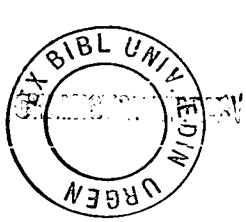
HETEROCYCLIC COMPOUNDS OF NITROGEN, OXYGEN, AND QUINQUEVALENT PHOSPHORUS

by

ROBERT STEWART STRATHDEE, B.Sc.

THESIS PRESENTED FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

University of Edinburgh



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DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a higher degree.

This thesis describes results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Professor J.I.G.Cadogan since 1st October 1975, the date of my admission as a research student.

Acknowledgements

I should like to thank Professor J.I.G. Cadogan for stimulating my initial interest in this research topic, and for his continued encouragement throughout the course of the research project. I am greatly indebted to Dr. N.J. Tweddle and Dr. I. Gosney for many fruitful discussions and invaluable advice. Many other colleagues and members of staff at Edinburgh are due my thanks, but especially Mr. J.R.A. Millar for his patience and assistance in recording variable temperature n.m.r. spectra.

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Lecture Courses

The following postgraduate courses have been attended:

N.M.R. Spectroscopy (7 lectures), Dr. R.K. Harris;

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Organic Sulphur Compounds in Organic Synthesis (5 lectures), Dr. D. Leaver;

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From Crawford to Kemball - 250 Years A-Growing (5 lectures), Dr. W. Doyle;

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Publications

A report on some aspects of this work has been published, and is included as an appendix to this thesis:

"Direct Observation of Diastereoisomers in Chiral Oxazaphosphoranes [3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles] by ^{1}H and ^{31}P Nuclear Magnetic Resonance Spectroscopy," by J.I.G. Cadogan, R. Stewart Strathdee, and Neil J. Tweddle, J.C.S.Chem.Comm., 1976, 891.

ABSTRACT

The reaction of tervalent phosphorus reagents with aryl 2-nitrophenyl ethers to give 3-aryl-2,3-dihydro-benzoxazaphosph(v)oles has been successfully extended to cover a range of asymmetrically substituted ethers and various tervalent phosphinites and phosphines. The effect of this asymmetry on the barriers to intramolecular stereomutation in the derived pentacoordinate phosphoranes has been examined by variable temperature n.m.r. spectroscopy. Steric factors have been shown to have a major influence on the results, which are rationalised in terms of regular pseudorotational pathways. These studies have culminated in an attempt to isolate an optically active monocyclic pentacoordinate phosphorane. In this respect, reaction of (+)-sec-butyl methylphenylphosphinite with 2-nitrophenyl 2-tert-butylphenyl ether gave a pair of non-interconvertible chiral diastereoisomers. Fractional crystallisation proved unsuccessful, however, and attempts to isolate a single diastereoisomer by chromatography were frustrated by hydrolysis and poor separation.

The hydrolysis reactions of several 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles have been investigated and the products rationalised in terms of competing steric and electronic factors. These results are consistent with a general "dipole-dipole interaction" mechanism for base catalysed hydrolysis of pentacoordinate phosphoranes.

C O N T E N T S

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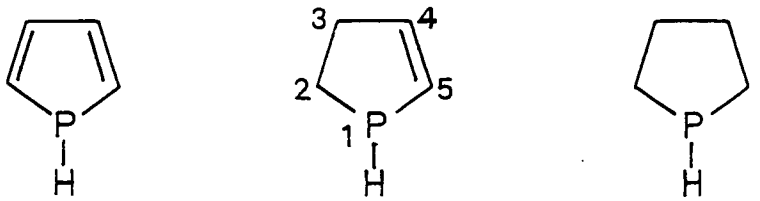
Note on Nomenclature

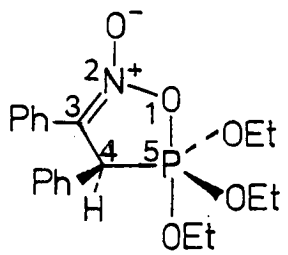
Compounds which incorporate a phosphorus atom in a ring follow the general rules for naming heterocyclic compounds (Hantzsch-Widman). Structures (a), (b), and (c), for example, are named as phosphole, 2,3-dihydrophosphole, and phospholan respectively, with the stem "-ole" indicating a five-membered unsaturated system (qualified by the prefix "2,3-dihydro-" in (b)).



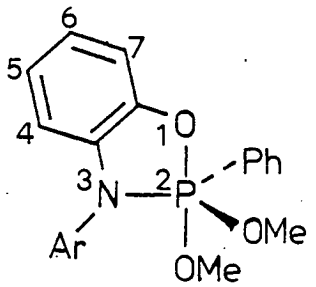
(a) (b) (c)

In monocyclic compounds containing several heteroatoms in the ring, the locant 1 is assigned to the atom of highest priority in the order O>S>N>P. This same priority applies in the sequence of heteroatom prefixes. Numbering of the ring proceeds so as to assign the lowest possible locants to the remaining heteroatoms, the order of priority now being of secondary importance. When numbering fused ring systems, precedence is given to assigning the lowest possible set of locants to the heteroatoms, with the rule of priority becoming a secondary consideration. Two compounds which illustrate this nomenclature are 4,5-dihydro-3,4-diphenyl-5,5,5-triethoxy-1,2,5-oxazaphosph(v)ole-2-oxide (d), and

3-aryl-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benz-oxazaphosph(v)ole (e).



(d)



(e)

The phosphorus atom can exist either in oxidation state (III) or (V), which is often indicated by insertion of the appropriate symbol between prefix and stem, as used in naming compounds (d) and (e) above.

SECTION I

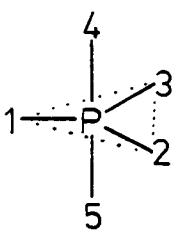
INTRODUCTION

INTRODUCTION

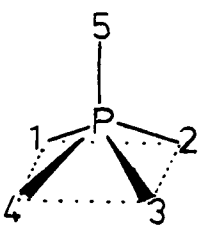
1. Pentacoordinate Phosphorus Compounds: General Features

1.1 Structure and bonding

Pentacoordinate phosphorus compounds, often encountered in the literature under the general title of phosphoranes, may be considered as derivatives of the hypothetical phosphorus pentahydride, PH_5, in which the central phosphorus atom is covalently bound to five ligands. The preferred spacial distribution of five ligands around a central phosphorus atom is usually trigonal bipyramidal (1)[1,2], although occasionally tetragonal (square) pyramidal (2).



(1)



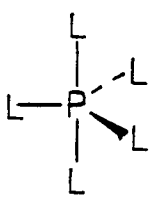
(2)

In an ideal trigonal bipyramid (TBP) three equatorial ligands (ligands 1, 2 and 3) lie coplanar with the phosphorus atom, mutually disposed at an angle of 120°, and two axial or apical ligands (ligands 4 and 5) lie orthogonal to the equatorial plane on either side of the phosphorus atom.

Even in pentacoordinate structures containing five identical ligands, apical bonds are found to be longer than equatorial bonds[3], as determined from electron diffraction studies of phosphorus pentahalides[4,5], and X-ray crystallographic analysis of pentaphenylphosphorane[6]. In the latter case, for example,

the molecule was found to have a trigonal bipyramidal structure with mean equatorial P-phenyl bond length of 1.850 Å, compared with 1.987 Å for apical P-phenyl bonds.

These observations can be explained by simple electrostatic or electron repulsion models. In contrast with four or six coordinate systems, the laws of symmetry do not allow for five ligands to be symmetrically arranged equidistant from each other on the surface of a sphere. There are, however, two structures in which mutual repulsion of valence shells would result in minimal energy states being attained - these are the trigonal bipyramid (3) and the square or tetragonal pyramid (4).



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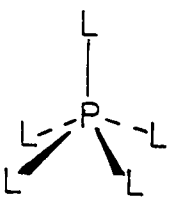


(4)

Calculations based on electrostatic models show the TBP structure to be lower in energy by about 6 kJmol^{-1} [7]. Each of the above structures has two non-equivalent ligand positions i.e. positions in which two sets of ligands experience different environments. In the TBP, each apical position has as its neighbours three equatorial ligands making an angle of 90° with the central phosphorus atom, and one neighbour at 180° (the other apical ligand). Each equatorial ligand, on the

other hand,has only two 90^{o} neighbours and two 120^{o} neighbours. Given that the greatest repulsive interaction will arise from 90^{o} neighbours, then if all bond lengths were equal, the apical ligands would be subject to greater repulsive or steric interactions than equatorial ligands. Allowing the system to attain an equilibrium situation of minumum overall energy, however, the TBP will tend to equalise these interactive forces by lengthening the apical bonds. This model therefore concurs with experimental observations that apical bonds are longer than equatorial bonds. In addition, apical bonds will generally be weaker than equatorial ones, since bond strength is inversely proportional to bond length.

Useful though the simple electrostatic model may be,perhaps a more detailed understanding of pentacoordinate structures can be gained from consideration of molecular orbital bonding principles.

Being an element near the centre of the periodic table, phosphorus has a high ionization potential, hence is found covalently bonded in the majority of its compounds. The outer shell electronic configuration of $3s^{2}3p^{3}$ suggests that the bonding electrons should occupy singly each of the three p-orbitals. Consequently formation of tervalent compounds might be predicted, with bond angles close to the theoretical p-orbital distribution of 90^{o}.

Tervalent compounds do of course constitute a large part of phosphorus chemistry, but observed bond angles range from about 93^{o} in phosphine to 100^{o} in phosphorus trifluoride, indicating that some degree of hybridised bonding occurs.

However, the degree of s-character in the σ-bonding orbitals of tervalent phosphorus compounds is significantly less than in the corresponding nitrogen compounds. There, for example, the bond angle of greater than 106^{o} in ammonia approaches the true tetrahedral angle associated with full sp^3-hybridisation.

For a phosphorus atom to bond covalently with five other atoms, then one of the paired 3s-electrons must be promoted to a vacant orbital of higher energy than the 3p-orbitals. The vacant 3d orbitals meet this requirement, but promotion of an electron from the 3s to 3d level requires an energy input of about 1780 $kJmol^{-1}$. For formation of a stable pentacoordinate molecule to occur, there must be an energy gain at least equivalent to this promotional energy requirement. Such a gain is realised because the formation of hybridised molecular orbitals allows greater overlap with ligand molecular orbitals, thus giving greater bond strength to the pentacoordinate molecule and lower overall energy state to the phosphorus atom.

The most stable pentacoordinate structural form may now be rationalised as a particular combination of possible hybridised molecular orbitals which leads to optimum overlap with ligand bonding orbitals. Consider the five atomic orbitals available for bonding on the phosphorus atom (one s-orbital, three p-orbitals, and one d-orbital). Hybridisation of the d_z^2-orbital with the p_z-orbital gives rise to two pd-hybrid orbitals directed along the z-axis. Combination of the three remaining orbitals gives three sp^2-hybridised orbitals with trigonal distribution in the xy-plane. The net result is a trigonal bipyramidal structure.

By a similar argument, a combination of four hybridised orbitals (s, p_x, p_y, $d_{x^2-y^2}$) and one p_z orbital would give rise to a tetragonal pyramidal structure, which, for the vast majority of ligands, would result in poorer orbital overlap; such a geometrical configuration would therefore be a less stable or higher energy structure than the TBP.

In a TBP, it has already been shown that steric interactions are greater at the apical positions, which are therefore better suited to accommodate pd hybridised orbitals. Having no s-character, these are long, narrow orbitals which consequently possess a high electron density. In contrast, the broader sp^2 hybridised orbitals are more diffuse in electron density and are better accommodated in the less crowded equatorial positions. As a result, not only will apical bonds tend to be longer and weaker than equatorial bonds, but apical positions will be favoured by small electronegative ligands, capable of bearing a higher electron density, while electropositive ligands prefer to occupy the equatorial positions.

The above polarity rule[8] is incorporated in the concept of 'apicophilicity' i.e. the affinity of a ligand to occupy an apical position. Apicophilicity, however, is not solely governed by electronegativity. As has been inferred already, the size of a ligand also has an influence on its preferred position in a TBP, with larger groups preferring an equatorial situation. Comparison of the relative electronegativities: Ph>Me>H, with their relative apicophilicities: H>Me>Ph, demonstrates the importance of ligand bulk, although the phenyl ligand's low apicophilicity can also be accounted for by the third important factor governing apicophilicity - that of π-donor

ability. The presence on an atom bonded to phosphorus of a lone pair of electrons favours occupation of an equatorial position, since in such a position, the available electrons can best stabilise the phosphorus atom by back-donation of electron density to the low-lying vacant phosphorus d-orbitals. This pd-π back-bonding also contributes to the shortening of equatorial bond lengths. Thus dialkylamino and phenyl groups are less apicophilic than their electronegativities alone would suggest, due to their π-donor capacities. Indeed, atoms such as nitrogen and sulphur, which possess only one donor orbital, will preferentially lie with the lone pair orbital occupying the equatorial plane[9].

It can therefore be generalised that π-donor ligands prefer equatorial sites, while π-acceptors prefer apical sites, and that an "ideal" apicophilic ligand would possess high electronegativity, poor π-donor ability, and low bulk.

By utilising the concept of apicophilicity, it is possible to predict the most stable TBP structure from all the possible isomeric structures which could arise for any particular permutation of five ligands. This is especially important as pentacoordinate phosphorus compounds exhibit stereochemical non-rigidity i.e. the apical and equatorial ligands are constantly interchanging positions in a rapid and regular bond deformation process.

This permutational isomerisation, or "pseudorotation" as it is often called, can be readily studied using variable temperature n.m.r. spectroscopy, and is discussed in greater detail in Chapter 1.3.

1.2 Stability

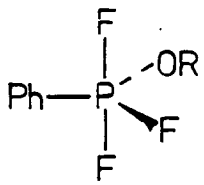
The preference for certain ligands to occupy a particular site within a TBP structure has been indicated as being an important factor in determining the lowest energy "ground state" isomer, but this is only one of several factors, outlined below, which determine the likelihood of phosphorane formation in the first place, and their subsequent stability.

Firstly, there is a tendency for electronegative ligands to stabilise phosphoranes. Phosphorus pentafluoride, for example, is relatively stable, whereas pentaethoxyphosphorane is unstable at ambient temperatures, and pentaalkylphosphoranes are rarely isolable. Tris(trifluoromethyl)dihydrophosphorane has been prepared[10], the presence of the three electronegative groups presumably increasing its stability relative to the as yet unknown parent compound, phosphorus pentahydride (PH_5).

The crowded TBP structure can be destabilised by the presence of bulky groups. This may be a contributory factor to the increase in stability which generally accompanies the substitution of more electronegative ligands, since the more electronegative the atom (F>O>N>C) bonded to phosphorus, the fewer substituents it is likely to carry.

The effect of bulk on stability, separated from any electronic interactions, is illustrated by the observations[11] that the alkoxyphenyltrifluorophosphorane (5) decomposed at temperatures of between 60° and 120° when R was a primary alkyl group, but decomposed below -50° when R was a tertiary alkyl group.

The incorporation of small rings has a major stabilising influence in pentacoordinate phosphorus chemistry, four- and



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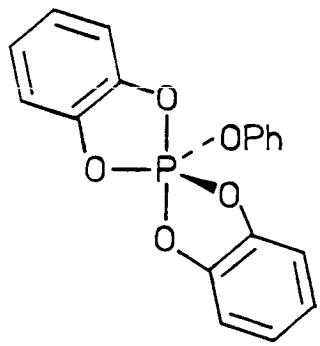
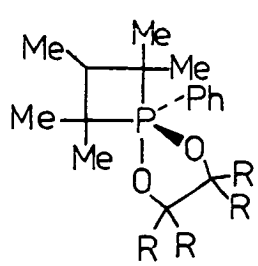


(6)

five-membered rings being particularly effective[12], spanning apical-equatorial positions and thus reducing intramolecular crowding by holding ligands planar and facing outwards.

Thus pentaphenoxyphosphorane was found to react with two equivalents of catechol to give the spirocyclic phosphorane[13] (6). The monocyclic phosphorane was isolable if less catechol was used, but there was a strong driving force towards formation of the spirocyclic phosphorane, perhaps aided by an overall increase in entropy.

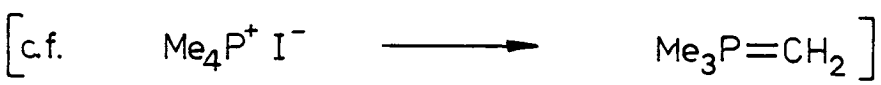
The stability of small ringed spirocyclic phosphoranes is exemplified by the fact that the dialkoxyphosphorane (7) can be recrystallised from water[14], whereas acyclic pentaalkoxy-phosphoranes are often thermally unstable[15], and both acyclic and monocyclic alkoxyphosphoranes are susceptible to hydrolytic degradation.



(7)

The relief of steric strain, which is the driving force in converting many tri- and tetracoordinate compounds into pentacoordinate species[16,12], has a corollary in that the TBP structure, once formed, should be more stable than its acyclic analogue with respect to reaction to give tetracoordinate products. This factor was utilised by Katz *et al.*[17] in the synthesis of trimethylhomocubylphosphorane (8), the first example of a stable pentaalkyl phosphorane (Scheme 1). The

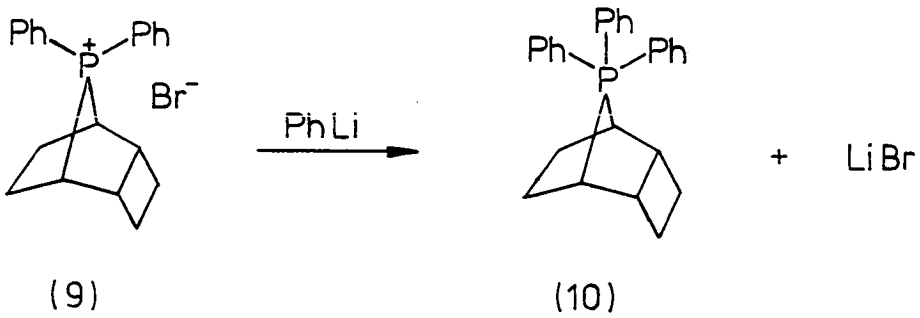
(8)



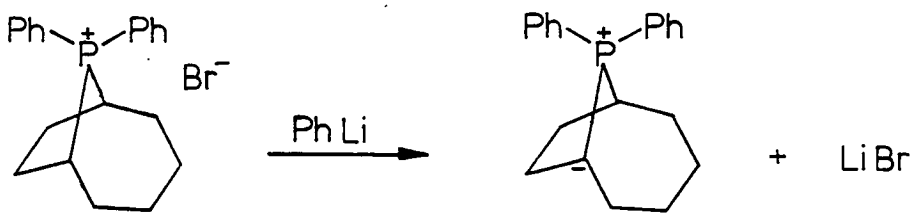
Scheme 1

analogous reaction between tetramethylphosphonium iodide and methyl lithium produced only the ylide, trimethylmethylene phosphorane[18].

