield, P–O bond cleavage occurring with inversion of configuration. Under suitable conditions the P–N bond cleaved product (**60**) was also isolated. However, the usually quite vigorous conditions required to carry out the alkaline alcoholyses of cyclic phosphoramidates had the consequence that controlled comparisons of the effects of stereochemistry on ring openings were not easy to achieve.

A clearer picture of the effect of stereochemistry on P–O and P–N bond breaking reactions might result from aqueous alkaline hydrolytic studies when presumably the initial ring opened products would not be subject to subsequent migrations. No stereochemical studies of alkaline hydrolysis of 6-membered cyclic phosphorus amidates have been reported in contrast to various studies in 5-membered analogues (Section 6.2). In the latter cases hydrolysis reactions do not necessarily parallel alcoholysis reactions and the same complicating factors could apply in the 6-membered rings.

Acid catalysed P–N bond cleavage in methanol, ethanol and n-propanol occurs with inversion of configuration and there is as yet no example of endocyclic P–O or P–N bond cleavage in 1,3,2-oxathiaphosphorinanes that does not occur with inversion of configuration. However, caution must be exercised in interpreting the stereochemistry of endocyclic hydrogen chloride catalysed P–N bond alcoholysis because the corresponding reactions in acyclic phosphoramidothioates sometimes occur with apparent retention of configuration; this results from P–N bond cleavage with inversion of configuration by chloride ion and displacement of chloride with inversion of configuration by the alcohol.[49]



Scheme 12.



Scheme 13.

4. EXOCYCLIC DISPLACEMENT REACTIONS IN 1,3,2-DIOXAPHOSPHORINAN-2-ONES AND RELATED COMPOUNDS

In 1967, Kirby and Warren were able on the basis of the then available evidence to state that for reactions at phosphorus in 6-membered rings there were no differences from corresponding reactions in acyclic derivatives.[50] As a consequence of further experimental results this statement is clearly in error. Whether or not displacements of exocyclic groups at phosphorus occur with retention or inversion of configuration depends on the nature of the nucleophile, leaving group, solvent, other ionic species present and on the other heteroatoms in the 6-membered ring. Tables 1 and 2 summarise the data obtained in these laboratories for phosphorus–carbohydrate adducts.[51] References are given to supporting data, usually from monocyclic systems obtained elsewhere.

Firstly it appears that the stereochemical course of displacement reactions is independent of the initial axial or equatorial orientation of the leaving group if the close correspondence of the results in Table 2 with Table 1 fully reflects all equatorial leaving groups.

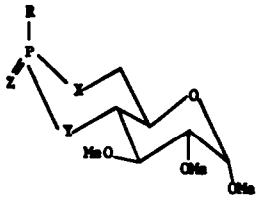
Another clear result is that in 1,3,2-oxazaphosphorinanes all displacements occur with preponderant inversion of configuration, even displacements of halides with Grignard reagents which in other 1,3,2-phosphorinanes seem to occur with preponderant retention of configuration.

Other instances where displacements appear to be reproducibly highly stereoselective are: displacement of Cl by alcohols with inversion, displacement of Cl by nitrophenoxide with inversion, displacement of equatorial nitrophenoxide by nitrophenoxide with inversion, displacement of nitrophenoxide by ethoxide with retention (except in the 1,3,2-oxaza ring) and displacement of thioalkyl by alkoxide with retention. Displacements of amines by acidic alcohols occur with inversion of configuration.

Other reactions, notably the displacement of halides by alkoxides have a stereochemical course that is dependent on the precise reaction conditions. This type of situation was investigated systematically by Wadsworth *et al.*[52] who found that the higher the basicity of the nucleophile the greater the degree of retention of configuration observed on displacement of chloride by substituted phenoxides in **61**. Thus in acetonitrile whereas sodium *p*-nitrophenoxide displaces chloride from **61** with 4% inversion of configuration, sodium *p*-methoxyphenoxide effects the same displacement with 57% retention of configuration at phosphorus. In benzene, under heterogeneous conditions there was an increase in the retention products but under homogeneous conditions in other solvents the results were similar to those obtained in acetonitrile.

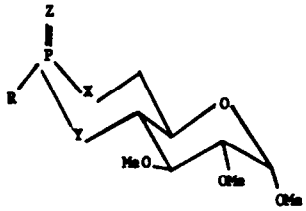
The addition of lithium and other salts to reaction mixtures can also have a pronounced effect on reaction stereochemistry in 1,3,2-dioxaphosphorinan-2-ones.[55,58-60] For example treatment of **62** with 1

Table 1.

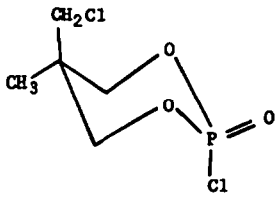


Ring hetero-atoms			Leaving group	Nucleophile	Preponderant Stereochemistry (% Yields of major and minor isomers where isolated)
X	Y	Z	R		
O	O	O	Cl	EtOH	Inversion (93:4)
S	O	O	Cl	EtOH	Inversion (78:-)
O	S	O	Cl	EtOH	Inversion
O	O	S	Cl	EtOH	Inversion (81:-)
O	O	O	Cl	NaOEt/EtOH	Retention (54:42)
S	O	O	Cl	NaOEt/EtOH	Retention (60:-)
O	S	O	Cl	NaOEt/EtOH	Retention (28:-)
O	O	S	Cl	NaOEt/EtOH	Retention (65:31)
NMe	O	O	Cl	NaOEt/EtOH	Inversion (80:-)
NMe	O	S	Cl	NaOEt/EtOH	Inversion (87:-)
O	O	O	Cl	Me_2N/PhH [52]	Inversion (87:9)
O	O	O	Cl	NaSPr/PhH [53]	Inversion (47:4)
O	O	O	Cl	NaOPh.pNO_2 (1 equiv)	Inversion (60:-)
S	O	O	Cl	NaOPh.pNO_2 (1 equiv)	Inversion (53:-)
NMe	O	O	Cl	NaOPh.pNO_2 (1 equiv)	Inversion (56:-)
O	O	O	SPr	NaOEt/EtOH [54,55]	Retention (77:-)
O	O	O	OPh.pNO_2	NaOEt/EtOH	Retention (88:-)
NMe	O	O	OPh.pNO_2	NaOMe/MeOH	Inversion (68:-)
O	O	O	F	NaOEt/EtOH [56,57]	Retention (46:16)
O	O	O	Cl	MeMgI/Et_2O/PhH	Retention (32:6)
NMe	O	O	Cl	PhMgBr/Et_2O/PhH	Inversion (46:4)
NMe	O	S	Cl	MeMgI/Et_2O/PhH	Inversion (- :-)
O	O	O	Me_2N	EtOH/H	Inversion (>95:-)

Table 2.

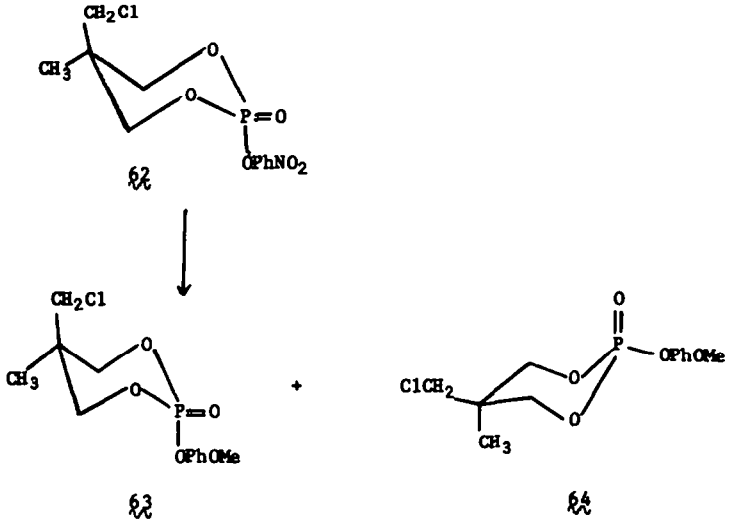


Ring hetero-atoms			Leaving group	Nucleophile	Preponderant Stereochemistry (% Yields of major and minor isomers where isolated)
X	Y	Z	R		
O	O	O	SPr	NaOEt/EtOH	Retention (67:-)
O	O	O	OPh.pNO_2	NaOEt/EtOH	Retention (75:15)
O	O	O	OPh.pNO_2	OPh.pNO_2/CH_3CN	Inversion (75:-)
NMe	O	O	OPh.pNO_2	NaOMe/MeOH	Inversion (67:9)
O	O	O	Me_2N	EtOH/H^+	Inversion (>95:-)