The critical point at which ylide formation is preferred to the pentacoordinate product was studied by Katz[19], using bridged bicyclic phosphonium bromides of varying ring size. Thus, in Scheme 2, the phosphonium salt (9) reacts with phenyl lithium to give the phosphoranes (10), whereas (11) gives the phosphonium ylide (12). Therefore the additional ring strain associated with the smaller bridged bicyclic system in (10) disfavours ylide formation.



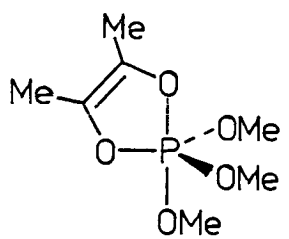
(9) (10)



(11) (12)

Scheme 2

The stabilising influence of a five-membered ring can also be seen in the relative reactivities of cyclic and acyclic pentaoxyphosphoranes. Thus, pentaethoxyphosphorane reacts with benzyl alcohol at -20° to give mainly phosphate products[20], while the cyclic phosphorane (13) gives no phosphate products



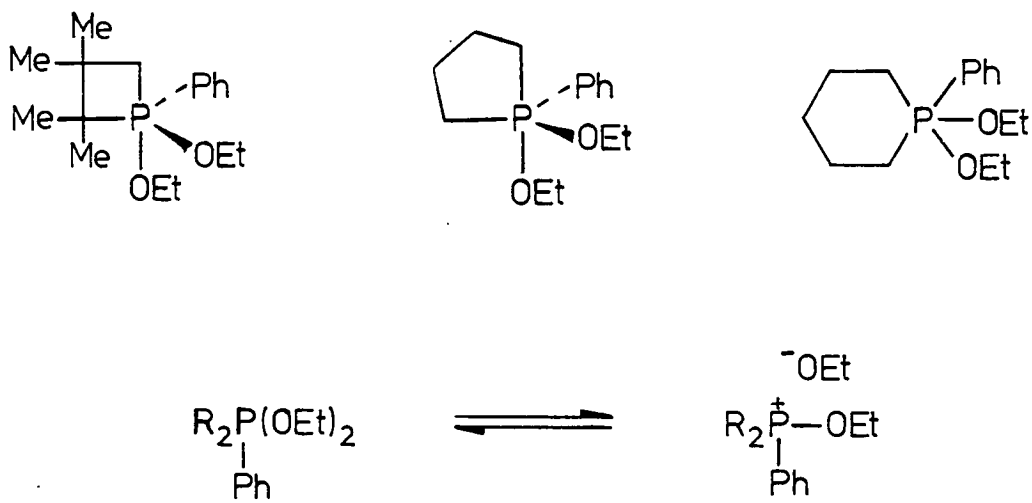
(13)

even after heating with benzyl alcohol at 100°[21].

Stabilisation is not so marked in the presence of a six-membered ring, which can exist in puckered form. Hence there is less release of steric strain to favour phosphorane formation

and subsequent stability, compared with smaller ring sizes.

A comparative study of the effect of small rings in stabilising pentacoordinate structures against ionisation to the phosphonium form was made by Denney *et al.*[22]. Using variable temperature n.m.r. spectroscopy, Denney observed that as ring size decreased in the three phosphoranes shown (Scheme 3), the temperature at which loss of phosphorus

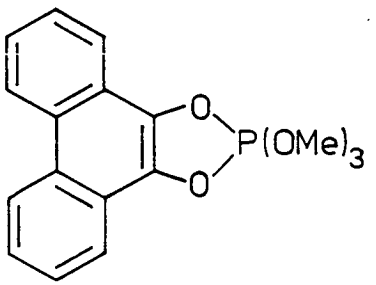


Scheme 3

coupling occurred increased. Since loss of coupling is attributed to the ionisation process shown in Scheme 3, it is apparent that the tendency to ionise decreases with decreasing ring size due to the increase in ring strain which would result from formation of the cyclic phosphonium ion.

Ring opening of cyclic phosphoranes to the zwitterion is normally found to result from steric requirements. Thus ^{31}P n.m.r. studies have shown that (14) has the pentacoordinate form (^{31}P δ = -49 ppm)[23], whereas the tris(dimethylamino) analogue (15) exists as a zwitterion (^{31}P δ = +38.5 ppm)[24]. Although there may be some increased electronic stabilisation

of the phosphonium form by the three amino groups, steric



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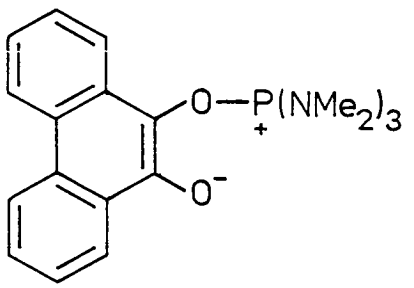
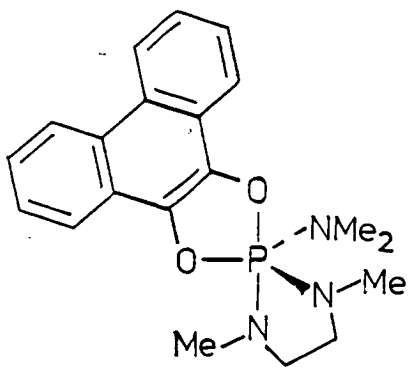


(15)

effects must be the major consideration, since the cyclic analogue of the amino derivative (16), once more assumes the pentacoordinate structure (^{31}P δ -29.8 ppm)[24].



(16)

A similar phosphorane (Scheme 4) has been isolated in both ring-opened and ring-closed forms[25], the ^{31}P n.m.r. shift, and hence the form, being strongly dependent on the nature and dilution of solvent, indicating a rapid equilibration of the two forms.

Scheme 4

1.3 Permutational isomerisation

As discussed in Chapter 1.1, the preferred geometry for five ligands bonded to a central phosphorus atom is usually trigonal bipyramidal. This gives rise to two sets of ligands, apical and equatorial, which experience different environments, as seen in the i.r. spectrum of PF_5 [26]. The ^{19}F n.m.r. spectrum of PF_5 however, shows only one signal over a wide temperature range[27], which suggests that all fluorine ligands have identical environments.

These apparently contradictory observations can be satisfactorily explained if a process is occurring which interchanges ligands between apical and equatorial positions at such a rate (10^2-10^8 times per second) that they are interchanging more rapidly than the n.m.r. timescale can detect, but less rapidly than the i.r. timescale.

This phenomenon of rapid ligand interchange or Permutational Isomerisation (P.I.) is commonly found in pentacoordinate phosphorus chemistry, and numerous variable temperature n.m.r. studies have demonstrated how rapidly interchanging ligands, which give a single averaged n.m.r. signal at high temperature, can be slowed down sufficiently on the n.m.r. timescale by reducing the temperature to reveal the separate signals of the most stable TBP isomer, with its ligands "frozen" in their apical and equatorial positions.

The relatively small activation energy required for P.I. to occur can conveniently be determined from the coalescence temperature (T_c) of the two exchanging signals in the variable temperature n.m.r. spectra. Using a combination of the simplified Gutowsky-Holm equation[28], and the Eyring equation[29], the free energy of activation (ΔG^*) for a two-site exchange process can be calculated.

1.3.1 Mechanisms for permutational isomerisation

Two types of process could account for the spectral changes observed when P.I. occurs, viz. (i) regular P.I. processes, in which ligand reorganisation about a central phosphorus atom proceeds by simple bond deformation; (ii) irregular P.I. processes, which involve bond breakage and reformation. Both types of process have been observed, but regular P.I. is the more commonly encountered and the only type considered in detail here.

Two mechanisms have been postulated for regular P.I. processes. The first of these was proposed by Berry[30], which he called "Pseudorotation." Muetterties later examined all conceivable regular modes for interchange of ligands and concluded that only Berry's mechanism was feasible from consideration of transition state symmetries[31]. Whitesides and Mitchell[32] then produced experimental evidence confirming Muetterties' conclusion by comparing variable temperature ^{31}P n.m.r. spectra of dimethylaminotetrafluorophosphorane with simulated spectra of all possible modes of ligand interchange.

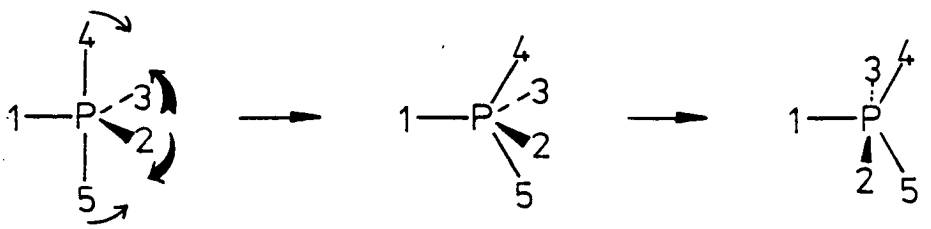
More recently, however, an alternative mechanism which was not considered by Muetterties, but which is also consistent with the observations of Whitesides and Mitchell, was proposed by Ramirez and Ugi[33].

This mechanism was called "Turnstile Rotation" (TR) because of its obvious similarities to the motion of a turnstile gate. These alternative mechanisms are discussed in greater detail below.

(i) Berry Pseudorotation (BPR). This mechanism effectively exchanges pairs of apical and equatorial ligands in a concerted

bond bending process, while the remaining equatorial ligand stays stationary and acts as a "pivot." Thus in the starting TBP (17) of Scheme 5, the pivot (ligand 1) remains stationary while the apical ligands, 4 and 5, move in the plane of the page away from the pivot, and at the same time the equatorial ligands, 2 and 3, move apart in the plane perpendicular to the page.

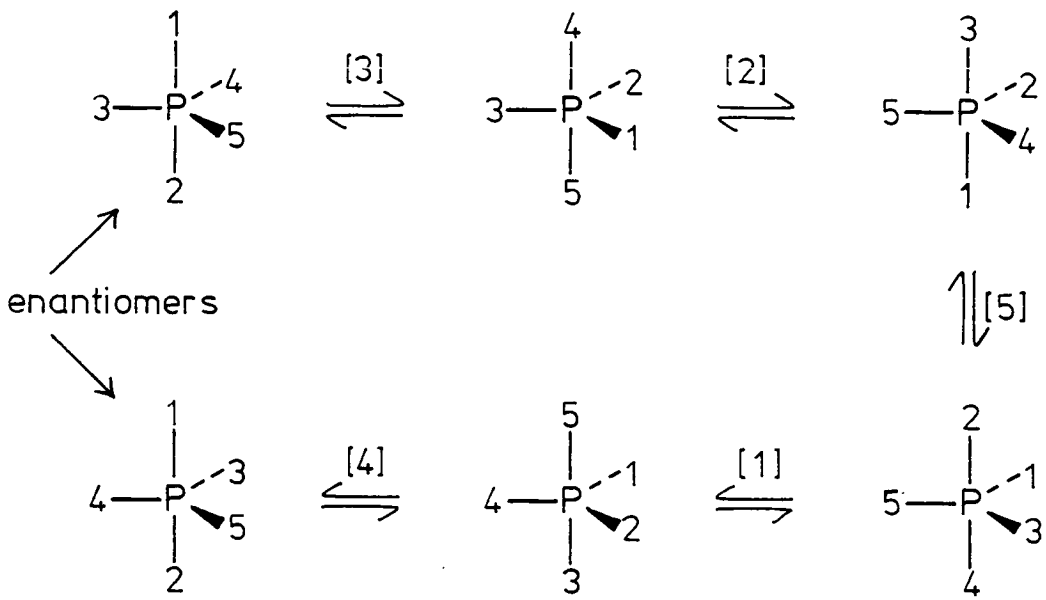
As the ligands move, the equatorial bonds lengthen and the



(17) (18) (19)

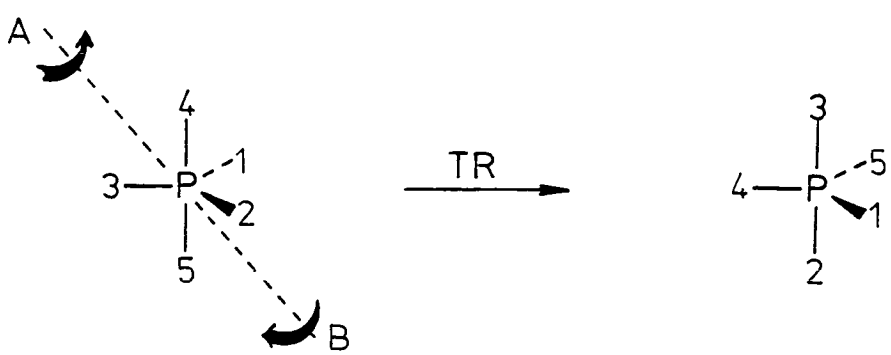
Scheme 5

apical bonds shorten to give a transition state (18) in which the pivot ligand forms the apex of a tetragonal pyramid with idealised C_{4v} symmetry. Continuing the bond bending process, ligands 2 and 3 now take up apical positions, while ligands 4 and 5 assume equatorial positions in the final TBP (19). Scheme 5 represents one"pseudorotation", so named because of the apparent rotation through 90° about the pivot axis of the original TBP. A sequence of five pseudorotations, taking each ligand in turn as pivot, generates the enantiomer of the original TBP, as demonstrated in Scheme 6, where the number in square brackets denotes the pivot ligand used. A further five sequential pseudorotations are required to regenerate the original TBP.



Scheme 6

(ii) Turnstile Rotation (TR). This is a more complex mechanism than BPR to visualise in detail, but the net effect of a single turnstile rotation is easily demonstrated in Scheme 7.



Scheme 7

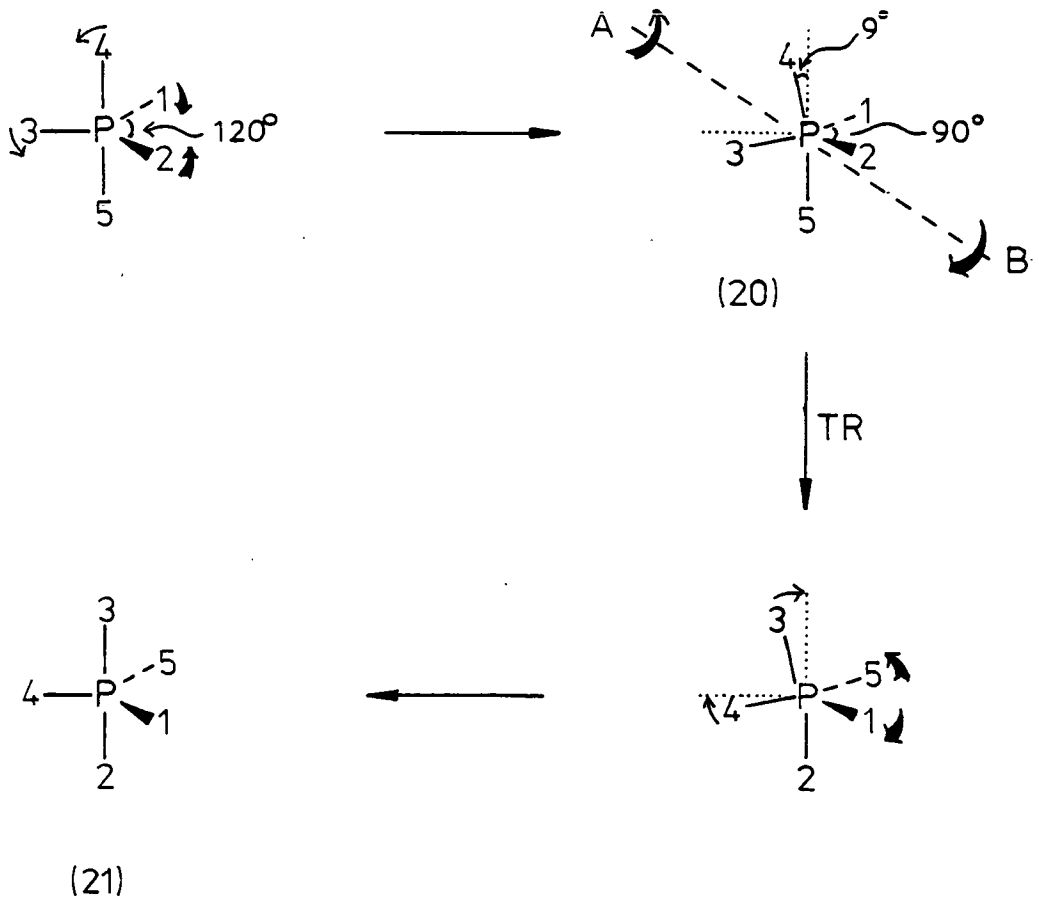
Line AB bisects the right angle formed by apical and equatorial ligands 3 and 4, and therefore constitutes a C_2

axis for this part of the molecule. Line AB also bisects the solid angle formed at phosphorus by the bonds from ligands 1, 2 and 5, and is therefore a C_3 axis for this part of the molecule. Turnstile rotation occurs about this common axis AB, with the two parts of the molecule defined above moving simultaneously in opposite directions.

Thus, the pair of ligands, 3 and 4, rotate 180° about their local C_2 axis AB, while the trio of ligands 1, 2 and 5 rotate concertedly, in the opposite direction, about their local C_3 axis AB. The net effect of these rotations (Scheme 7) is to exchange the positions of ligands 3 and 4, while displacing the trio by 120° about AB. This single TR rotation thus exchanges pairs of apical and equatorial ligands with the same overall result as a single BPR. However, only six such rotations about axis AB are required to regenerate the original TBP structures, although six different axes like AB exist for any given TBP.

Examination of a single TR in greater detail reveals a complex series of concerted bond and angle deformations[33], which give the TR mechanism several advantages over the simple BPR concept. Separating these complex motions into their individual components, the course of a single TR may be pictured as shown in Scheme 8.

. Thus, the diequatorial angle between ligands 1 and 2 decreases from 120° to 90°, while the ligand pair, 3 and 4, tilt by about 9° in the plane of the paper towards the apical ligand 5 of the trio. The intermediate structure obtained (20) then undergoes the internal rotations about axis AB as previously described. Reversal of the tilt of the ligand pair, and restoration of the diequatorial angle to 120° finally



Scheme 8

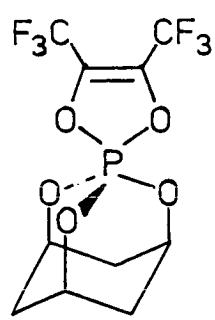
generates the new TBP (21).

After a first relative rotation of 60° in the TR, it may be energetically more favourable to rotate a further relative 60° before ligand unbending occurs. This is known as a double turnstile rotation, $(TR)^2$, and gives the TR mechanism the added flexibility over BPR of being able to by-pass particularly unfavourable, high energy TBP structures.

The relative merits of BPR and TR mechanisms in describing regular P.I. processes continues to be the subject of some debate[34], and indeed the TR mechanism has been reported in the literature as being but an excited vibrational state of BPR[35].

Hoffmann and Muetterties[36] compared the theoretical energies involved in both BPR and TR pathways for the phosphoranes PF_5 and PH_5, and concluded that the BPR energy barrier (with C_{4v} symmetry) was lower than that of TR (C_s symmetry). This comparison, however, refers to the ideal situation with five identical ligands having ideal TBP and transition state geometries. In practice, non-ideal conditions prevail due to electronic and steric interactions, leading to structures which may be considerably distorted from either idealised mechanism[36].

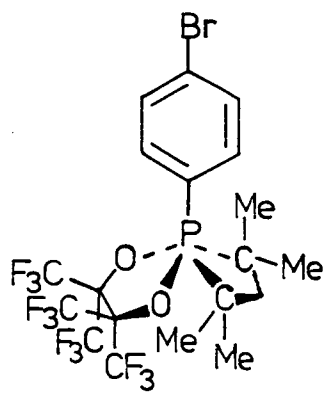
Ramirez, Ugi and co-workers[33] consider either mechanism acceptable in describing acyclic phosphoranes, but that only the TR mechanism can adequately explain P.I. processes involving one or more small ring ligands. An interesting example in support of this claim concerns the caged polycyclic phosphorane (22)[37], for which the single ^{19}F n.m.r. signal down to $-50^{o}C$ is interpreted as indicating a rapid P.I. process which makes the quasi-apical and quasi-equatorial trifluoromethyl groups equivalent.



(22)

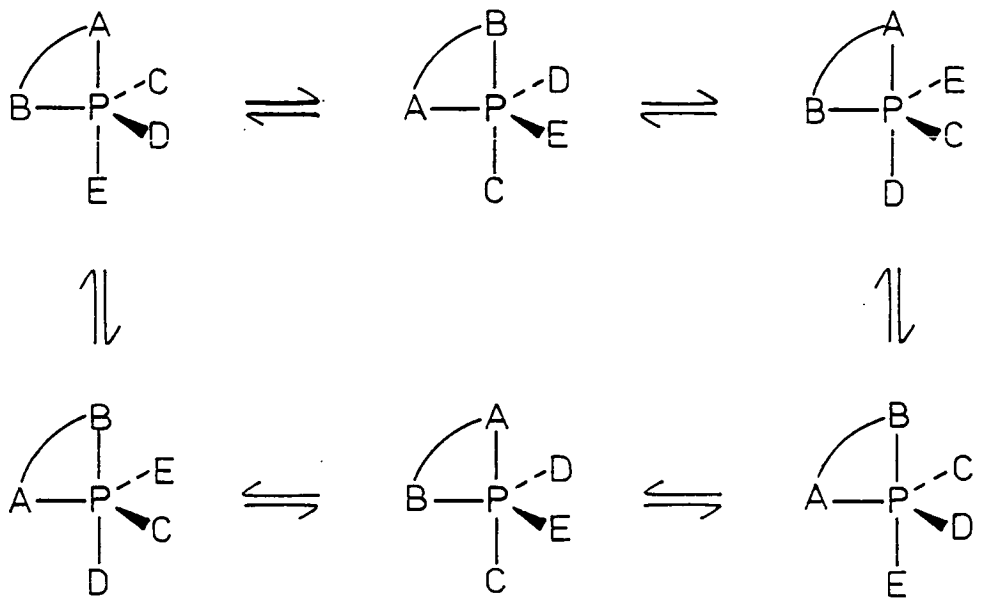
Such a process is readily rationalised in terms of the TR mechanism if the dioxaphospholene ring acts as the pair, and the caged phosphite the trio. Severe steric limitations, on the other hand, serve to totally preclude a BPR mechanism for such a phosphorane.

The isolation and X-ray structure of the first known pentacoordinate phosphorus compound having square pyramidal geometry (23)[38] refutes the views of Ramirez et al. since this bicyclic structure actually possesses the geometry which the BPR mechanism would represent as the transition state between TBP structures with both rings occupying apical-equatorial positions, and with the 4-bromophenyl ligand as pivot.



(23)

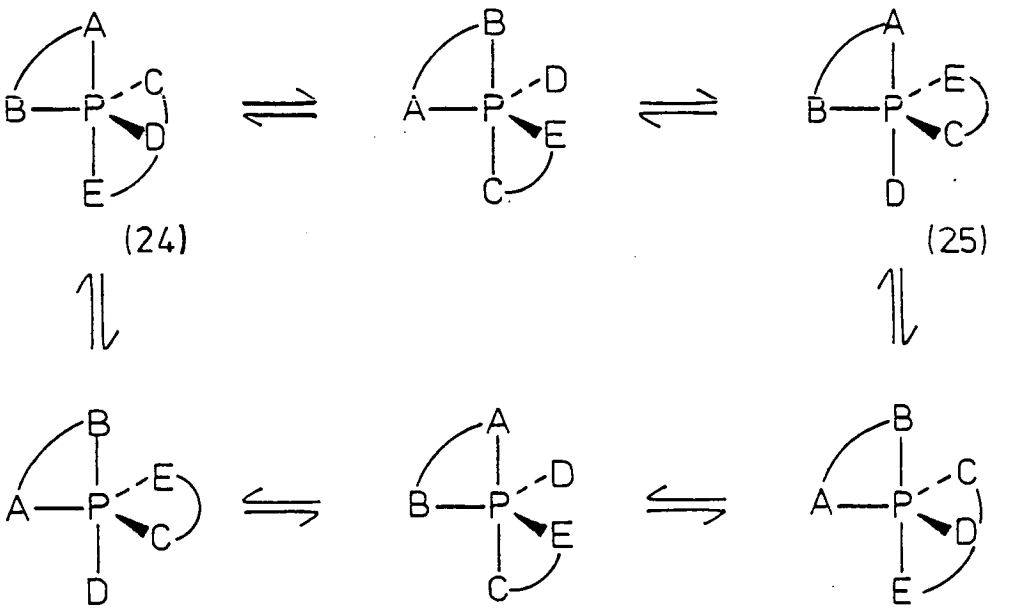
In the context of this thesis, the debate over which mechanism best describes any P.I. process is of little consequence, the more important fact being that either mechanism can provide a model for determining the relative energies of various interconverting TBP structures. Dynamic n.m.r. studies of monocyclic phosphoranes are commonly encountered, and can best be depicted using the general "pseudorotation cycle" shown in Scheme 9. It can be seen that this cycle is equivalent to six consecutive TR rotations (pair A,B; trio C, D, E), and



Scheme 9

regenerates the original TBP structure without having to place a small chelated ring in a sterically less favourable diequatorial position. Diequatorial ring placement is unavoidable, however, in spirobicyclic phosphoranes for which fully averaged ligand environments are observed in high temperature n.m.r. spectra. Such a P.I. process normally requires a higher activation energy which, by analogy with Scheme 9, may be represented by the pseudorotation cycle shown in Scheme 10, or alternatively by a shortened cycle, (24)⇌(25)⇌(26), which nevertheless indicates the highest energy TBP as having a diequatorial ring.

Finally, it should be noted that irregular processes, in which bonds are broken and reformed, can also lead to ligand reorganisation about a pentacoordinate phosphorus atom. Irregular processes generally proceed via a tetracoordinate intermediate in the case of acid catalysed[39] or thermal reactions[40], or via a hexacoordinate species for base catalysed reactions[41].



(24) (25)

(26)

Scheme 10

These processes can usually be differentiated from regular P.I. processes by loss of phosphorus coupling in the n.m.r. spectra on bond cleavage, and by a characteristic large chemical shift difference in solvents of differing polarity, indicating the presence on ionic intermediates.

1.3.2. Factors affecting permutation isomerisation.

As most pentacoordinate phosphorus compounds exhibit fluxional lability to varying degrees, it is desirable to be able to predict which, of the many rapidly interconverting TBP structures, are the most stable, low energy forms, seen to be "frozen" in low temperature n.m.r. spectra.

Ligand site preferences and the concept of apicophilicity have been mentioned earlier as influencing the stability of

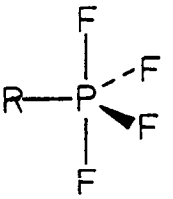
phosphoranes, as have the presence of bulky ligands and small rings. These same factors, not surprisingly, govern the stability of individual interconverting TBP isomers in a pseudorotation cycle, and hence affect the ease with which permutational isomerisation can occur.

The ease with which isomeric TBPs interconvert will depend on the energy difference between ground state and transition state i.e. the free energy of activation (ΔG^*) as measured in dynamic n.m.r. studies.

If the high energy TBP structure is an intermediate rather than a true transition state, then the free energy of activation will be an overestimate of the energy difference between the two states. However, pseudorotation pathways between TBPs of identical energy are thought to be very low energy processes[42], hence high energy TBPs can normally be regarded as transition states, with any overestimate from ΔG^* being small.

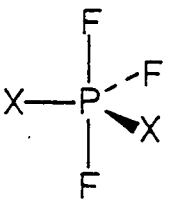
In order to predict the likely energy difference between two isomeric TBPs, it is necessary to compare changes which occur in the relative apicophilicity of ligands, changes in ring strain, and changes in steric strains, when apical and equatorial ligands exchange positions. These changes are now considered in detail below.

(i) Changes in relative apicophilicity. A phosphorane with four identical ligands can interchange apical and equatorial ligands in a facile process which does not involve changes in any of the above factors, merely by using the dis-similar ligand as a pivot in a single Berry pseudorotation. Thus Schmutzler[43] observed just one signal in the ^{19}F n.m.r. spectra of the tetrafluorophosphoranes (27) down to $-120^{\circ}C$.

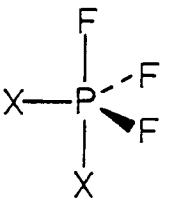


(27)

This contrasts with the trifluorophosphoranes (28) which can interchange ligands only via higher energy TBPs such as (29). Thus, below 25°C, two distinct fluorine environments



(28)



(29)

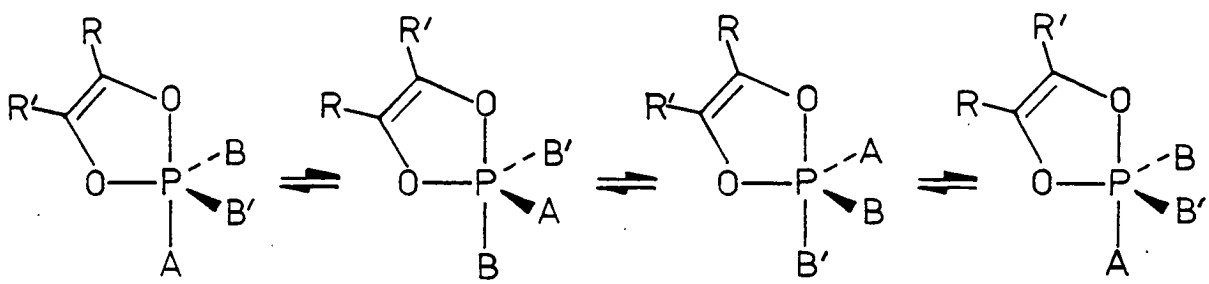
are seen for (28) (X = Cl, CF_3)[33], indicating a P.I. process which is slow on the n.m.r. timescale due to the higher activation energy barrier. Since the only difference between TBPs (28) and (29) is the exchanged equatorial and apical ligands, the free energy of activation for such a process gives a direct measure of the relative apicophilicities of ligands F and X.

Trippett and his co-workers[44] have made extensive dynamic n.m.r. studies of monocyclic and spirobicyclic phosphoranes from which a tentative scale of relative apicophilicities has been built up for a large range of ligands. In order of decreasing apicophilicity, this scale reads:

$$F>H>Hal>PhO>RO>R_2N>Me>Bu^t>Ph$$

The energy difference covered by this scale is approximately 80 kJ mol^{-1} i.e. an activation energy of ca.80 kJ mol^{-1} must be overcome to exchange an apical fluorine ligand and an equatorial phenyl ligand.

Typical of the systems studied by Trippett et al. in constructing this apicophilicity scale are the hexafluorobiacetyl adducts (Scheme 11). When A is more apicophilic than B, then structures (30) and (31) are the most stable isomers, and equivalence of the CF_3 groups is achieved via the higher energy isomers (32) and (33). The free energy required for this process therefore corresponds to the



(30) (32) (33) (31)

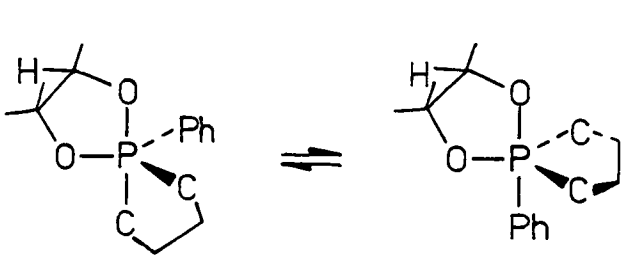
Scheme 11 B = B′ ; R = R′ = CF_3

difference in relative apicophilicities of ligands A and B.

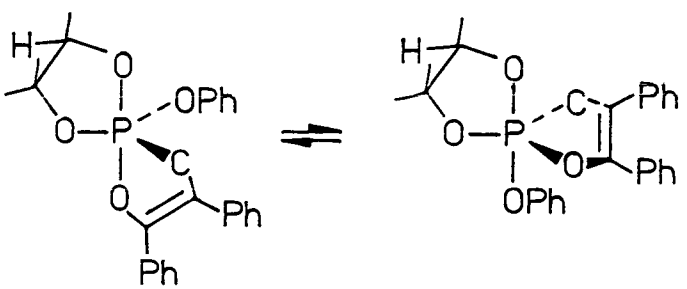
(ii) Changes in ring strain. Consideration of models, natural bond angles, and spectroscopic studies have all led to the generally accepted conclusion[45] that four and five-membered rings prefer to span apical-equatorial (ae) rather than diequatorial (ee) positions in a TBP. P.I. processes in which intermediate high energy TBPs can maintain small ring ligands in this preferred (ae) position (e.g. Scheme 11) generally

give rise to fairly low free energy barriers of ca 40-50 kJ mol^{-1}, explicable in terms of differences in relative apicophilicities.

Variable temperature n.m.r. studies on bicyclic spirophosphoranes, on the other hand, generally give rise to a higher activation energy, reflecting the mechanistic requirement for P.I. of spirophosphoranes that one of the small rings must be diequatorially positioned in a high energy intermediate TBP. Scheme 12 illustrates a few of many such spirophosphoranes studied by Trippett et al.[44], together with their high energy isomers having a diequatorial five-membered ring, and the corresponding free energy of activation (ΔG^*) obtained from coalescence of the CH_3 or CF_3 n.m.r. signals in the substituted ethylenedioxy ring.