61

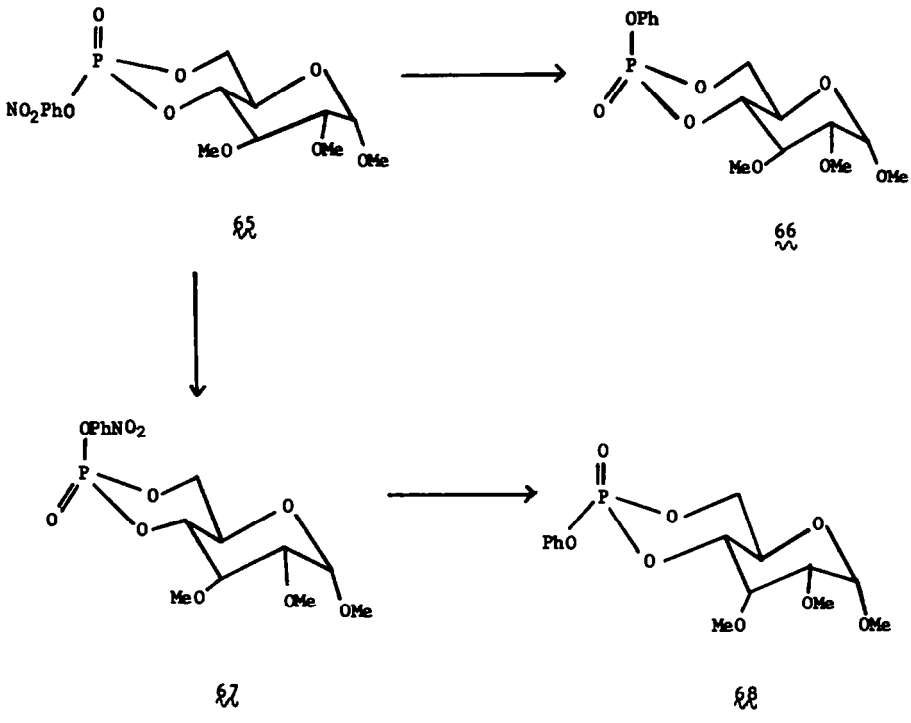
equivalent of potassium *p*-methylphenoxide in dimethylformamide afforded a 1:1 mixture of **63** and **64** (Scheme 14). In the presence of 4 equivalents of potassium perchlorate the ratio of **63** and **64** remained 1:1 but in the presence of 2 equivalents of lithium perchlorate the ratio favouring the retention product (**63**) was 10:1. As well as affecting the stereochemistry of substitution added lithium ion also retards the rate of substitution by phenoxides and in particular the rate of the inversion pathway for reactions in dimethylformamide. However, in other reactions and in other solvents added lithium can increase the rate of substitution. One such case is the acyclic system diphenyl *p*-nitrophenylphosphate where added $LiClO_4$ dramatically increased the reaction rate with *p*-cresol in acetonitrile in the presence of triethylamine.



62 63 64

Scheme 14.

In this laboratory preliminary attempts[29] have been made to repeat experiments similar to those reported by Wadsworth, to examine the effect of added lithium salts on the stereochemistry of substitution of chloride and *p*-nitrophenol in chiral ethyl methyl phosphorochloridate and ethyl methyl *p*-nitrophenyl phosphate respectively and in the cyclic nitrophenate (**65**) derived from the sugar system. In the acyclic cases, substitution of chloride by phenol/triethylamine in acetonitrile and of *p*-nitrophenol by potassium phenoxide in dimethylformamide were essentially unaffected by the addition of one and four molar equivalents of lithium perchlorate, both substitutions occurring with inversion of configuration. In the cyclic nitrophenate, the effect of added lithium salts was more variable but in many cases had no significant effect on the stereochemistry of substitution. It was observed however that overall stereochemistry could be modified by changes in rates of addition of reagents. For example (Scheme 15) addition of 1.2 equivalents of sodium phenoxide rapidly to **65** gave **66** with inversion of configuration. However addition of sodium phenoxide slowly to **65** gave a preponderance of the retention product (**68**). The explanation for this difference is that nitrophenoxide formed following the initial reaction converts **65** into **67** which subsequently reacts with phenoxide to give **68**. This latter result is reported not to discount the fact that in some cases added lithium salts can affect reaction stereochemistry, but to emphasise that great care must be taken in determining which variables are paramount in causing changes in the observed stereochemistry.



Scheme 15.

It is pertinent to compare the stereochemistry of exocyclic displacement reactions in 6-membered rings with similar reactions in acyclic phosphoro† derivatives which may be summarised as follows:

(*a*) *Displacements of chloride.* Displacements of chloride in acyclic phosphorothiochloridates occurs with inversion of configuration with sodium hydroxide and alkoxides and similarly alkoxides displace chloride from phosphorochloridates with inversion.[61]

(*b*) *Displacements of fluoride.* No unequivocal results on the stereochemistry of displacement of fluoride in acyclic phosphorofluoridates have been reported. However the supposition must be that such reactions occur with inversion of configuration particularly if the kinetic comparisons of displacements from acyclic phosphorofluoridates and acyclic methylphosphonofluoridates which take place with inversion of configuration are considered,[44] and since there is other tentative evidence favouring a displacement with inversion of configuration.[61]

(c) In acyclic *p*-nitrophenyl phosphates substitution of nitrophenol by ethoxide occurs with inversion of configuration in direct contrast to the similar reaction in 1,3,2-dioxaphosphorinan-2-one.[48]

(d) Displacement of *S*-alkyl occurs with retention of configuration in acyclic phosphoro (but not phosphono) derivatives.[43,44]

(e) The influence of solvent or of added lithium salts has not been studied in detail in acyclic derivatives. Solvent effects may be important particularly for displacements of *S*-alkyl groups. Preliminary results suggest the effect of lithium salts may be less important than in cyclic derivatives.

(f) Acid catalysed P–N bond cleavage in acyclic phosphoro derivatives occurs with inversion of configuration unless there are special circumstances which lead to overall retention of configuration by a double inversion mechanism.[49].

(g) Grignard reagent–halide displacements have not been studied stereochemically in acyclic phosphoro-derivatives.

To fully evaluate any mechanistic differences between cyclic and acyclic systems, comparison between rates of reactions in acyclic and 6-membered ring systems is necessary. Unfortunately few measurements have been made, and in particular not where the stereochemistry of the reaction has also

†Since there are differences between phosphoro and phosphono derivatives the only valid comparison is with phosphoro derivatives and not with the phosphono derivatives of which there are more examples and which usually take place with inversion of configuration. In phosphonates of general formula $RP(X)(OR^1)Cl$ where R,R^1 = alkyl or aryl and X = O or S, chlorine is displaced from phosphorus with inversion of configuration by HO^-,[62] RO^-, RS^-,[63] F^-, Br^- and R_2NH.[64] Where chlorine is replaced by bromine subsequent displacement of Br by HO^-[65] and F^-[66] occurs with inversion, as does displacement of F by RO^-.[67]

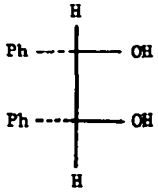
been established unequivocally. Where data is available the indications are that rates of displacement from 6-membered rings are very similar to those in acyclic systems. For example the rate of alkaline hydrolysis of diethyl *p*-nitrophenyl phosphate is 0.94 mol^{-1} min^{-1} and the hydrolysis rate of 2-*p*-nitrophenyl-1,3,2-dioxaphosphorinan-2-one is 1.5 mol^{-1} min^{-1}. The rate of hydrolysis in the 6-membered ring varies slightly with other ring substituents.[68]

Where comparisons have been made between displacement rates of axial and equatorial substituents all the indications are that equatorial isomers are hydrolysed more readily. Thus, aqueous hydrolysis of fluoride[69] and alkaline hydrolysis of benzyl[70] and phenyl[71] ester groups show this pattern although it was not possible to determine the stereochemical course of these reactions.