ΔG^* (kJ mol^{-1}): 37



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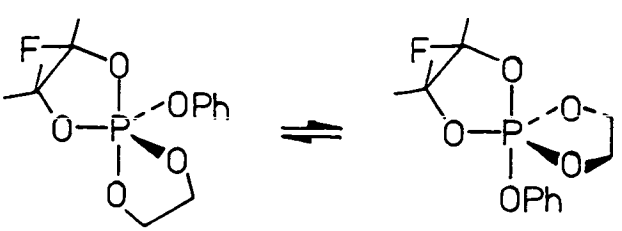

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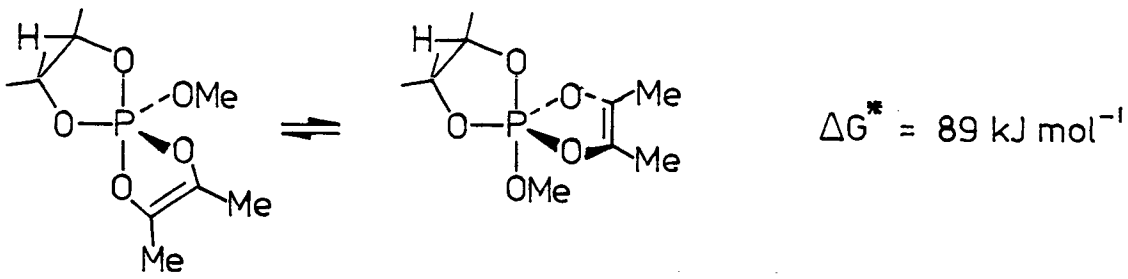


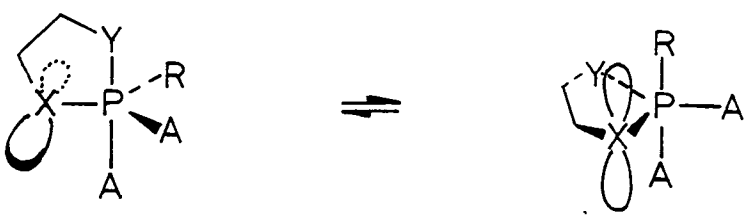
H ≡ 4 × CH_3

F ≡ 4 × CF_3

Scheme 12

In the above cases the contribution to ΔG^* from the changes in apicophilicity as the exocyclic ligand moves from an equatorial to an apical position is relatively small. The large increase in ΔG^* going down Scheme 12 can largely be accounted for by (i) an increase in angle strain at phosphorus for the unsaturated diequatorial phospholene, compared with the corresponding phospholan ring, and (ii) the preference for lone pair orbitals on equatorial hetero-ring atoms to lie in the equatorial plane, so that back-donation of electron density to the vacant phosphorus d-orbitals is maximised.

To illustrate the importance of this latter factor, Scheme 13 may be used as a model.



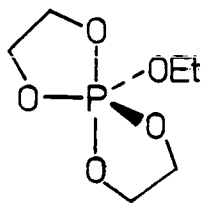
Scheme 13

In order to displace the five membered hetero-ring from an (ae) to an (ee) position in Scheme 13, an additional energy has to be supplied to rotate the lone pair orbital of the equatorial atom X from its low energy equatorial orientation in which back-bonding is maximised, to the less favourable apical plane. This induced restriction to free rotation about the equatorial P-X bond is particularly strong when X is a nitrogen[46] or sulphur[47] atom, and corresponds to an energy barrier of 40-50 kJ mol^{-1}. For oxygen, this barrier is less[48] (ca.20-30 kJ mol^{-1}), and when X is a carbon atom, there is no additional energy barrier as the possibility of lone pair orbitals does not arise.

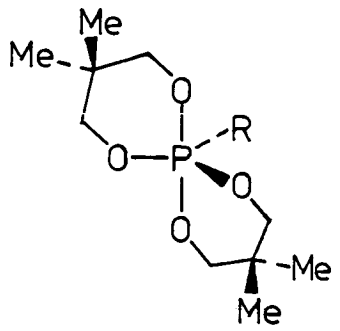
It can therefore be concluded that the nature of the heteroatom (X) which remains equatorial in any pseudorotation pathway which involves diequatorial placement of a five-membered ring, has an important effect on the free energy of activation required for such placement.

Six-membered rings, in contrast, have a lesser preference for the apical-equatorial geometry in phosphoranes than the smaller ring ligands, possibly because of their greater flexibility in terms of internal conformational isomers, thus better accommodating changes in geometry and ligand orientation. Thus Denney et al.[20] observed the ^1H n.m.r. spectra of the spirobicyclic phosphoranes (34) and (35) at various temperatures. Equivalence of all the ring methylene protons in (34) was observed at $+172^{\circ}C$, a process which necessitates diequatorial placement of the five-membered ring (ΔG^{*} = 22 kcal mol^{-1}).

In the six-membered ring phosphoranes, all of the ring



(34)



(35)

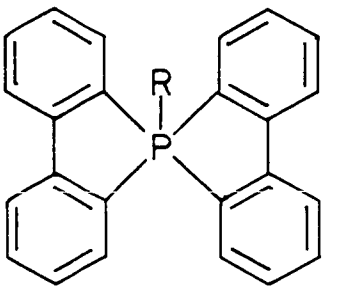
methyl substituents of (35) (R = OEt) remained equivalent even at -65°C, at which temperature the analogue with R=Ph had broadened to give two sets of signals with ΔG^* of 12 kcal mol^{-1} for the corresponding P.I. process which placed a six-membered ring diequatorially.

(iii) Changes in steric strain. In the absence of electronic (apicophilic) and ring strain effects, ligand size may affect barriers to pseudorotation in two ways:

(a) by ligand-ligand interactions restricting interconversion of TBP isomers in a pseudorotation pathway;

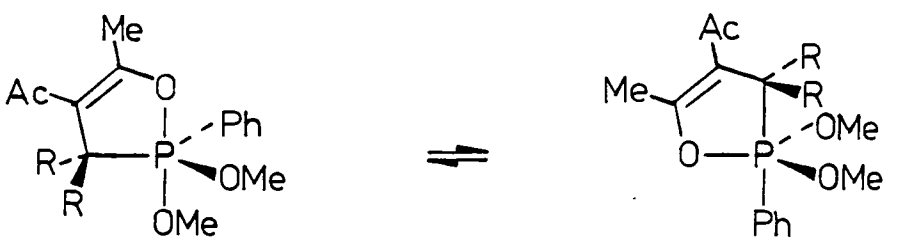
(b) by destabilising any TBP isomer which places a bulky ligand in the more crowded apical position.

Thus, the room temperature n.m.r. spectra of the substituted bis-biphenylene derived phosphoranes (36) showed a single averaged methyl resonance when R = phenyl but two separate methyl signals when R = 1-naphthyl[49]. This suggests a higher activation energy for pseudorotation of the latter due to the increased steric interactions between interconverting TBP isomers when R = 1-naphthyl.



(36)

Gorenstein[50] observed a further type of steric interaction in the case of small ring phosphoranes bearing two substituents on the α-carbon atom of the ring (Scheme 14). Thus the free energy barrier to P.I. in the phosphoranes (37) increased from ca.10 kcal mol^{-1} when R=H, to ca.16 kcal mol^{-1} with the introduction of gem-dimethyl groups (R=Me). This large increase in the barrier to P.I. is almost certainly



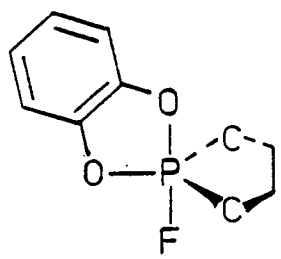
(37) (38)

Scheme 14

attributable to the increase in steric strain in the high energy TBP (38) when complete eclipsing occurs between the gem-dimethyl groups and the two equatorial methoxy ligands.

The three factors outlined above as affecting the energy barrier to P.I. processes, viz., changes in relative apicophilicity, ring strain, and steric strain, can often be seen to act in opposing directions. In such cases, the most stable TBP structure will tend to reflect the most dominant

factor. The spirophosphorane (39), for example, has a stereochemistry which shows that the strong apicophilic character of the fluorine ligand outweighs the steric strain incurred by placing the phospholan ring diequatorially[51].



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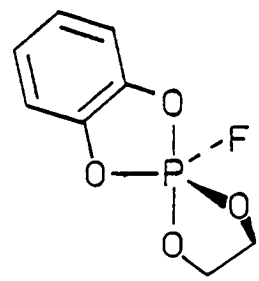
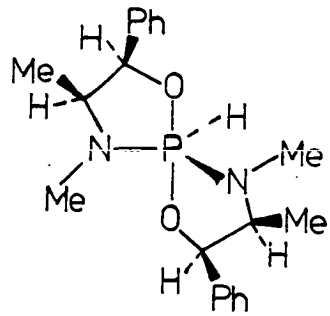


(40)

By increasing the apicophilicity of ring atoms bonded to phosphorus, this overall balance can be tipped in favour of the ring strain effect, as seen in the spirophosphorane (40), which was the first reported example[51] of the most electronegative ligand in a phosphorane occupying an equatorial position in the ground state TBP configuration.

While the major method of studying regular P.I. processes employs variable temperature n.m.r. spectroscopy to reveal both the nature and free energy of activation of such processes, an alternative technique involving polarimetry has also been used, for the purpose of monitoring the rate of racemisation of an optically pure sample of the spirophosphorane (41)[52].



(41)

The free energy of activation obtained (23.8 kcal mol^{-1}) is consistent with values obtained from n.m.r. studies, and provides further evidence that diequatorial placement of a hetero-bonded five-membered ring (a necessary requirement for racemisation) requires a high activation energy.

Aspects of chirality in pentacoordinate phosphoranes, and how the ease of permutational isomerisation affects the ability to isolate optically pure phosphoranes are considered in the following Chapter.

1.4 Chirality in pentacoordinate phosphoranes

A 'chiral' molecule can be defined as one which possesses no symmetry element other than rotational axes. Chirality is therefore a necessary condition for the existence of enantiomers - molecules which are non-superimposable mirror images of each other, possessing the ability to rotate plane polarised light in equal and opposite directions.

Conversely, achiral molecules possess symmetry elements and thus cannot exist in enantiomeric (optically active) forms.

If a pentacoordinate phosphorus compound possesses a chiral centre at phosphorus, it is useful to be able to predict whether any P.I. process is likely to lead to rapid intramolecular racemisation, or whether optically activity can be preserved. A series of general phosphorane structures (acyclic, monocyclic, and spirobicyclic) are considered below, and for each structure, all possible isomeric TBP structures arising from pseudorotation pathways can be designated as either chiral or achiral from their symmetry elements. By ranking the ligands in these general structures in order of relative apicophilicity, those chiral structures of lowest thermodynamic energy, and requiring the highest activation energy to pseudorotate to achiral structures, can be predicted as the most likely, in theory, to retain optical activity if they can be synthesised. In addition to considering all possible TBP structures, the symmetry of tetragonal pyramidal structures (intermediates in Berry pseudorotation) may also influence the ease of racemisation of a chiral TBP.

The following symbols are used to represent the various types of ligands present in the general Schemes described below:

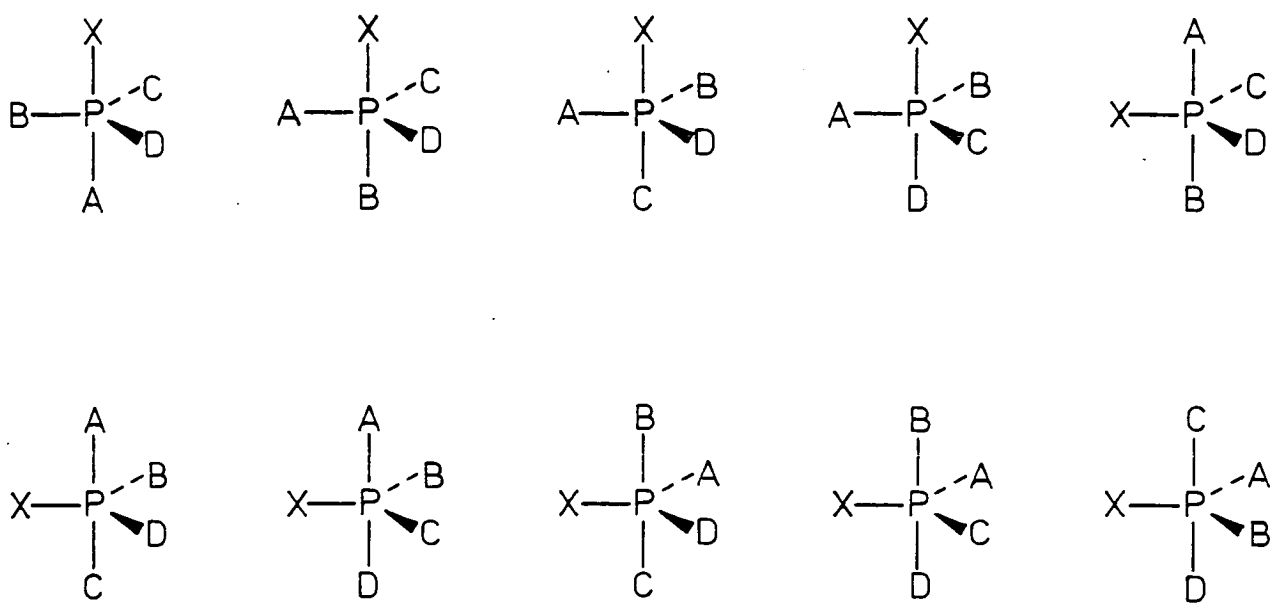
(a) Order of relative apicophilicity: X>A>B>C>D

(b) Bidentate ligands: (A-A), (B-B) etc. represent symmetrical chelate rings; (A-B), (C-D) etc. represent asymmetrical chelate rings.

1.4.1 Phosphoranes with five unidentate ligands

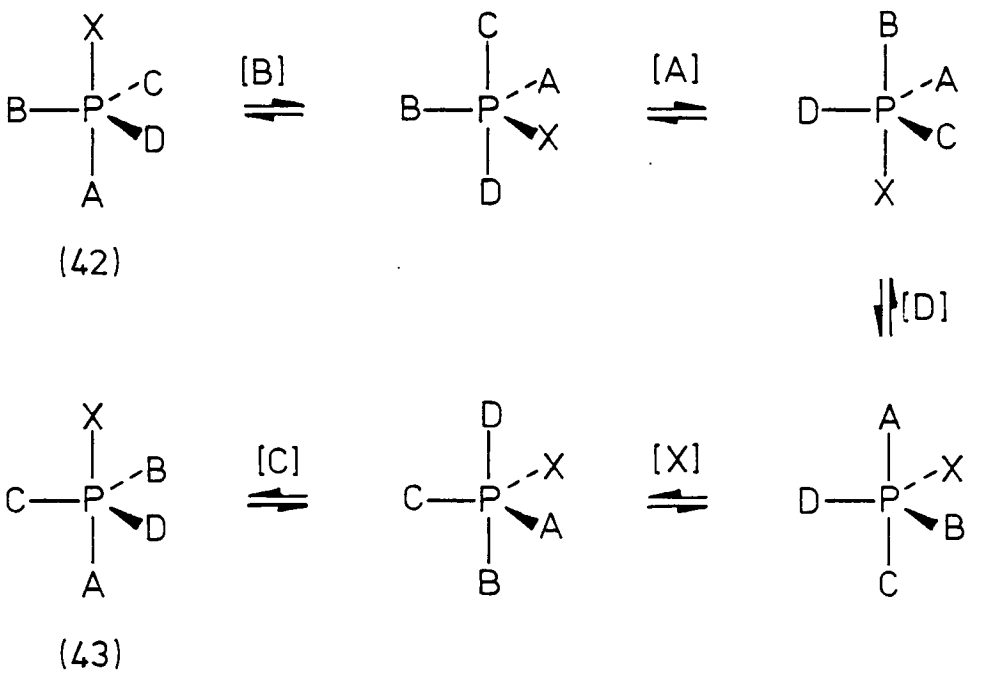
As acyclic chiral phosphoranes are not particularly relevant to this thesis, only the most commonly encountered class, having the general structure XPABCD, will be considered here.

For such a structure with five different ligands, all ten possible TBP isomers are chiral (Scheme 15), as are their ten enantiomeric TBPs, and all possible intermediate tetragonal pyramidal structures.



Scheme 15

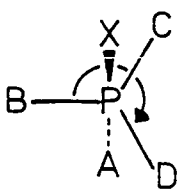
The only way by which a given phosphorane of this type can undergo racemization, other than by bond fission, is by a P.I. process. Five consecutive Berry pseudorotations, using each ligand in turn as pivot, are required to generate the enantiomer of any given TBP. Such a sequence of pseudorotation is shown in Scheme 16, in which the pivot ligand is indicated in square brackets.



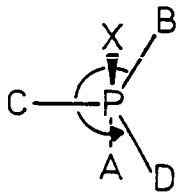
Scheme 16

The enantiomeric relationship between TBPs (42) and (43) is more clearly seen when viewing the structures from above the apical position. Thus in structure (44), the sequence of ligands B, C, and D is clockwise, but the same sequence occurs in an anticlockwise direction in TBP (45).

If a sufficiently high energy barrier can be created by the appropriate choice of ligands to disfavour five consecutive



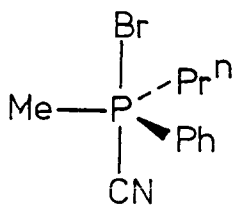
(44)



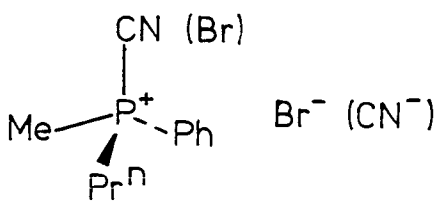
(45)

pseudorotations, then by the BPR mechanism, it may theoretically be possible to prevent racemization and thus isolate an optically active phosphorane having five different unidentate ligands. The TR mechanism for P.I., however, enables particularly disfavoured TBP structures to be by-passed, and hence would be more likely to facilitate racemization.

Horner and Winkler[53] tested this hypothesis by reacting cyanogen bromide with optically active methyl-n-propylphenyl-phosphine, which the above reasoning predicts should give rise to an optically active adduct, whether as a TBP (46) or an ionic structure(47).