In summary, of the results available, none show that displacements that occur with retention of configuration in acyclic systems, occur with inversion in the 6-membered ring. However there are cases for example, displacement of nitrophenol by ethoxide which occur with inversion in acyclic derivatives but with retention in the 1,3,2-dioxa ring system and other cases which proceed highly stereoselectively with inversion in acyclic derivatives which show lower stereoselectivity with a retention mechanism sometimes preponderating in cyclic systems (except in 1,3,2-oxazaphosphorinanes). The incorporation of phosphorus into a 6-membered ring, in itself provides no over-riding influence on reaction since whereas in 1,3,2-oxaza systems only reactions with inversion of configuration have been observed, in 1,3,2-dioxa and 1,3,2-oxathia systems reactions occur with both inversion and retention of configuration.

5. STEREOCHEMISTRY OF FORMATION OF 5-MEMBERED CYCLIC PHOSPHORUS ESTERS

The stereochemistry of formation of 5-membered rings containing phosphorus has been little studied. One report[72] of a reaction between meso-hydrobenzoin (**69**) and thiophosphoryl chloride in pyridine that was monitored by ^{31}P NMR indicated that after 30 min **70** and **71** were present in the ratio 1:3 but that after a further 20 min only **70** was present; i.e. **71** was the kinetic product and **70** the thermodynamic product. Since in all examples reported exocyclic displacement of chloride and bromide (except by fluoride) in 5-membered rings occurs with retention of configuration[73] it was suggested that in pyridine the equilibration of **71** to **70** occurred by reversible ring opening of the cyclic chloridate.



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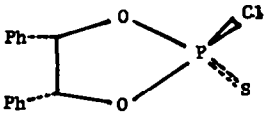

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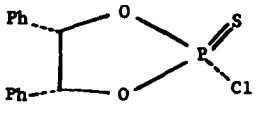

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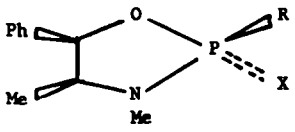
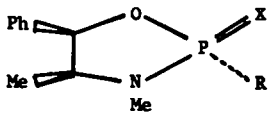
^{31}P NMR monitoring of the ring forming reaction between (−)-ephedrine and phosphoryl or thiophosphoryl chloride in a solution of dichloromethane and triethylamine revealed that in both cases the isomer ratio of the product did not vary during or after the reaction.[29] The ratio for $POCl_3$ was ~5:1 (**72** to **73**) and that for $PSCl_3$ was ~9:1 (**74** to **75**).



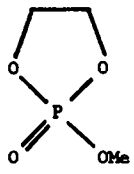


	X	R
72	O	Cl
74	S	Cl
85	S	OiPr
87	S	$OPhNO_2$

	X	R
73	O	Cl
75	S	Cl

6. RING OPENING REACTIONS OF 5-MEMBERED CYCLIC PHOSPHORUS ESTERS

The stereochemistry of ring opening of 5-membered phosphorus-containing heterocycles has not been thoroughly investigated despite the obvious importance of such derivatives in hydrolysis and migration reactions of various nucleotides[74-76] and despite the fact that the kinetic and product analysis studies for ring opening of the cyclic phosphates and phosphonates such as **76** and **77** have contributed significantly to present concepts of TBP's which undergo ligand reorganisation.[77,78] Indeed, it has only been demonstrated recently that ring opening of compounds related to uridine 2',3'-cyclic phosphates[79] occur chemically and biochemically with inversion of configuration at phosphorus.[80] It is not possible to compare the effects of ring heteroatoms on the stereochemistry of ring opening reactions since suitable experimental data for such comparisons is not available. Indeed the only 5-membered ring system which has been investigated in any detail is the 1,3,2-oxazaphospholidine system which is easily generated by condensation of suitable phosphorus halides with amino-alcohols; ephedrine and ψ-ephedrine are the readily available chiral aminoalcohols which have usually been used to facilitate stereochemical studies.[81-84] The results that have been obtained for ring opening of the 1,3,2-oxazaphospholidine system provide a clear indication that ring opening of 5-membered rings are equally complex as those in 6-membered rings. The stereochemical studies of the 1,3,2-oxazaphospholidines will be described first and then some comparison will be made with reactions of 1,3,2-dioxa and -oxathiaphospholanes which have been studied in detail except for their stereochemistry.



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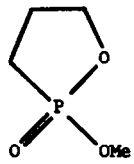

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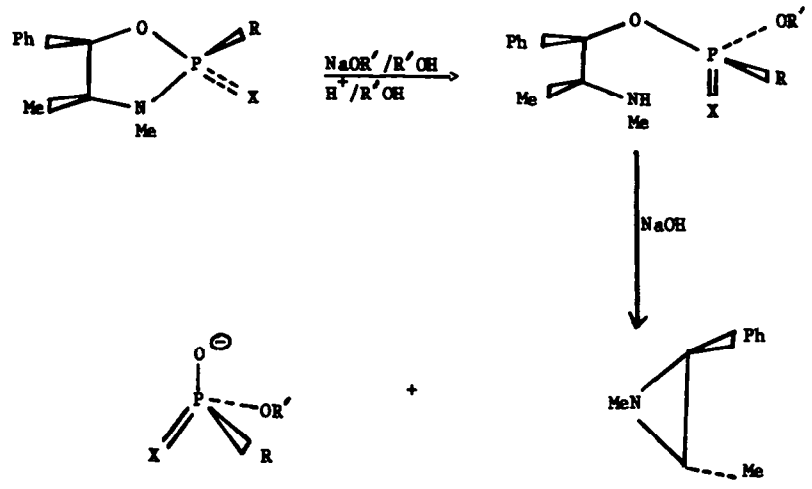
6.1 1,3,2-*Oxazaphospholidin*-2-*ones* (*thiones*) *with sodium alkoxides* (*Scheme* 16)

On treatment with sodium alkoxides in alcohol a variety of 1,3,2-oxazaphospholidin-2-ones (thiones, seleneons) undergo P–N bond cleavage with *inversion* of configuration at phosphorus.[82-84]

The reaction is slower than the corresponding acid catalysed cleavage of the P–N bond by alcohol but the product stereochemistry is the same. Where the cyclic derivative is derived from (−)-ephedrine and is a thiophosphate ester the initial P–N bond cleavage with inversion of configuration is the first step of a general stereospecific synthesis of a variety of simple chiral phosphorus derivatives. Such sequences have been described in detail elsewhere;[49,84,86,87] the fact that some of the products have unambiguously assigned absolute configurations confirms that the initial endocyclic P–N bond cleavage by acidic or basic alcohol occurs with inversion of configuration.

6.2 1,3,2-*Oxazaphospholidines with sodium hydroxide*

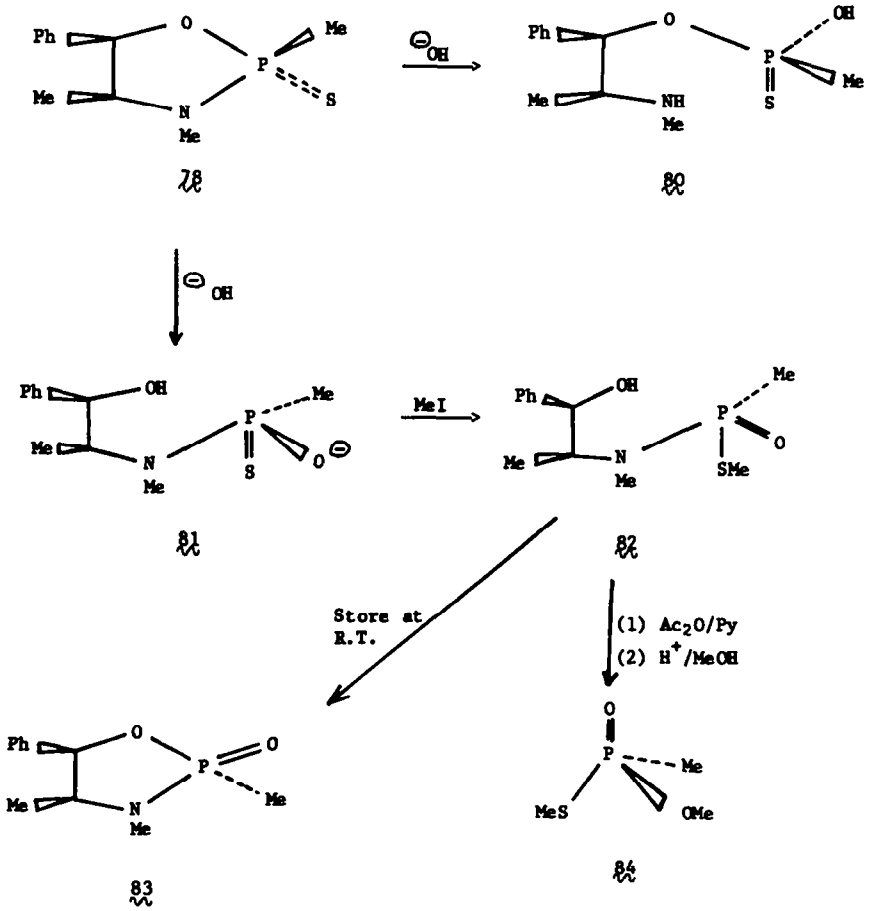
Hudson *et al.*[17,88,89] reported that the aqueous alkaline hydrolysis of 1,3,2-oxazaphospholidin-2-ones occurred with both P–O and P–N bond cleavage, the relative proportions of products depending on the



X = O, S, Se; R = alkyl, alkoxy, amino; R = alkyl

Scheme 16.

nature of the substituents on P and N. The stereochemistry of the P–O and P–N bond breaking reactions was not established. Recently, in this laboratory it has been shown that aqueous alkaline hydrolysis of some cyclic derivatives from (−)-ephedrine, in contrast to reactions with alkoxides, also occurs with some P–O bond fission.[90] In fact P–O bond fission usually preponderated, the relative proportions depending on the experimental conditions. For example (Scheme 17) when **78** was treated with 4N



Scheme 17.

NaOH in aqueous ethanol a 5:1 ratio of **81** and **80** was obtained. The P–N bond cleavage occurred stereospecifically with inversion of configuration. The P–O bond cleaved product **81** was 80% of the isomer formed with inversion of configuration but contained about 20% of the isomer formed with retention of configuration. The configuration of **81** was established as shown either by recyclisation of **82** to a 4:1 mixture of isomers in which **83** preponderated or by degradation to **84** which was shown to contain 80% of the isomer indicated, by an NMR procedure using chiral lanthanide shift reagents.[84] When the alkaline hydrolysis was performed in aqueous dioxan rather than aqueous ethanol only a trace of P–N bond cleavage occurred. The preponderant P–O bond cleavage in this case occurred with only 60% inversion of configuration. The experiments described with **78** were also repeated with the isomer **79** when similar results were obtained.

There is clearly scope for extending these studies to include compounds where there may be competition between exocyclic and endocyclic bond cleavage, for example in compounds such as **85**.

6.3 1,3,2-*Oxazaphospholidines with Grignard reagents and alkyllithium*

Treatment of 1,3,2-oxazaphospholidine-2-ones with Grignard[91] or alkyllithium reagents[92] results in preponderant P–O bond cleavage. The stereoselectivity of the reaction varies considerably (i.e. from 98% R to 80% I) with both the substrate and the reactant. With alkyllithium the major product is always that formed with retention of configuration; with Grignard reagents however products with both preponderant retention and with inversion are formed (Table 3).

Table 3. Stereochemistry of P–O bond cleavage with Grignard and alkyllithiums in 1,3,2-oxazaphospholidine-2-ones

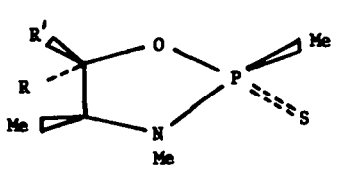
Stereochemistry	% P – O bond cleavage				% P – O bond cleavage	Stereochemistry
72% R	63%	←PhLi	~ R = Me	PhMgBr→	78%	98% R
90% R	60%	←MeLi	~ R = Ph	MeMgBr→	75%	80% I
75% R	50%	←PhLi	~ R = Me	PhMgBr→	68%	No preponderant isomer
95% R	80%	←MeLi	~ R = Ph	MeMgBr→	100%	60% I

With 1,3,2-oxazaphospholidine-2-thiones alkyllithiums again cause P–O bond cleavage. The yields are lower than for the corresponding 2-ones. Any P–N bond cleavage that occurs is masked by more rapid subsequent reactions. The variation in stereochemistry with lithium reagent and substrate is summarised in Table 4.

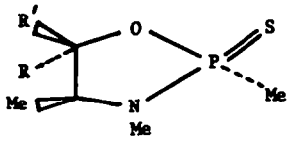
Table 4. Stereochemistry of the endocyclic P–O bond cleavage in 1,3,1-oxazaphospholidine-2-thiones with alkyl and aryllithiums

Precursor	PhLi	nBuLi	EtLi
78	98% R	95% R	95% R
79	70% R	70% I	75% I
86	94% R	90% R	85% R
87	85% R	65% I	85% I

Yields 20% – 60%



	R	R′
78	H	Ph
86	Ph	H



	R	R′
79	H	Ph
87	Ph	H

When single isomers of the 2-thiones (**78**, **79**, **86** or **87** were treated with Grignard reagents in benzene the products of both P–O and P–N bond cleavage were isolated. Their ratio depended on the nature of the starting material and the Grignard reagent used (Table 5). The products of P–O cleavage (e.g. **88**, Scheme 18) were isolated by quenching the reaction mixture with saturated aqueous ammonium chloride followed by extraction into ether. The products of initial P–N cleavage (e.g. **89**) were not stable under the reaction conditions, being converted into the corresponding phosphinothioic acids (e.g. **90***S* and (2*S*, 3*R*)-1,2-dimethyl-3-phenylaziridine (**91**). After recovery of the P–O cleaved product, acidification of the remaining aqueous layer followed by extraction with chloroform enabled isolation of the thioic acid (**90***S*). Thus treatment of **86** with PhMgBr gave **88** (30%) and enantiomerically pure (−)-(*S*)-methylphenylphosphinothioic acid (**90***S*; 25%). Since cleavage of the benzylic C–O bond in **89** does not involve attack at phosphorus, the initial P–N cleavage in **86** must occur with inversion of configuration. Hydrolysis of **88** or its O-acetate with dilute hydrochloric acid afforded enantiomerically pure (+)-(*R*)-methylphenylphosphinothioic acid (**90***R*). Thus both enantiomers of **90** were obtained from a single precursor. The stereochemical result of endocyclic P–O cleavage followed by acyclic P–N cleavage is inversion of configuration at phosphorus. Since it is likely that P–N cleavage in **88** occurs with inversion, then initial P–O cleavage in **86** must occur with retention.

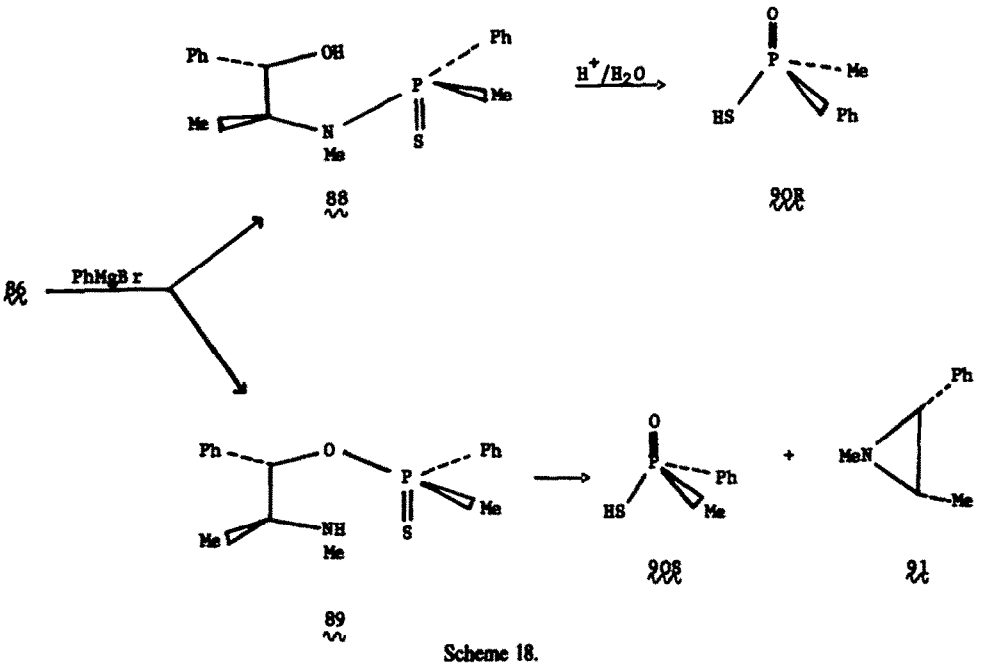
6.4 *Ring opening of* 1,3,2-*dioxaphospholanes and* 1,3,2-*oxathiaphospholanes*