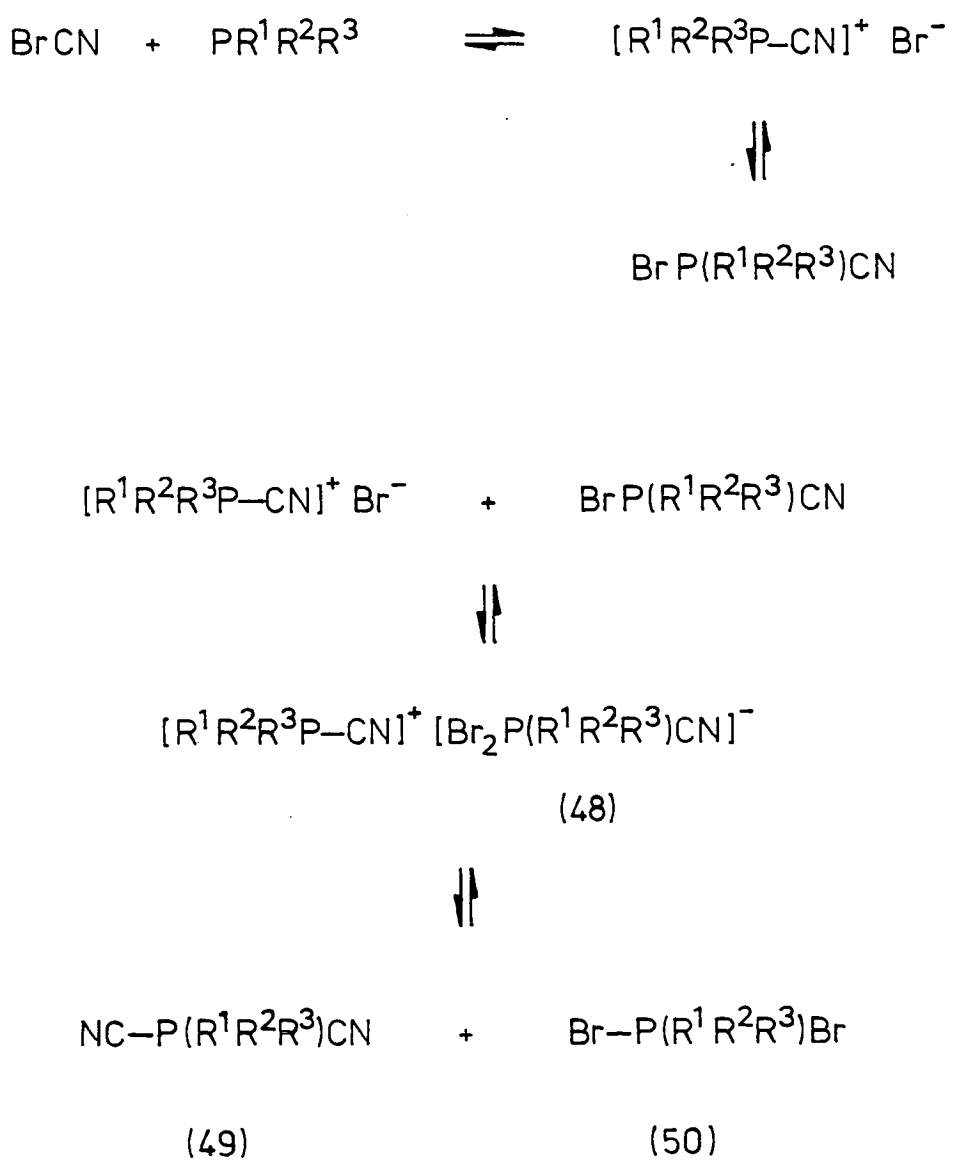
(46)



(47)

In practice, no optical rotation was found for the adduct solution. A possible explanation[53] invokes the formation of an ion-pair type structure (48) as shown in Scheme 17, and

subsequent disproportionation of this gives rise to two achiral TBPs (49) and (50).



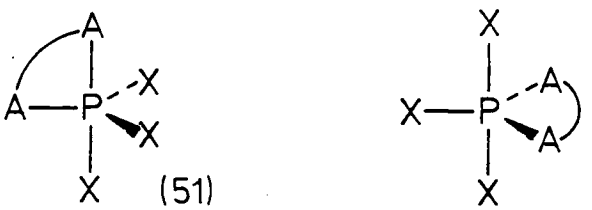
Scheme 17

1.4.2 Phosphoranes with one bidentate ligand

It is useful to consider all possible geometrical isomers which can theoretically be formed (including tetragonal pyramidal structures where relevant), and to define these in terms of their chirality and probable stability.

Using the general ligand notation described earlier, the following types of phosphoranes can be classified:

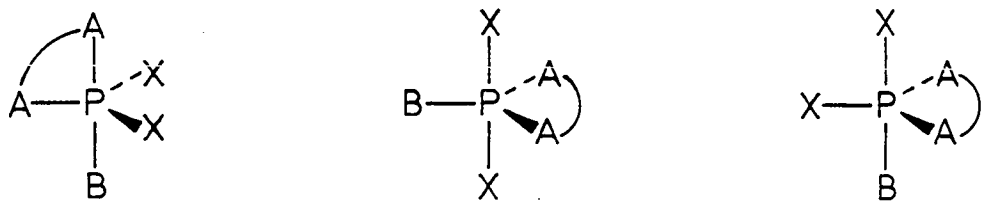
(i) $\underline{X_3P(A\text{-}A)}$. This simplest class of monocyclic phosphorane can exist in two possible TBP geometries, both of which are achiral, but TBP (51) will probably be the



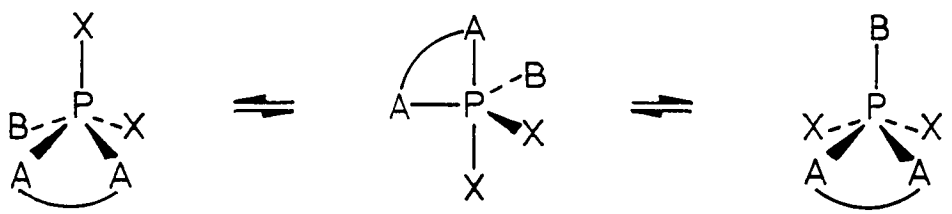
(51)

preferred structure for small ring compounds due to ring strain considerations.

(ii) $\underline{X_2P(A\text{-}A)B}$. When two different unidentate ligands are present with a bidentate ligand, four geometric TBP structures are possible (Scheme 18), one of which is chiral (52). This chiral TBP, however, can racemize by pseudo-rotation either in a one-step process to the achiral tetragonal pyramid (53), or in a two-step operation via chiral tetragonal pyramid (54) to the achiral TBP (55). Racemization by either process does not involve diequatorial placement of the chelated ligand, and hence is likely to be a relatively facile process.



(55)

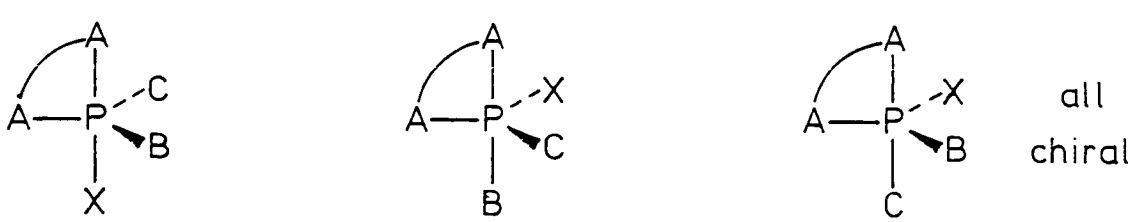


(54) (52) (53)

(chiral)

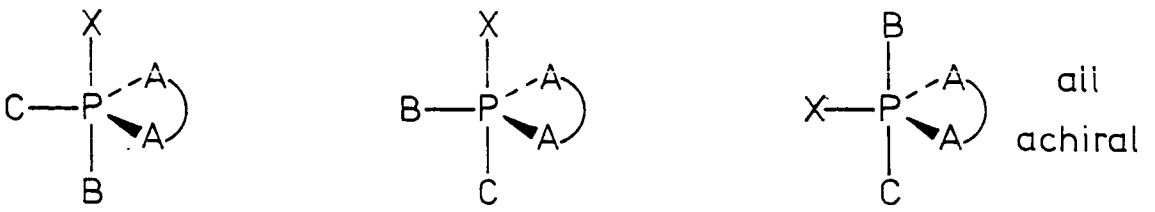
Scheme 18

(iii) XP(A-A)BC. This type of phosphorane, having three different exocyclic ligands and one bidentate chelate ring, can have 6 possible TBP geometrical isomers, of which three are chiral (Scheme 19).



(56)

(cont'd)



Scheme 19

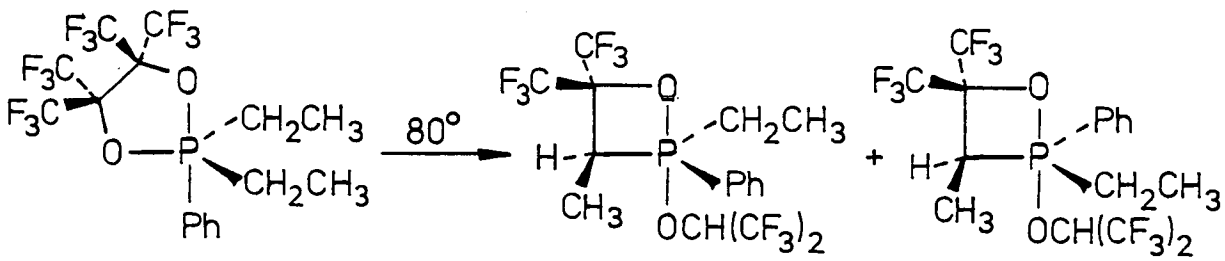
When four- or five-membered rings are present, the chiral TBPs should be particularly favoured over their achiral isomers which have diequatorial rings. In addition, all possible tetragonal pyramidal intermediate structures are chiral. Hence racemization by pseudorotation would require a high activation energy for diequatorial ring placement, giving a reasonable opportunity in theory to isolate chiral TBPs such as (56) in optically active forms.

The above classifications have assumed symmetrical and planar bidentate chelate rings. Obviously, if asymmetric or non-planar rings are involved, the number of possible chiral structures will increase at the expense of achiral structures.

In practice, when stable chiral phosphoranes are synthesised, they tend to exist as enantiomeric pairs, which then prove difficult to detect and to separate, thus making measurement of optical rotation extremely unlikely. Such problems may be lessened by incorporating a second chiral centre into the structure, which leads to the formation of diastereoisomers.

One such example of diastereomeric monocyclic phosphoranes is illustrated in Scheme 20[54]. Phosphoranes (58) and (59), containing a four-membered ring, possess chiral centres at

phosphorus and at the equatorial endocyclic carbon atom. Both isomers are formed in the thermal rearrangement of the five-membered ring phosphorane (57), and differ only in their configuration at phosphorus.



(57) (58) (59)

Scheme 20

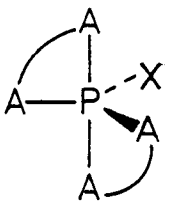
The observed interconversion of (58) and (59) on heating[54] strongly suggests the intermediacy of a high energy TBP during P.I. in which the four-membered ring occupies a di-equatorial position. Although the presence of two chiral centres enabled two separate ^{31}P n.m.r. signals to be observed for (58) and (59) (and their enantiomers), the isolation of a single diastereoisomer proved elusive.

1.4.3 Phosphoranes with two bidentate ligands

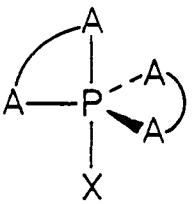
This group of spirobicyclic phosphoranes can once again be sub-divided into general classes, and all possible geometrical isomers considered in terms of chirality and the effect of P.I. processes on that chirality.

(i) $XP(A\text{-}A)_2$. This simplest class of spirobicyclic phosphoranes has two symmetrical and identical bidentate

chelate rings, and gives rise to two possible TBP structures. TBP (60) has both rings spanning an apical-equatorial position and is chiral, whereas the less favoured structure (61) with one diequatorial ring is achiral. Racemization of the chiral



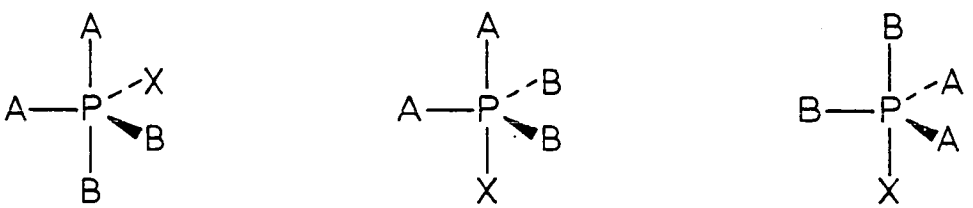
(60)



(61)

TBP is likely to be a facile process, however, since the first step in any BPR mechanism involves formation of an achiral tetragonal pyramidal intermediate.

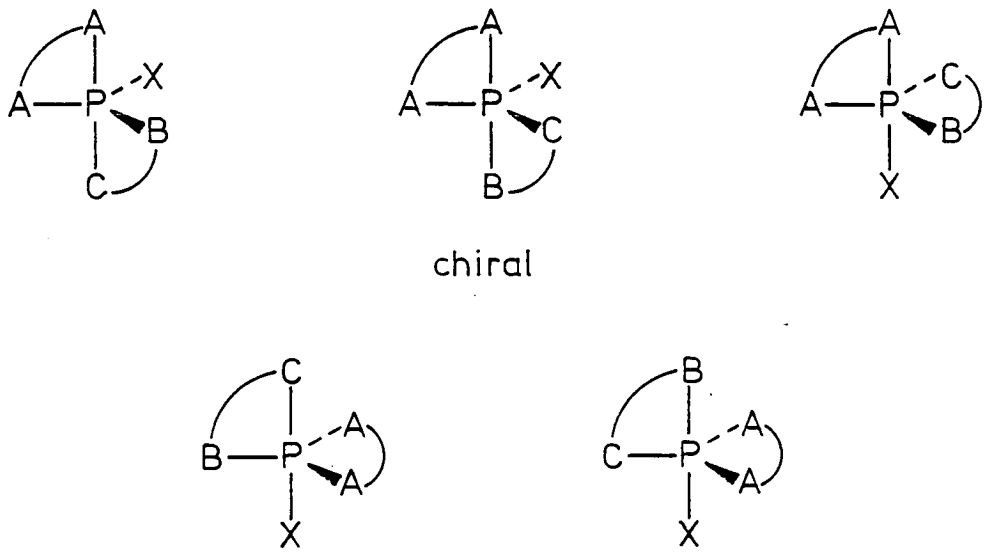
(ii) XP(A-A)(B-B). Phosphoranes containing two different but symmetrical bidentate ligands are similar to the previous class, in that the only chiral structure (62) among the three possible TBPs (Scheme 21) is also likely to be the most stable, but can racemize easily as the first step in any pseudorotation generates an achiral tetragonal bipyramidal intermediate.



(62)

Scheme 21

(iii) XP(A-A)(B-C). This class of spirophosphoranes has one symmetrical and one asymmetrical bidentate chelate ring and can give rise to five possible TBP structures, three of which are chiral (Scheme 22).



Scheme 22

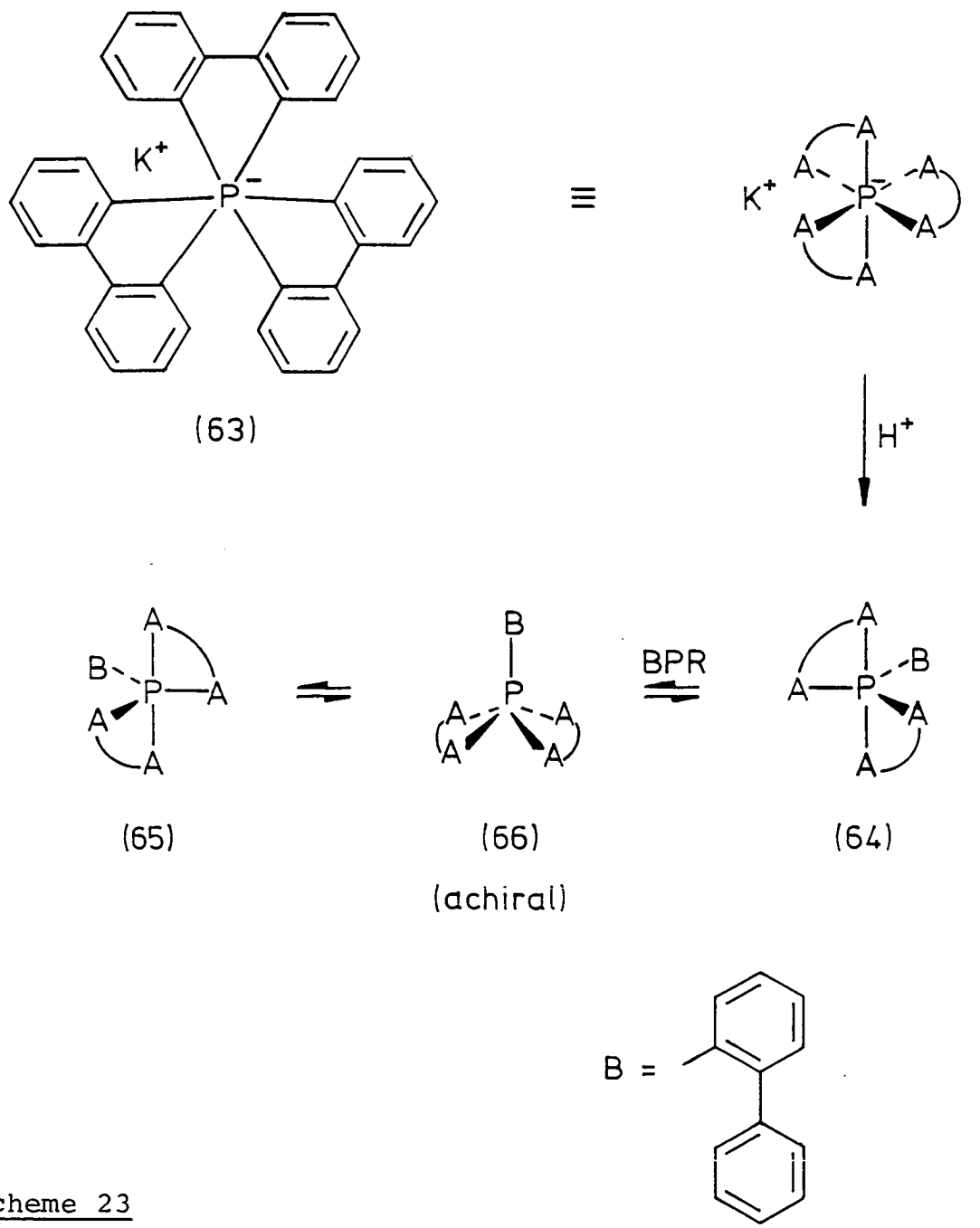
Racemization of these chiral TBPs is not easily achieved. All tetragonal pyramidal intermediates are also chiral, and pseudorotation to any achiral TBP structure requires placement of the symmetrical chelate ring in an energetically unfavourable diequatorial position.