Hydrolytic studies of methyl ethylene phosphate are usually discussed by reference to schemes such as Scheme 19.[7] Under basic conditions ring opening is a major reaction pathway whereas under acidic conditions loss of the exocyclic Me group can preponderate. Schemes such as Scheme 19 describe the major reaction pathways and allow rationalisation of the observed migrations and hydrolyses of various phosphate groups. However, such schemes which were derived from extensive kinetic studies over a wide pH range,[77,78] do not utilise any stereochemical data and consequently give little indication of any competition between various possible reaction mechanisms. By analogy with the ring opening of the 6-membered rings with alkoxides summarised in Scheme 7, mixed reaction mechanisms will almost certainly occur in the hydrolyses of 5-membered rings. It is probable that stereochemical experiments with appropriate chiral methyl ethylene thiophosphate derivatives would provide valuable insight into the more subtle aspects of the reaction mechanisms and also permit a more detailed examination of the

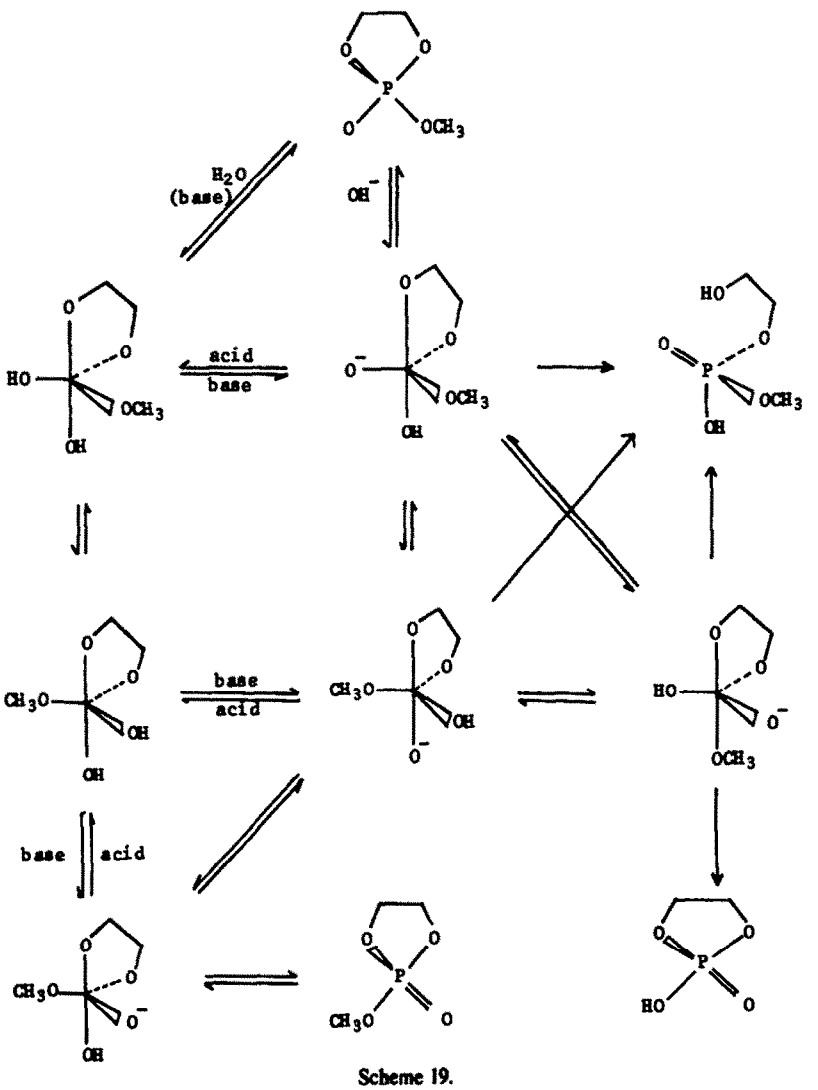
Table 5. The reaction of 1,3,2-oxazaphospholidine-2-thiones with Grignard reagents

Precursor	RMgBr	Yield and (Stereochemistry) P – O Cleavage	P – N Cleavage
78	R = Ph	76% (R)	Trace
79	Ph	11% (50% R)	36% (I)
86	Ph	30% (R)	25% (I)
87	Ph	34% (R)	44% (I)
86	Et	35% (80% R)	15% (I)
87	Et	61% (60% R)	27% (I)

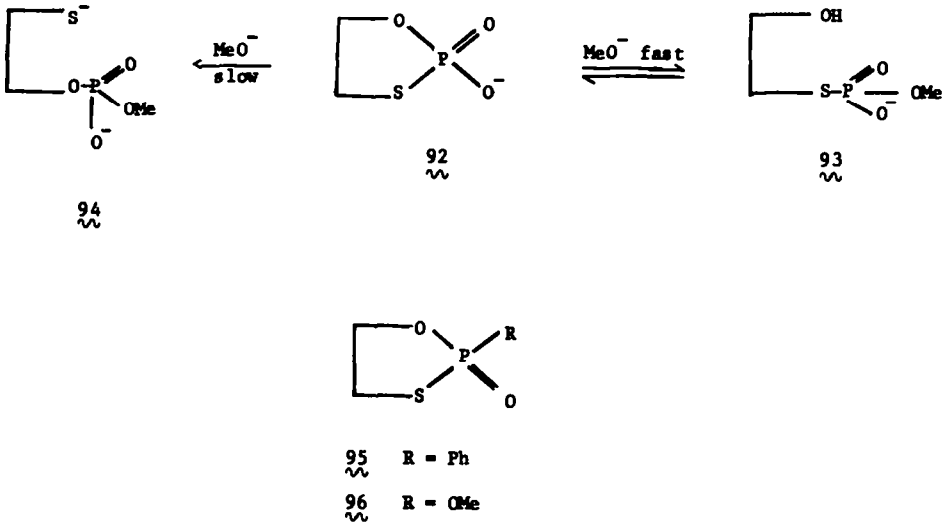
Reactions are essentially stereospecific except where the percentage of the major enantiomer is quoted.



Scheme 18.



Scheme 19.



Scheme 20.

effect of solvent on reaction course; that solvent can have an important effect was implied by results which showed that exocyclic cleavage was preferred in aprotic solvents.[93]

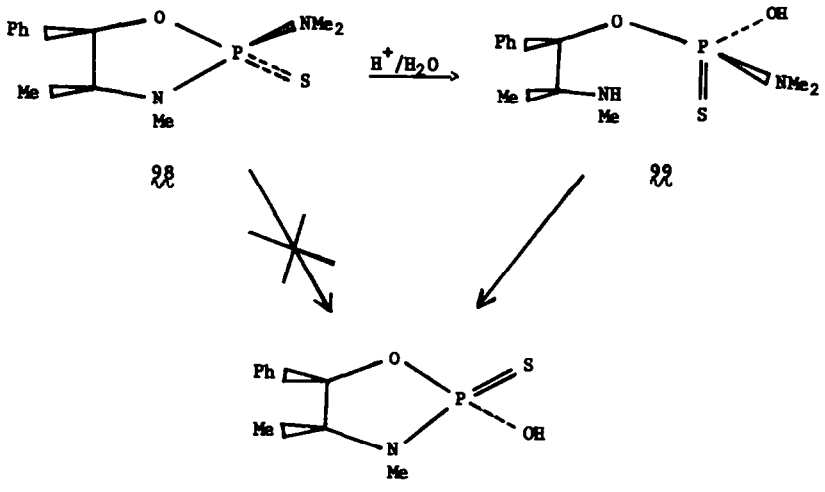
Stereochemical studies would probably provide further insight into the hydrolysis reactions of 1,3,2-oxathiaphospholane ring systems described by Hamer *et al.*[94,95] For example, (Scheme 20), with methoxide endocyclic P–O bond cleavage in **92** was more rapid than endocyclic P–S bond cleavage but since the former process was reversible the final products were those from **94** following P–S bond cleavage. These results are similar to those described in Scheme 11 for 6-membered ring phosphonate neutral esters and indeed exclusive P–O bond fission was observed in the aqueous alkaline hydrolysis of **95**. In contrast, the ester (**96**) underwent P–S bond cleavage with aqueous alkali, a result similar to that obtained when 6-member phosphate esters were treated with alkoxide (Scheme 10). The results of the experiments with the 1,3,2-oxathiaphospholidines were discussed on the basis that oxygen is more apicophilic than sulphur and that P–S bond cleavage would occur only after pseudorotation had occurred. In view of more recent results this may not be the case and it is clearly necessary to establish whether P–S and P–O bond cleavage occur by inversion or retention of configuration before further attempts are made to elucidate the details of the ring opening processes. Examples have been given, in the oxaza ring system of discussions of reaction mechanisms which are completely inconsistent with stereochemical results.[88,89]

7. EXOCYCLIC DISPLACEMENT REACTIONS IN 1,3,2-OXAZAPHOSPHOLIDIN-2-ONES AND RELATED COMPOUNDS

In 5-membered rings, provided bond forming and breaking reactions occur at apical positions in a TBP it is to be expected that all nucleophilic exocyclic displacement reactions at phosphorus will require ligand reorganisation following attack initially opposite ring heteroatoms and will occur with retention of configuration. In 1,3,2-oxazaphospholidines such displacements appear to occur with retention of configuration. This has been demonstrated chemically[82,84] where it has been shown that direct displacement of chloride by isopropoxide (i.e. **74** to **85**) gives the same product and sequential displacement of chloride by nitrophenoxide by isopropoxide (i.e. **74** to **97** to **85**) and in many other experiments involving cyclic esters from (−)-ephedrine and *ψ*-ephedrine where the configuration at phosphorus in starting materials and products have been unequivocally established by NMR techniques.

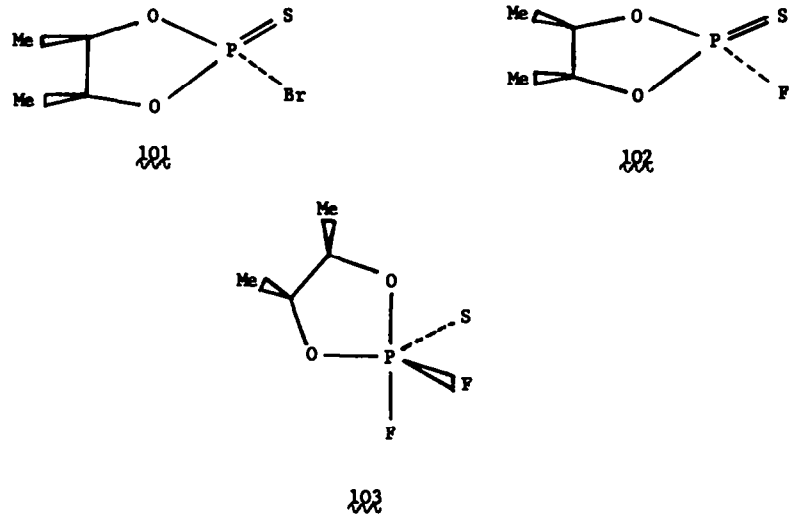
One apparent anomaly to the general pattern was found (Scheme 21) when a 20% yield of **100** was obtained on treatment of **98** with aqueous hydrochloric acid; i.e. hydrolysis occurred with inversion of configuration. (The major product was that resulting from endocyclic P–N bond cleavage). A route which provides an explanation of the apparent anomaly is that which invokes the intermediacy of the ring opened material (**99**) which then ring closes with displacement of dimethylamine to give **100**. There is ample evidence for such facile exchange of amine groups in phosphoramidomonoacids.[96]

Displacements of chloride by bromide, alcohols, amines and thiols in 1,3,2-dioxaphospholan-2-thiones also occur with retention of configuration.[73] In this series however ambiguous results were obtained with reactions involving fluoride and **101** of various diastereoisomeric compositions when it is possible that



Scheme 21.

ligand reorganisation of intermediates such as **103** gave the observed 3:1 *cis*:*trans* mixture of **102**, no matter what the initial composition of **101**.



8. PENTACOORDINATE INTERMEDIATES AND THEIR REORGANISATION

To simplify any discussion of the involvement of intermediates in nucleophilic substitution reactions at tetracoordinate pentavalent phosphorus it is reasonable to assume that the pentacoordinate intermediates have TBP geometry and that bond breaking and forming processes occur only in the apical positions of the TBP. (One suggestion,[17] that square planar pyramidal intermediates (SBP) might be involved in the ring opening of 1,3,2-oxazaphospholidines does not appear to be consistent with the stereochemical data now available).[84] It may be argued that this assumption, which is adopted for the subsequent discussion in this Section, is supported by the fact that no migration of the phosphorus group from nitrogen to O-4 to give **105** occurs during the acidic alcoholysis of **104** to **106**[47] whereas the intramolecular acid catalysed conversion of **107** into **108** is favoured.[38] In the former case it is not possible to form the required TBP with O-4 and N both apical and migration could only occur if apical entry with equatorial departure of groups were possible or if the intermediate was a SBP; in the latter case it is possible to form an intermediate with O-4 and N apical so ring closure rapidly takes place. Alternative interpretations of these results are however also possible. The inability to cause migration of a phosphinate group across a 1,3-diol may also be considered as being consistent with a requirement for nucleophilic attack opposite an apicophilic group in a TBP. However, migrations of phosphinate groups across 1,2-diols show that such factors are not an insuperable obstacle.[37]

Scheme 22.

Much has been written[1-6] about the mechanisms by which the ligands attached to pentacoordinate phosphorus are able to undergo reorganisation by BPR and TR processes in TBP's and evidence has been provided by NMR studies that is consistent with the occurrence of multiple BPR and complex TR processes in phosphoranes.[97] Such evidence has been interpreted as favouring TR processes particularly where the pentacoordinate phosphoranes incorporate ring systems.[6]

The question remains, however, as to the extent such processes occur in pentacoordinate reaction intermediates. Reactions which occur with retention of configuration only provide an indication that a TBP is formed and undergoes at least one BPR or TR process before decomposition. It is usually not possible to determine whether or not the observed retention of configuration results follow more than one ligand reorganisation. Similarly, for reactions which occur with inversion it is usually not possible to determine whether direct displacement has occurred or whether displacement occurs after the appropriate BPR's and TR's. The various possibilities have been discussed in detail particularly with reference to the hydrolysis of phosphonium salts.[1]

While not providing evidence to allow unequivocal distinction between the various possibilities, the results of the stereochemical studies summarised in this review appear fully consistent with the view that for reactions that proceed with inversion of configuration, displacement is direct and precedes any ligand reorganisation (Scheme 1) whereas for retention only one reorganisation occurs (e.g. Scheme 2) either by a BPR or TR process. For example, the fact that migration of **25** to **23** (Scheme 7) with retention of configuration is stereospecific[38] and that the much slower reverse migration of **23** to **25** is also stereospecific with retention of configuration, appears to allow BPR and single TR processes but to preclude multiple TR processes. Migration sequences involving TBP's which undergo more than single BPR's are precluded by the restraints inposed by the requirement (a) that the 6-membered ring spans only equatorial–equatorial or apical–equatorial positions in the TBP and (b) that the P–O group should remain in an equatorial position. The consequences are that migration can only occur with retention of configuration (except where exchange processes involving bond breaking may operate). Multiple TR or TR switch mechanisms, which would circumvent any restraints to ligand reorganisation imposed by the ring system, can in theory allow migration with "racemisation". In the migrations **23** to **25** and **25** to **23** where all the ligands attached to phosphorus are oxygen, it is reasonable to assume many of the TBP's will be of similar energy (excluding those causing the 6-membered ring to span apical positions, etc.), thereby facilitating their interconversion causing racemisation of the migrating phosphorus ester. The fact that no such "racemisation" is observed makes it extremely unlikely that multiple TR processes will make a significant contribution to any reactions involving TBP intermediates.