(iv) XP(A-B)(C-D). Phosphoranes with two dissimilar asymmetrical bidentate chelate rings are analogous to the acyclic class of phosphorane, XPABCD, having all possible structures chiral, whether as TBPs or tetragonal pyramidal intermediates. Classes (iii) and (iv) should therefore provide the best opportunity to isolate a stable, optically active phosphoranes.

An excellent illustration of the effect of introducing

an asymmetric ring into spirocyclic phosphoranes is found in Hellwinkel's work on the acid decomposition of hexaco-ordinate tris-biphenylene derivatives of phosphorus[7].

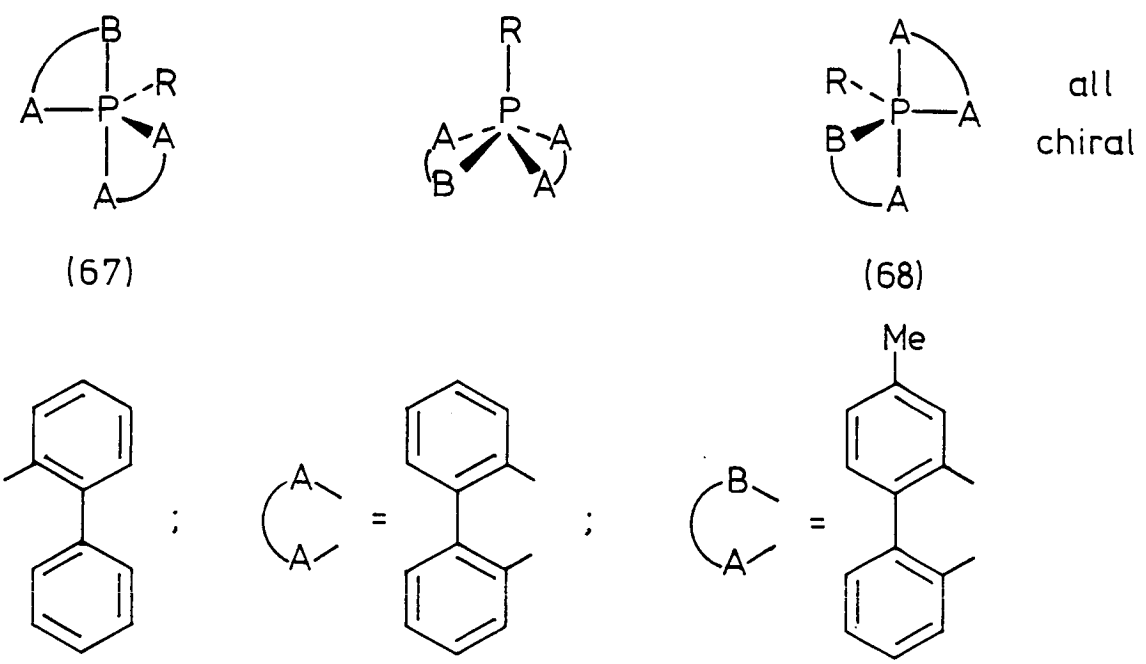
The unsubstituted octahedral anion of (63) is chiral and can be separated into its enantiomeric forms. Acid decomposition of the optically active potassium salt, however, gives only a racemic mixture of the phosphorane enantiomers (64) and (65) (Scheme 23). This loss of optical activity can be



Scheme 23

rationalised if a facile Berry pseudorotation is assumed; the first formed optically active phosphorane (64) is racemized in forming an achiral tetragonal pyramidal intermediate (66) as the first step in a BPR mechanism.

Hellwinkel then proposed introducing an asymmetrical element (methyl substituent) into one of the rings of the resultant phosphorane, so that the tetragonal pyramidal intermediate would now also be chiral, leaving no facile route for racemization by pseudorotation (Scheme 24). In contrast with Scheme 23, TBP structures (67) and (68) are not enantiomeric, as ligand B occupies an apical position in one structure, and an equatorial position in the other.

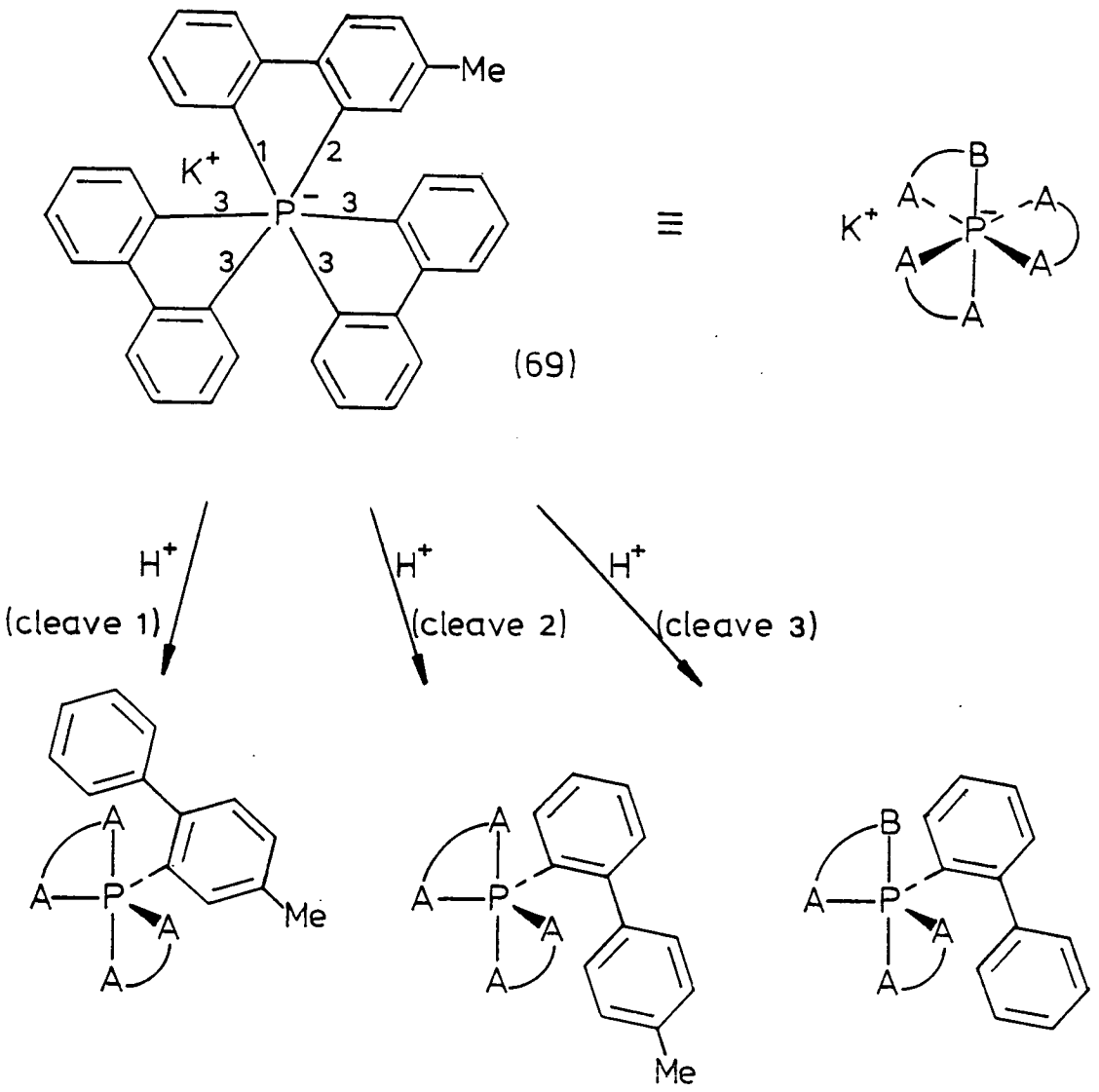


Scheme 24

In practice, Hellwinkel obtained a mixture of three phosphoranes on acid decomposition of the methyl substituted optically active octahedral complex (69), depending on which of the three possible types of P-C bonds were cleaved by acid

treatment (Scheme 25).

Two of these phosphoranes, (70) and (71), have identical symmetrical bidentate ligands (c.f. Scheme 23) and can thus easily racemize. The third phosphorane (72), however, has an asymmetrical ring as in Scheme 24, and by good fortune, was



Scheme 25

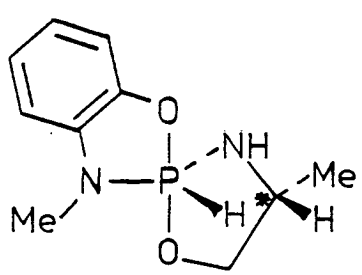
able to be separated from the product mixture by fractional crystallisation. A further consequence of the asymmetrical

methyl substituent was the preferential crystallisation of one enantiomer of (72), which enabled optical rotations of $+94^{o}$ and -94^{o} to be measured for the separate enantiomers of TBP (72).

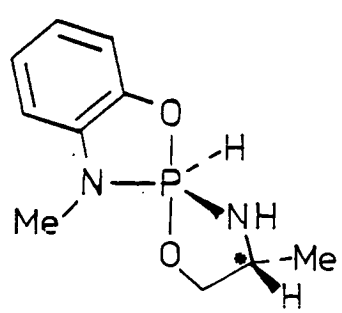
Thus Hellwinkel succeeded in isolating the first optically active pentaarylphosphorane by introducing into a phosphorane an element of chirality which could not be eliminated by a facile P.I. process.

The separation of optically active pentacoordinate phosphorus centres has also been widely studied by Wolf and his co-workers[55]. Here too, separation relies on the different physical properties of diastereoisomeric spirocyclic phosphoranes.

In one such example, synthesis from an optically active alcohol was used to introduce an optically active carbon atom as part of an asymmetric bidentate chelate ring. This gives rise to a diastereomeric mixture of phosphoranes (73) and (74), differing only in their configurations at phosphorus.



(73)



(74)

Slow crystallisation of this mixture of diastereoisomers not only gave a single isomer initially, but its precipitation displaced the equilibrium such that all crystallised material was composed of this single isomer[56].

Having isolated crystals of a single optically pure pentacoordinate phosphorus centre, the French workers were able to monitor the slow racemization of this isomer in solution at low temperatures using a polarimetric technique.

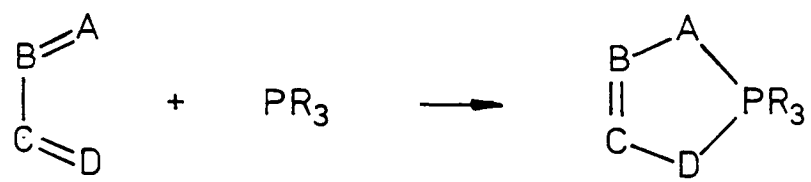
Thus, thermodynamic data was obtained which complements the more commonly encountered variable temperature n.m.r. techniques for studying the intramolecular stereolability of pentacoordinate phosphorus species.

2. Preparation of Pentacoordinate Phosphorus Compounds

Prior to 1950 few pentacoordinate phosphoranes were known, but since that time a vast number have been identified, ranging from short-lived intermediates formed by reaction of nucleophiles with tetracoordinate phosphorus centres[39] to the thermally stable compounds which are described in this Chapter. Preparative methods have been reviewed in detail by Hellwinkel[57], and only strictly organic phosphoranes are considered here.

2.1 Addition of tervalent phosphorus reagents to α,β-unsaturated systems.

This is probably the most extensively used method of preparing phosph(v)oles, i.e. compounds in which a pentacoordinate phosphorus atom is contained in a five-membered ring. The general reaction (Scheme 26) can be considered to involve

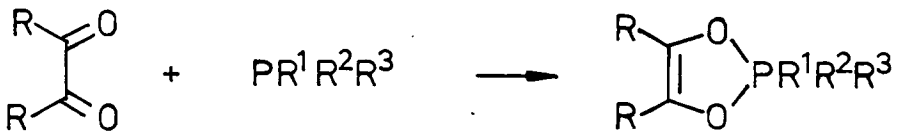


Scheme 26

Michael addition of the phosphorus reagent to the α,β-unsaturated system, although the precise mechanism is the subject of some conjecture[58-61].

α-Dicarbonyl compounds were first utilised by Kukhtin[62] when he reacted biacetyl with triethyl phosphite to give a pentacoordinate phosphorane. Extension of this reaction to a

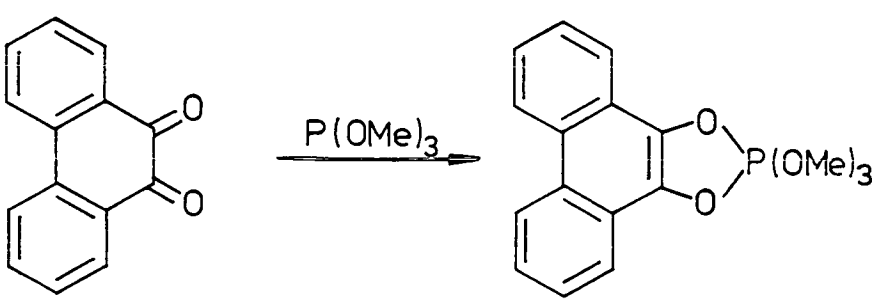
wide range of cyclic and acyclic tervalent phosphorus reagents, and to various dicarbonyl compounds[63-65] has provided a general route to 1,3,2-dioxaphosph(v)oles (Scheme 27).



Scheme 27

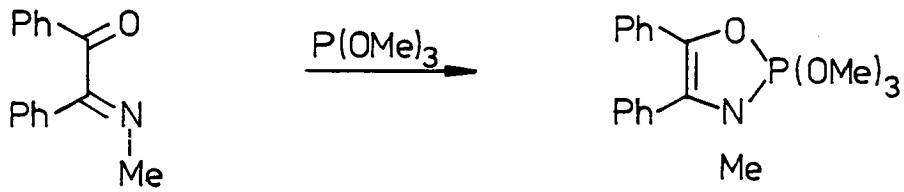
For example, Ramirez and Desai[63] obtained the oxyphosphorane (75) from reaction of 9,10-phenanthraquinone with trimethyl phosphite (Scheme 28), and data obtained from X-ray analysis of the tri-isopropyl analogue[66,67] provided some of the first evidence to substantiate earlier theories of pentacoordinate bonding and stability.

Other α,β-unsaturated systems which have been utilised in phosphorane synthesis are typified by the following examples. Burgada and Bernard prepared the 1,3,2-oxazaphosph(v)ole (77)[68] by treatment of the β-ketoimine (76) with trimethyl phosphite (Scheme 29). N-Alkylidene-N'-arylbenzamidines[69] can also be used (Scheme 30), while α,β-unsaturated ketones react to give 1,2-oxaphosph(v)oles with an endocyclic P-C bond (Scheme 31)[70].



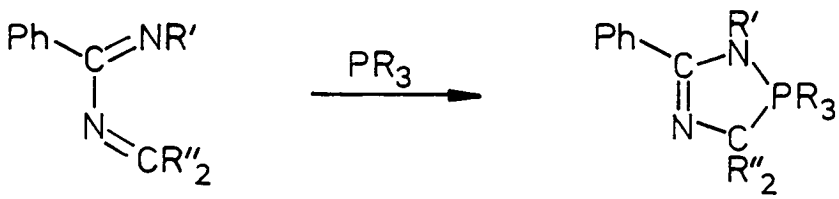
(75)

Scheme 28

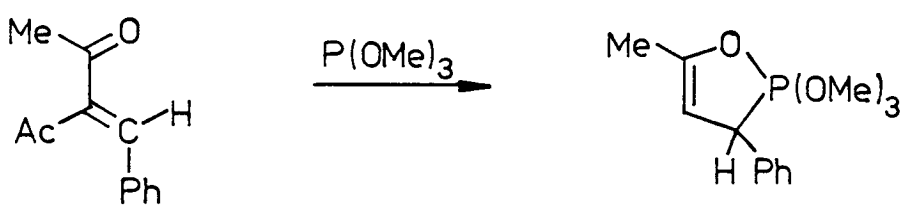


(76) (77)

Scheme 29



Scheme 30



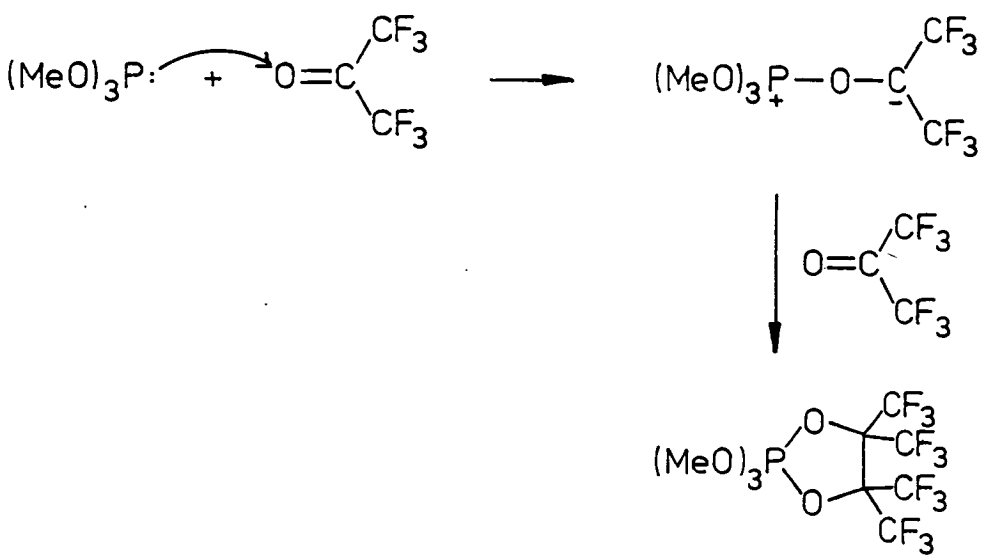
Scheme 31

Phosphonite and phosphinite esters can also be used[33], but phosphines are of limited use[2], in accordance with the tendency for phosphorane stability to increase with the number of P-O bonds[71].