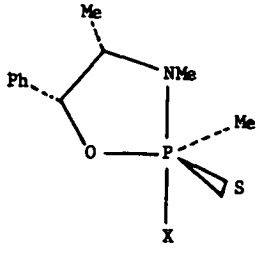
The above conclusion, if it can be substantiated, will be of some importance in allowing general predictive rules to be developed concerning the stereochemistry of displacements at phosphorus. At present, the major disadvantage of concepts of multiple TR processes is that they allow energetically unfavourable TBP's to be circumvented, so that it is difficult to rule out almost any possible reorganisation. If ligand reorganisations in reaction intermediates may justifiably be considered in terms of BPR's or single TR processes it at least becomes feasible to draw up guidelines as to what are and what are not probable ligand reorganisations.

If complex TR processes are unlikely in TBP reaction intermediates it follows that in ring opening reactions where the products have mixed stereochemistry, the nucleophile must attack phosphorus opposite different apicophilic groups, with direct displacement or with displacement following single BPR or TR processes. The results for ring opening are consistent with this. For example, the results in Scheme 7 are consistent with displacements involving attack opposite O-4 and O-6 and similarly the reactions of the Grignard reagents and alkyllithiums in Schemes 4 and 5 are consistent with each product being the result of a single simple stereochemical reaction course with the nature of the product being determined by the initial direction of attack and whether or not a single BPR or TR occurred. The reactions of MeMgI with **22eq** and **22ax** provide a particularly good example of this. In the former case the only isolated product was **19** formed with P–O6 bond cleavage with inversion of configuration whereas in the latter (**19**) was again the major product but formed by P–O6 bond cleavage with retention of configuration. That the attack in the latter case was initially opposite O-6 was implied by the formation of **18** by P–O6 bond cleavage with inversion of configuration.

The problem is to describe which factors determine the direction of attack and which facilitate or inhibit single BPR or TR processes. Those which influence the direction of attack and are related to the apicophilicity of the various groups attached to phosphorus are discussed in Section 9. With regard to factors which facilitate or inhibit single BPR or TR processes it is clear that at present no general

guidelines can be given. Previous guidelines, for example the strong preference for P–C bonds to remain equatorial as providing some resistance to ligand reorganisation, now have too many exceptions, for example as shown by the fact that ring opening of phosphonates by hydroxides and alkoxides such as **78** can at least in part occur with some retention of configuration. Also the reactions of Grignard reagents and alkyllithiums to form phosphinatederivatives with two P–C bonds are not easy to interpret since some reactions occur with inversion and others with retention of configuration.

However, as shown by the following example, once a TBP is formed, whether it breaks down immediately or whether ligand reorganisation occurs depends on a number of factors including the relative apicophilicity of the nucleophilic and of the other groups at phosphorus. Thus the results of ring opening of 1,3,2-oxazaphospholidine-2-thiones with Grignard reagents (Section 6.3) and alkoxides (Section 6.1) can be explained by assuming that in this system the nitrogen is more apicophilic than the oxygen (Section 10). Attack of a nucleophile X at **78** therefore occurs opposite nitrogen to generate a TBP (**109**). Where X = OEt direct apical P–N bond cleavage occurs resulting in inversion of configuration at phosphorus. Where X = Ph some direct P–N bond cleavage occurs but reorganisation of **109** to **110** is in this case competitive with bond breaking. Apical P–O cleavage in **110** results in retention of configuration at phosphorus. That the rate of reorganisation of **109** (X = Ph) is competitive with P–N bond cleavage whereas in **109** (X = OEt) it is not, presumably reflects a barrier to reorganisation in the latter case, caused by the much greater apicophilicity of OEt than Me. Ph and Me however have more similar apicophilicities. Other examples where product stereochemistry may be related to the apicophilicities of the nucleophile have been reported.[98]



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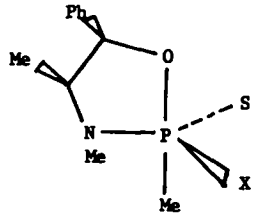

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It is necessary to enquire whether or not the conclusion that multiple TR processes are unlikely in TBP reaction intermediates, applies to acyclic as well as to cyclic intermediates. At present there is no evidence to suggest otherwise for all reported stereochemical studies of substitutions in phosphoro, phosphono and phosphino derivatives show the substitutions take place (a) with essentially complete inversion or retention of configuration, (b) with mixed stereochemistry because of multiple intermolecular interactions[49] or (c) with mixed stereochemistry reasonably ascribed to attack opposite different groups.[42,46]

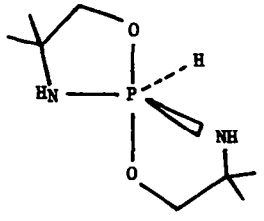
9. APICOPHILICITY

On the assumption that pentacovalent intermediates and pentacovalent phosphoranes have the geometry of a trigonal bipyramid it was considered initially on energetic grounds that the more electronegative a group was, the greater would be its predisposition to occupy an apical position in the TBP. Gradually experimental data was accumulated from dynamic NMR studies of stable phosphoranes which enabled the apicophilicity of one group relative to another to be obtained.[9,12] As a result of many such studies it is possible to list the following groups in approximate order of apicophilicity:[99] $F > H > CF_3 > OPh > Cl > SMe > OMe > NMe_2 > Me > Ph$. In acyclic systems (except where there is competition between S–R and OR leaving groups, and in phosphonium salts where all the ligands may be of equivalent apicophilicity) present evidence is that this order of apicophilicity is valid in pentacoordinate intermediates, since most reactions occur with displacement of the expected leaving group with inversion of configuration.

Unfortunately it now appears from a consideration of the stereochemical results in 5- and 6-membered rings that there is no easy way of relating the apicophilicity of groups obtained from measurements in stable phosphoranes to the effect of such groups in determining which bond is broken in reactions which probably involve unstable TBP's and whether the bond is broken with inversion or retention of configuration. For example, it would be anticipated on the basis of electronegativity,

measured apicophilicity and by analogy with results in acyclic systems, that displacement of fluoride and chloride from phosphorus in 1,3,2-dioxaphosphorinanes would occur with inversion of configuration. The fact that under certain conditions these and other displacements from 6-membered rings occur with significant degrees of retention of configuration has been interpreted as being consistent with initial attack of the nucleophile opposite a ring oxygen prior to pseudorotation and departure of the exocyclic leaving group. If such a mechanism is correct the implication is that conditions have been generated to make oxygen more apicophilic than fluorine. Other explanations that have been put forward to account for displacements from 6-membered rings with retention of configuration are also inconsistent with concepts of apicophilicity.[60]

Perhaps, the most intriguing result is the finding that under appropriate basic conditions P–N bonds may be broken with inversion of configuration when they form part of a ring system. Acyclic and exocyclic P–N bonds are resistant to base (except where proton abstraction leads to metaphosphorimidates[100]). Also NMR studies show nitrogen even as part of a ring system to have low apicophilicity and there are many X-ray results which show nitrogen occupying basal positions in TBP's in stable spirophosphoranes such as **14**,[37] **111**,[101] **112**,[102] **113**.[103] As a consequence it is not only necessary to provide an explanation as to why P–N bonds in 5- and to some extent in 6-membered rings are much weaker than in acyclic analogues and become weaker than P–O bonds but also to provide an explanation for the apparent reversal of apicophilicity in unstable as opposed to stable TBP's. Possibly, reasons for these apparent anomalies will be found, perhaps as concepts of stereoelectronic effects (Section 10) are further developed, but at present none of the current theories appears to be fully consistent with the facts. Additionally it is necessary to provide an explanation for the effect that reaction conditions have an apparent apicophilicity as illustrated by the change from preponderant P–N bond cleavage in **78** by methoxide in methanol to preponderant P–O bond cleavage in aqueous sodium hydroxide.



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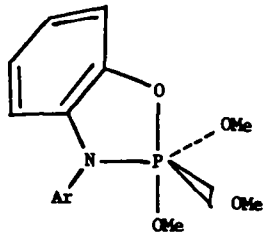

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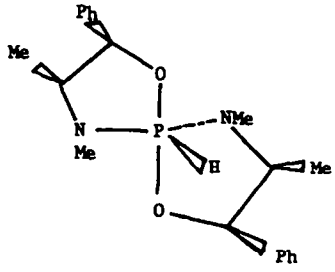

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It is apparent that subtle stereochemical factors can have a pronounced effect in determining the direction of attack at phosphorus and that such effects may completely override more usual considerations of apicophilicity. These effects are perhaps most evident in the ring opening of 1,3,2-dioxaphosphorinanes (Sections 3.2 to 3.6) where the direction of attack opposite O-4 and O-6 and the stereochemistry of P–O4 and P–O6 bond cleavage are functions of the initial stereochemistry and the nature of the exocyclic groups at phosphorus as well as of the different nucleophiles. There are no obvious stereochemical influences (by inspection of molecular models) to account for the observed differences, but perhaps it should be noted that calculations have shown that there are differences in electron distribution between endocyclic oxygens in most cyclic phosphate esters.[104]

The foregoing comments illustrate that in ring systems differences in apicophilicity are often minimised as far as the formation of unstable pentacovalent intermediates is concerned and the direction of addition of a nucleophile depends on the nature of the nucleophile, solvent, the other ligands present, and possibly on other reaction conditions. With regard to reactions of *S*-alkyl phosphorus derivatives however, there appears to be a delicate balance between the apicophilicities of oxygen and sulphur in acyclic as well as in cyclic derivatives and this balance depends particularly on the nature of the other groups attached to phosphorus and on the solvent.

10. STEREOELECTRONIC EFFECTS

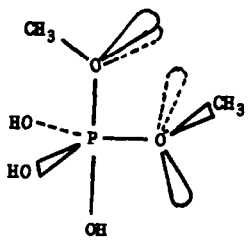
The stereochemical data described in this review are sufficiently varied to provide a severe test for some of the proposals that have been made about the way in which the orientation of lone pairs of

electrons on atoms directly attached to phosphorus influence the strengths of adjacent bonds.[74,105,106] As an example, in very simple terms, of the way in which these stereoelectronic factors affect bond strengths it is instructive to consider the TBP's **114** and **115**. Calculations show that in **114**, an axial P–OR bond which has an adjacent equatorial P–OR bond in a conformation where a lone pair of electrons on equatorial oxygen is antiperiplanar (app) to the axial P–OR bond, is weaker than when the equatorial P–OR bond is in some other conformation, e.g. **115**. Synperiplanar orientation of the equatorial group which produces two "partial" app lone pair interactions, e.g. **116**, perturb the overlap populations slightly more than a single pure app interaction and thus weaken the axial P–OR a little more. Such a synperiplanar interaction can only really be important in a ring system and it has been suggested that the fact that 5-membered rings are hydrolysed 10^6–10^8 times faster than their acyclic analogues, while due in part to relief of ring strain in forming a TBP, is also due to the app effect in the TBP.

The ring opening of 6-membered 2-alkyl 1,3,2-dioxaphosphorinan-2-ones under alkaline conditions and the subsequent migration of alkyl, alkyl phosphate without loss of alkoxy groups is consistent with bond weakening by app lone pair effects. In a TBP with one ring oxygen apical and the other ring oxygen equatorial the equatorial oxygen lone pair can only be app to the axial ring oxygen and not to the exocyclic apical group. There appears to be no obvious conformational preference for the exocyclic equatorial P–OR group, which may thus be considered to influence both the exocyclic and endocyclic axial P–O bonds in an equal manner. Whereas the stereoelectronic effects are consistent with the ring opening reactions of 5- and 6-membered rings in alkaline solution they are inconsistent with the exocyclic cleavage of groups observed with 5-membered rings in acidic solutions. It may be that in acidic solution lone pairs are wholly or partially protonated and hence less efficient at overlapping with adjacent anti-bonding orbitals. Their orientation would therefore have a reduced effect on the stereochemical course of substitution.

Another result to emerge from calculations of stereoelectronic effects in reactions of phosphate diesters is that the optimal conformations for bond forming processes in the generation of a TBP may not be the most favourable for bond breaking processes. Thus for hydrolysis of dimethyl phosphate the bond forming step requires the lone pair on the equatorial OMe to be app to OH, i.e. **117**, whereas for the bond breaking process rotation of the equatorial OMe is necessary to place the lone pair app to the axial OMe, i.e. **118**.

Experimental evidence about the possible role of conformational effects in bond forming and bond breaking processes was provided in Sections 2–6. Unfortunately it is difficult to relate that experimental



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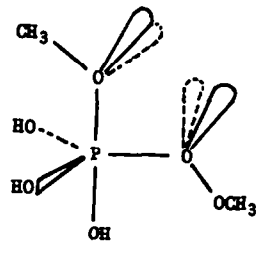

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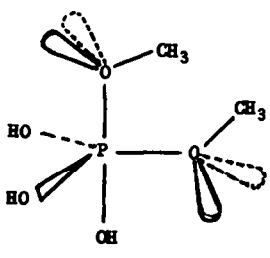

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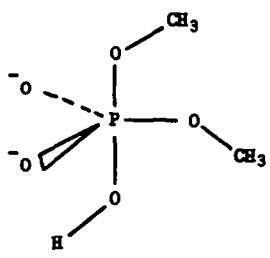

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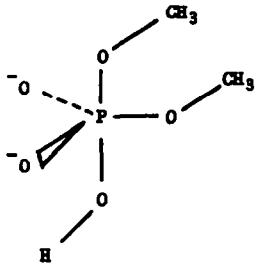

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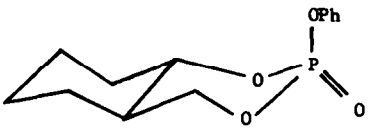
data to the concepts implicit in the calculations of the hydrolysis of dimethyl phosphate because in many of the bond breaking processes described, bond breakage occurred with inversion of configuration whereas in others retention of configuration was observed. Similarly, stereochemical effects were neglected[71] when it was suggested that the rapid rate of hydrolysis of OPh in **120** compared with the corresponding hydrolysis of **119** was explicable in terms of stereoelectronic effects. For example, the suggested "top side" attack for each molecule implies OPh displacement with inversion of configuration in **120** and retention of configuration in **119**, whereas available evidence (Tables 1 and 2) suggests the stereochemistry of displacement is independent of initial stereochemistry and for displacement of $OPhNO_2$ by ethoxide occurs with preponderant retention of configuration for both isomers. Further, only effects in the chair conformations depicted for **6** and **7** were considered. The outcome in other conformations could be quite different.

It is of interest to enquire whether or not present concepts of stereoelectronic effects provide any possible explanations to the relative case of P–O and P–N bond cleavage in 5- and 6-membered rings. If the possible TBP's (**121** and **122**) are considered it will be seen that in **121** with P–N apical the app lone pair effect on equatorial oxygen should weaken the P–N bond. In **122** the P–N bond is in its conformation of greatest strength, i.e. in the equatorial plane with the lone pair electrons perpendicular to the equatorial bond.[107,108] In this conformation there is no weakening effect on the apical P–O bond. The overall consequence is a situation in **121** where reaction is favoured compared to acyclic analogues by factors associated with relief of ring strain whereas in **121** the ring strain effects are augmented by the fact that the P–N bond is weaker relative to the P–O bond than in acyclic analogues and will break more readily. (Other factors which affect P–N bond properties have been reviewed).[109]



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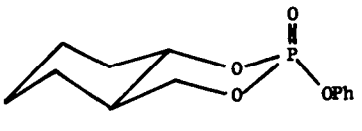

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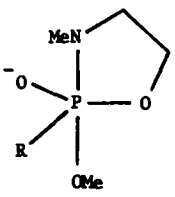

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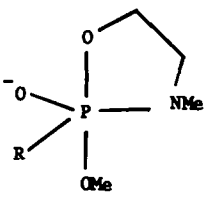

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Clearly, there are many dangers in attempting to apply the results of quantum mechanical calculations of isolated molecules in the gas phase to reactions of solvated molecules in solution. Nevertheless such attempts must be made if a reasonable degree of understanding of the many diverse stereochemical results of nucleophilic substitutions at phosphorus is to be achieved.

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