Monocyclic pentaoxyphosphoranes prepared from α-dicarbonyl compounds can be subsequently converted to spirobicyclic phosphoranes by ligand exchange reactions with diols[72] or aminoalcohols[73], which displaces two alkoxy ligands.

2.2 Reaction of tervalent phosphorus reagents with two equivalents of a reactive carbonyl compound.

This method gives a direct synthesis of phosphoranes with a 1,3,2-dioxaphospholan ring. For example, Ramirez et al.[74] found that hexafluoroacetone reacted with trimethyl phosphite to give the phosphorane (78) via an initial 1:1 dipolar adduct (Scheme 32).



(78)

Scheme 32

Any carbonyl group which is activated by electron-withdrawing substituents will react similarly e.g. 2- and 4-nitrobenzaldehydes[75].

2.3 Reaction of tervalent phosphorus reagents with diols and related compounds.

This type of reaction is often used to prepare symmetrically substituted spirophosphoranes. Burgada, Wolf and co-workers[76] have synthesised a wide range of such spirocyclic phosphoranes containing a P-H bond. Thus, treatment of tris-dimethyl-

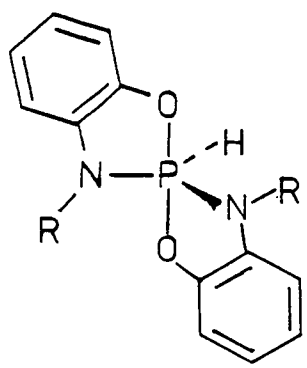
aminophosphine with two equivalents of pinacol gave the phosphorane (79) with release of dimethylamine (Scheme 33).

(79)

Scheme 33

This method has been extended by Burgada et al. by condensation of the P-H bond with aldehydes[77], ketimines[78], and carbocyclic acids[79].

σ-Aminoalcohols are equally effective, reacting with tris-dimethylaminophosphine to give spirocyclic benzoxaphosph(v)oles (80)[80,81].

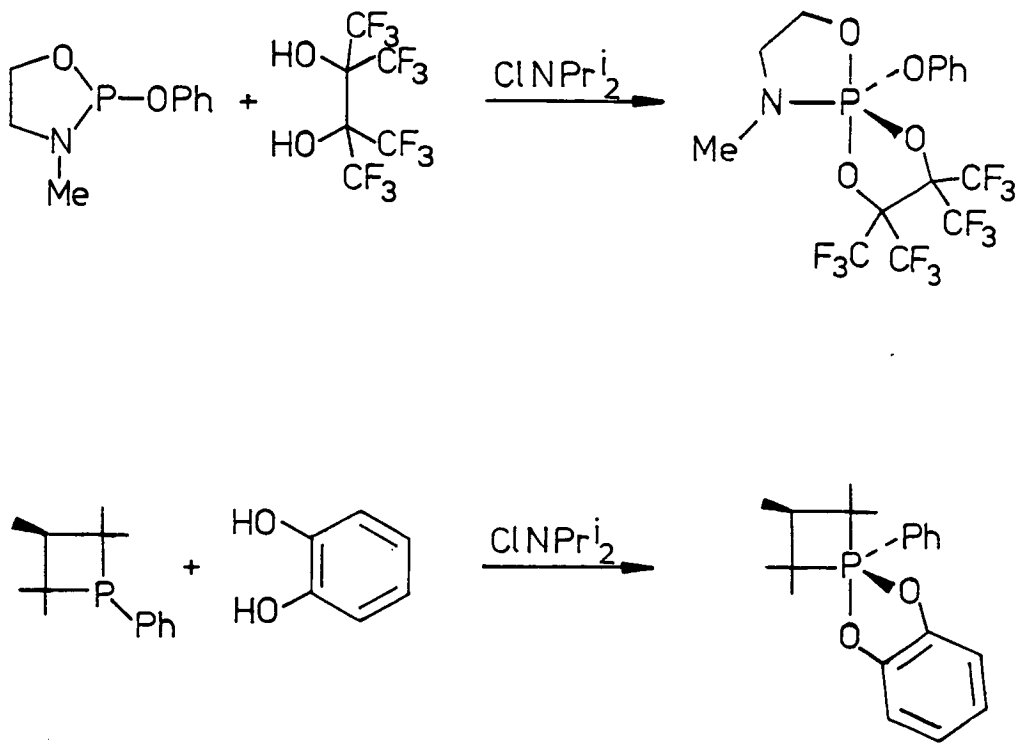


R = H, Me

(80)

More recently, Trippett et al.[82,83] have reported a general synthesis of pentacoordinate phosphoranes by the condensation of diols or their amino-analogues with a wide range of cyclic and acyclic tervalent phosphorus compounds, in the presence of N-chlorodiisopropylamine. By reacting at -78° in dry ether and filtering off the insoluble diisopropylammonium

chloride, evaporation enables isolation of phosphoranes which might prove hydrolytically and thermally unstable under alternative methods of preparation. Illustrated in Scheme 34 are two examples of spirocyclic phosphoranes which have been prepared by this method.



Scheme 34

2.4 Reaction of phosphorus ylides with 1,3-dipoles

This method has wide application in pentacoordinate phosphorane synthesis, especially in the preparation of 1,2,5-oxazaphosph(v)oles.

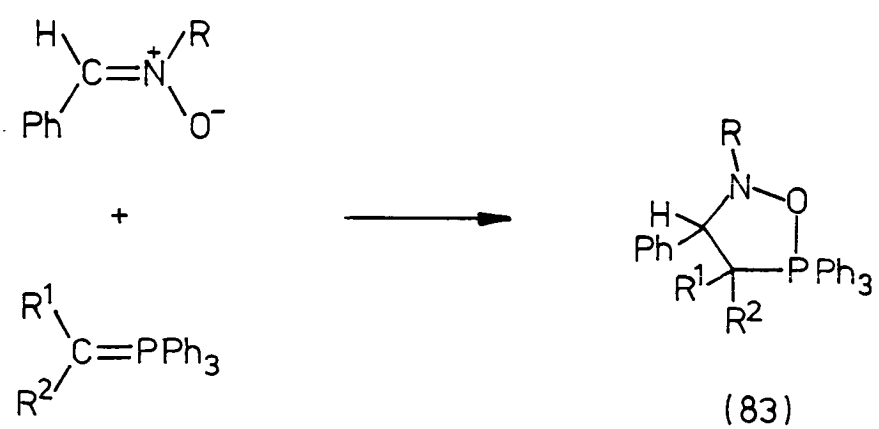
Huisgen and Wulff[84,85], for example, reacted methylene-triphenylphosphorane (81) with benzonitrile oxide to give the 4,5-dihydro-1,2,5-oxazaphosph(v)ole (82) (Scheme 35).

(81) (82)

Scheme 35

This reaction was extended by Bestmann and Kunstmann[86] using various alkylidenetriphenylphosphoranes and nitrile oxides.

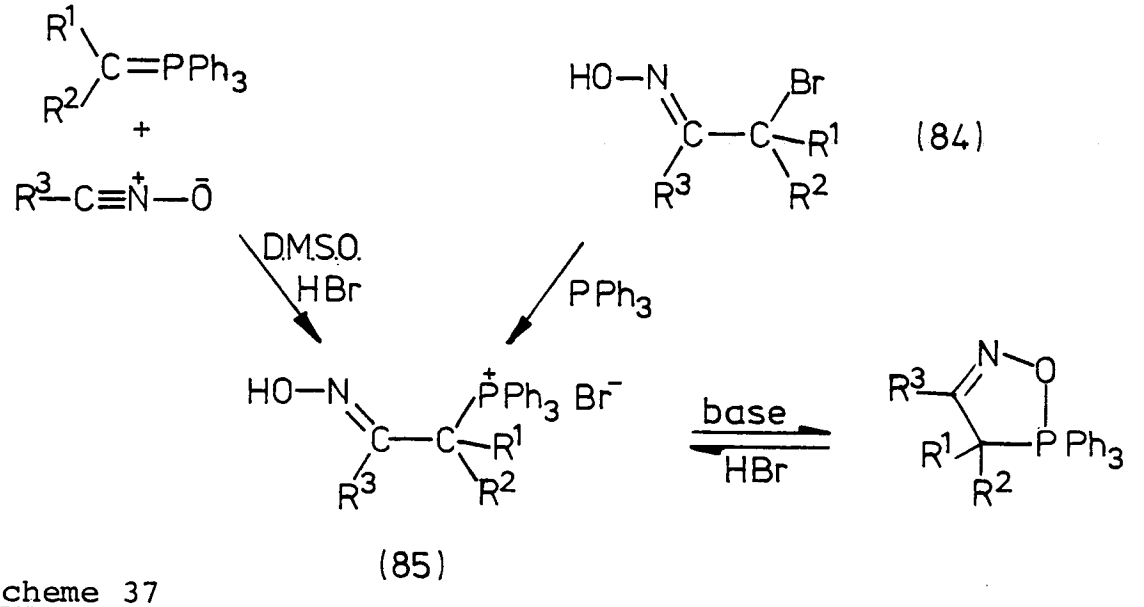
The analogous 1,3-cycloaddition of C-phenylnitrones to alkylidenetriphenylphosphoranes[87] gives rise to the corresponding pentacoordinate compounds (83) with a fully saturated five-membered ring (Scheme 36).



(83)

Scheme 36

4,5-Dihydro-1,2,5-oxazaphosph(v)oles may also be formed by cyclisation of 2-oximinophosphonium salts (85) in the presence of base, the phosphonium salts being obtained either

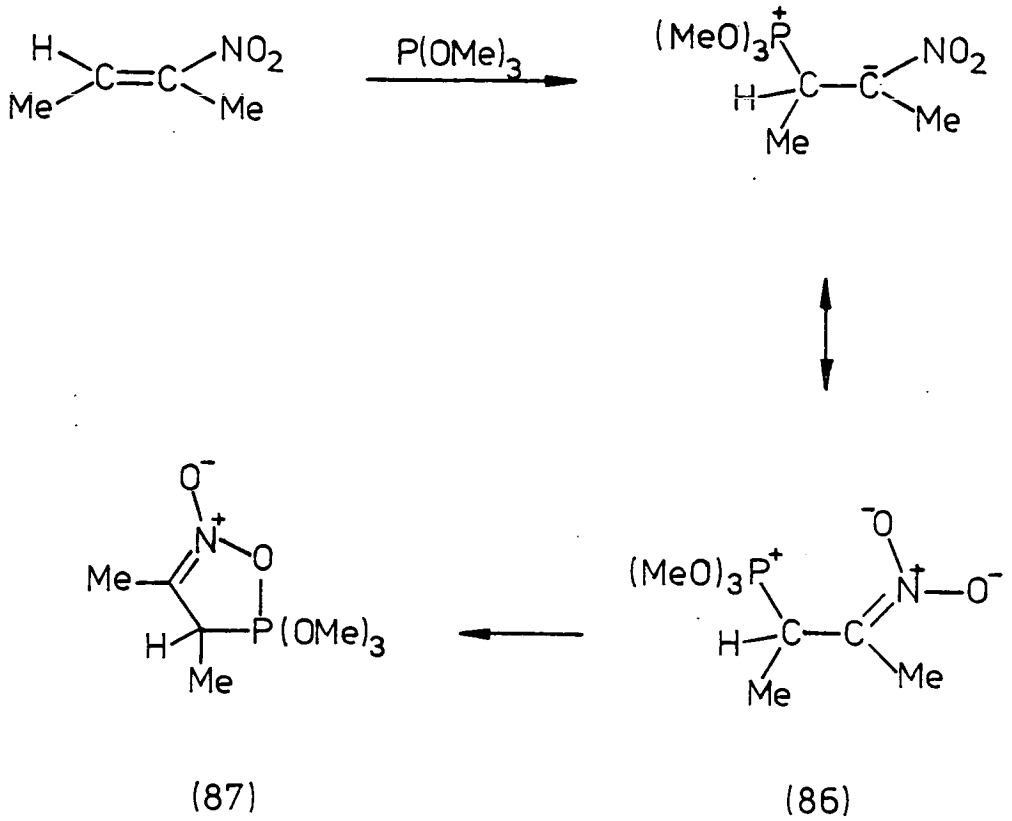


Scheme 37

from reaction of benzonitrile oxides with alkylidenetriphenylphosphoranes[88,89], or from α-halo-oximes[84] (84), as shown in Scheme 37.

2.5 Reaction of tervalent phosphorus reagents with 1-nitroethenes.

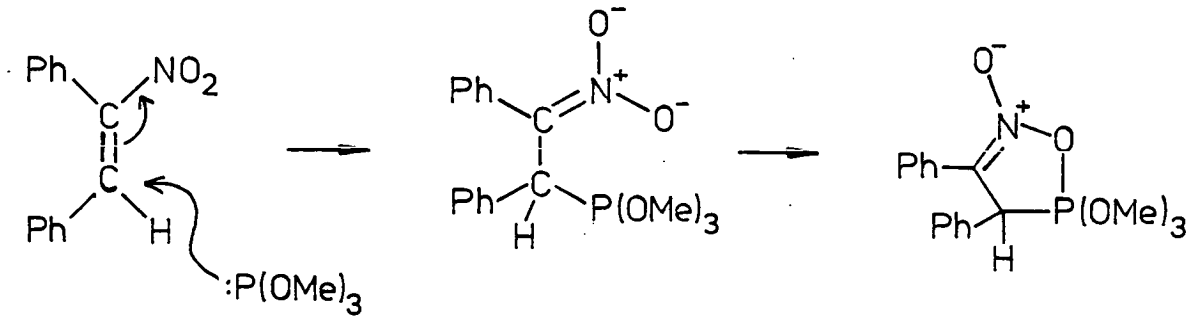
This type of reaction is similar to the cyclisation of phosphonium salts described above. The reaction between 2-nitro-2-butene and trimethyl phosphite, for example, was studied by Gareev et al.[90], who suggested that reaction occurred via Michael-type addition of the phosphite to the activated double bond (Scheme 38) to give a 1,5-dipole (86), which then cyclised to give the isolated product, a 4,5-dihydro-1,2,5-oxazaphosph(v)ole-2-oxide (87).



(87) (86)

Scheme 38

In the corresponding reactions of aromatic 1-nitroethenes, Cadogan and North[91] reacted 1,2-diphenyl-1-nitroethene with trimethyl phosphite in tertiary butanol to obtain the 1,2,5-oxazaphosph(v)ole-2-oxide (88) in 88% yield. Here too, a Michael-type addition mechanism is proposed (Scheme 39), and extension of this reaction to a range of 2-aryl-1-phenyl-1-nitroethenes and tervalent phosphorus reagents has provided a wide range of these novel 1,2,5-oxazaphosph(v)ole-2-oxides.

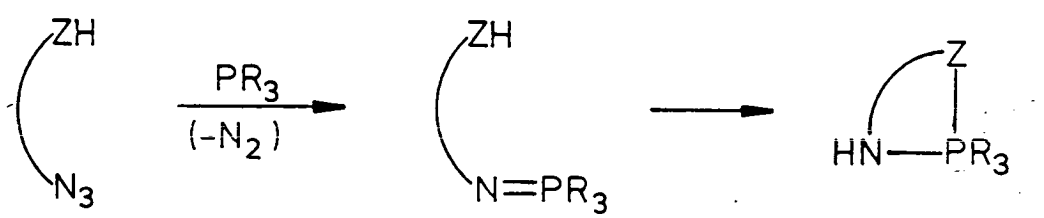


(88)

Scheme 39

2.6 Reaction of tervalent phosphorus reagents with azides.

A novel synthesis of pentacoordinate phosphoranes has been reported by Cadogan and his co-workers[92], involving the reaction of aliphatic bifunctional azides with tervalent phosphorus reagents. The general reaction proceeds via formation of an iminophosphorane (89), which then cyclises intramolecularly by addition across the P=N group to give a pentacoordinate aminophosphorane (90) (Scheme 40).



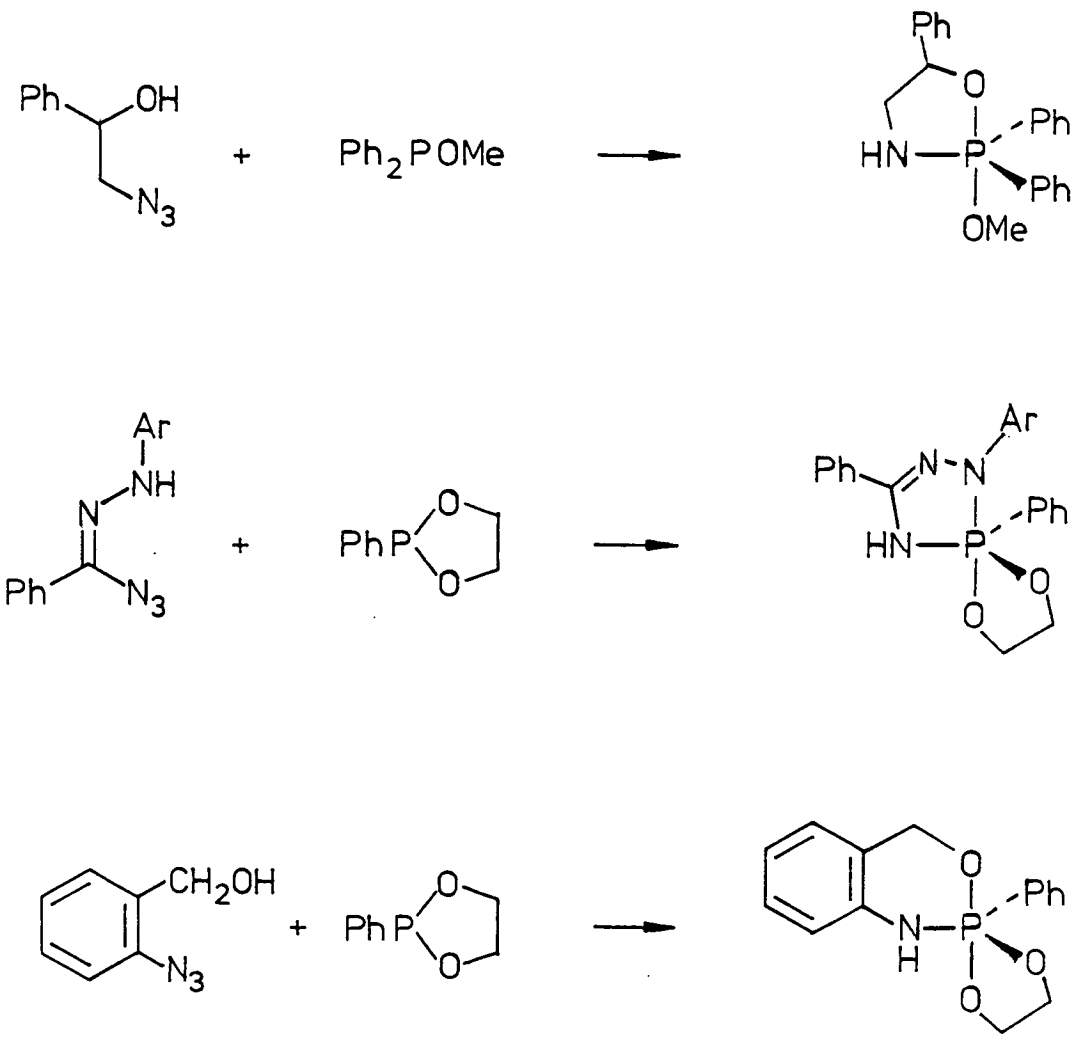
(89) (90)

Z = O , NH

Scheme 40

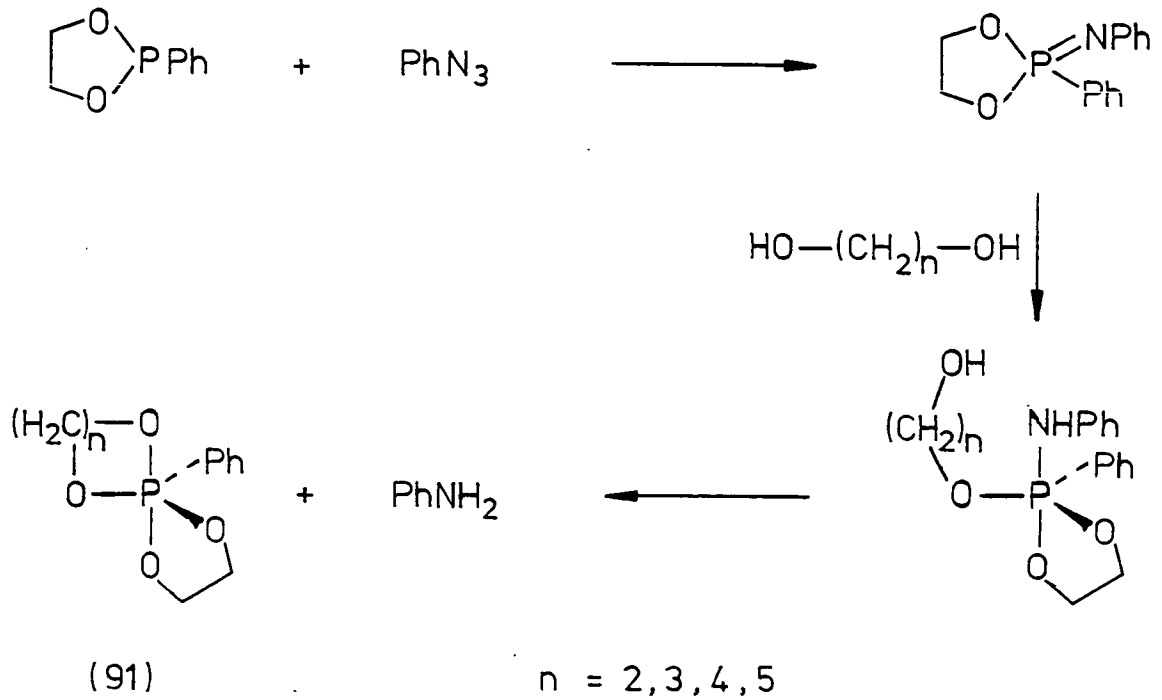
A wide range of bifunctional azido-compounds have been reacted with cyclic and acyclic tervalent phosphorus reagents, of which a few examples are shown in Scheme 41.

The analogous intermolecular reaction leads to a simple one-flask synthesis of pentacoordinate phosphoranes[93]; the



Scheme 41

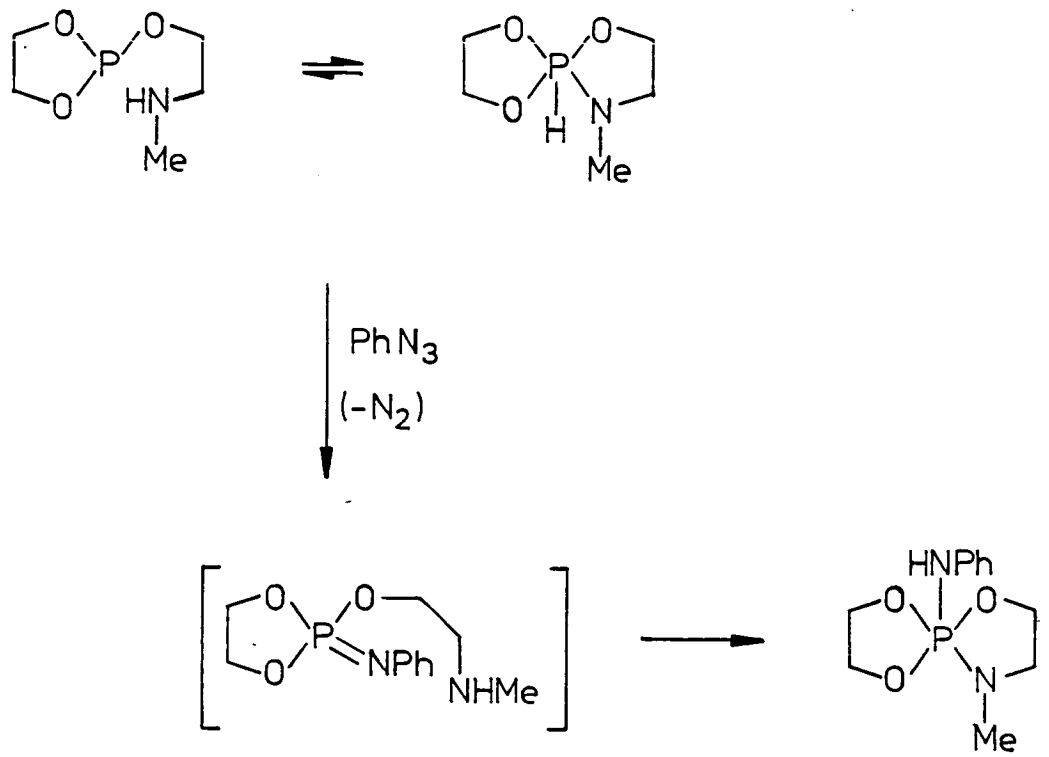
examples illustrated in Scheme 42 include the first isolated alicyclic phosphoranes containing seven- or eight-membered rings (91).



(91) n = 2,3,4,5

Scheme 42

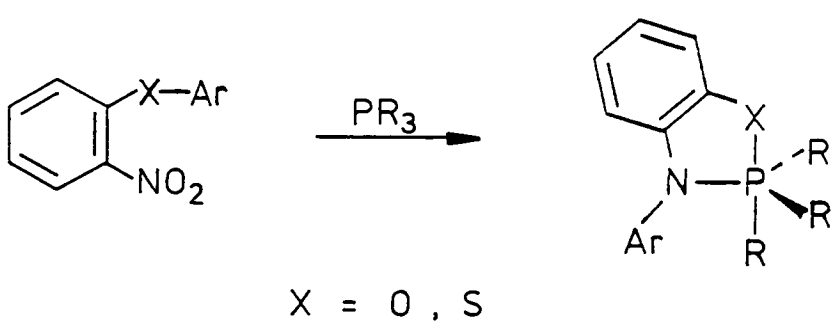
These examples of azido-compounds and tervalent phosphorus reagents reacting to give iminophosphoranes and subsequently pentacoordinate species complement the phosphoranes synthesised by Wolf et al.[94] by reacting amino-substituted phosphites with phenyl azide (Scheme 43).



Scheme 43

2.7 Deoxygenation of 2-nitrodiaryl sulphides and ethers by tervalent phosphorus reagents.

Cadogan et al. have prepared a large number of 1,3,2-benzoxazaphosph(v)oles[95,96] and 1,3,2-benzthiazaphosph(v)oles[97,98] by the reductive cyclisation of 2-nitrodiaryl sulphides and ethers (Scheme 44).



X = O , S

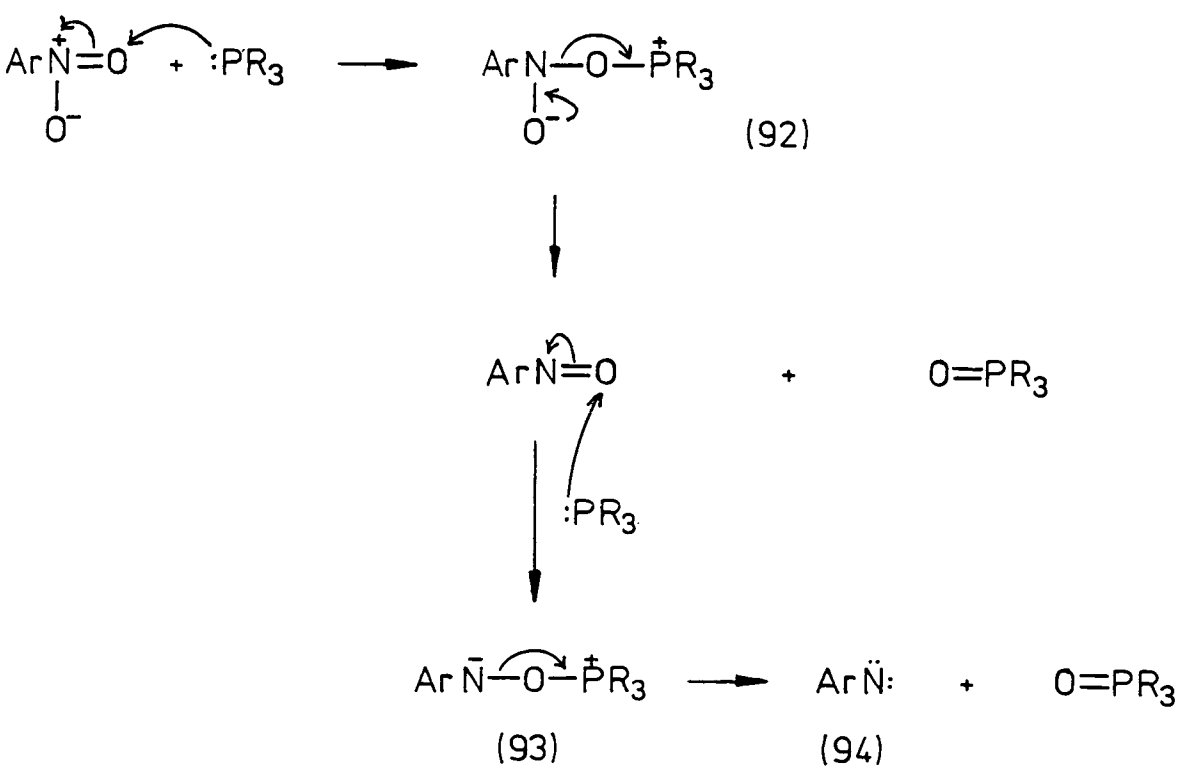
Scheme 44

As the major part of this thesis is concerned with further studies of the reactions of tervalent phosphorus reagents with 2-nitrodiaryl ethers, the remainder of this chapter describes previous work carried out in this laboratory to investigate the deoxygenation reactions of aromatic nitro-compounds.

2.7.1 Reaction of tervalent phosphorus reagents with 2-nitrodiaryl sulphides.

Although a large number of heterocyclic syntheses have been described based on the capacity of tervalent phosphorus compounds to deoxygenate aromatic nitro- or nitroso-compounds[99-102], the precise mechanism of deoxygenation remains in some doubt[102].

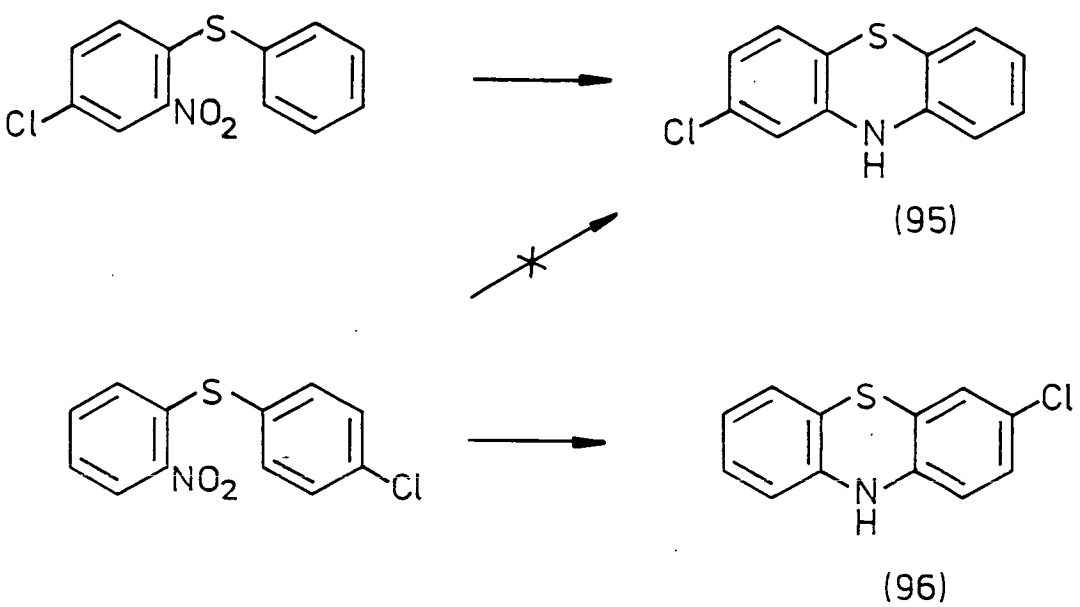
The balance of evidence from numerous reaction product studies tends to favour formation of a nitrene intermediate (94) as shown in Scheme 45, via dipolar "nitrenoid" species



Scheme 45

(92) and (93), although the possibility of competing pathways existing between true "nitrene" reactions and various dipolar species cannot be ruled out.

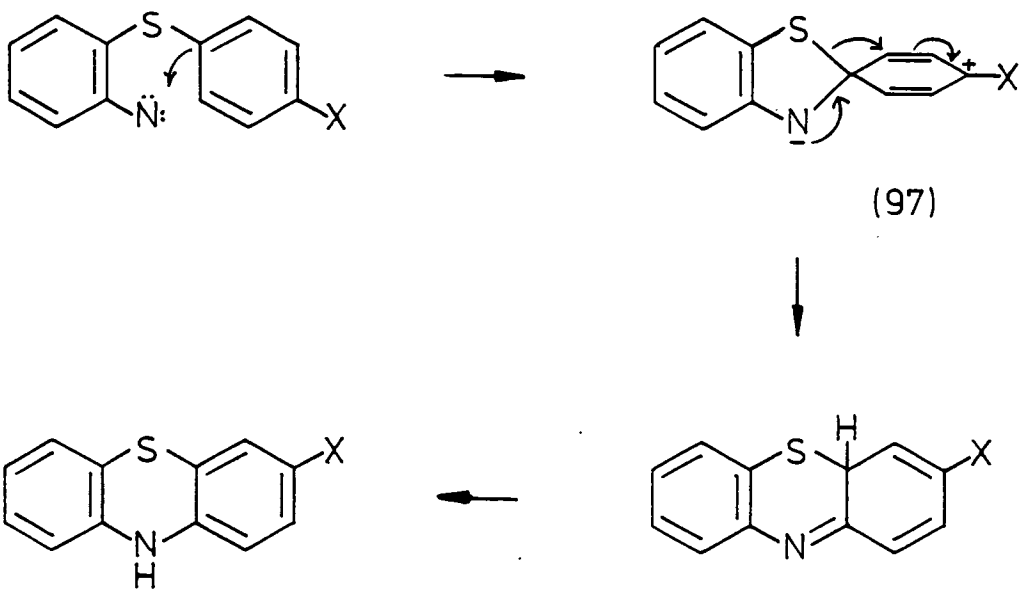
The isolation of unusually substituted phenothiazine products from the deoxygenation of 2-nitrodiaryl sulphides was explained by Cadogan et al[103,104] in terms of a particularly interesting rearrangement after initial nitrene formation. Thus, 2-nitro-4-chlorophenyl phenyl sulphide was found to react with triethyl phosphite to give 2-chlorophenothiazine (95), apparently by the simple insertion of a nitrene into the β-C-H bond of the adjacent phenyl ring (Scheme 46). 4-Chlorophenyl-2-nitrophenyl sulphide, however, did not give rise to the same phenothiazine as the simple insertion mechanism would predict, but instead gave 3-chlorophenothiazine (96).



Scheme 46

Cadogan proposed that both phenothiazines are formed by nitrene attack at the α-carbon atom (Scheme 47) giving a

spirodienyl intermediate (97), which subsequently undergoes a sigmatropic 1,2-sulphur shift, and rearomatises by a hydrogen shift to give a phenothiazine which is substituted at a different position to that expected from a simple C-H insertion mechanism.



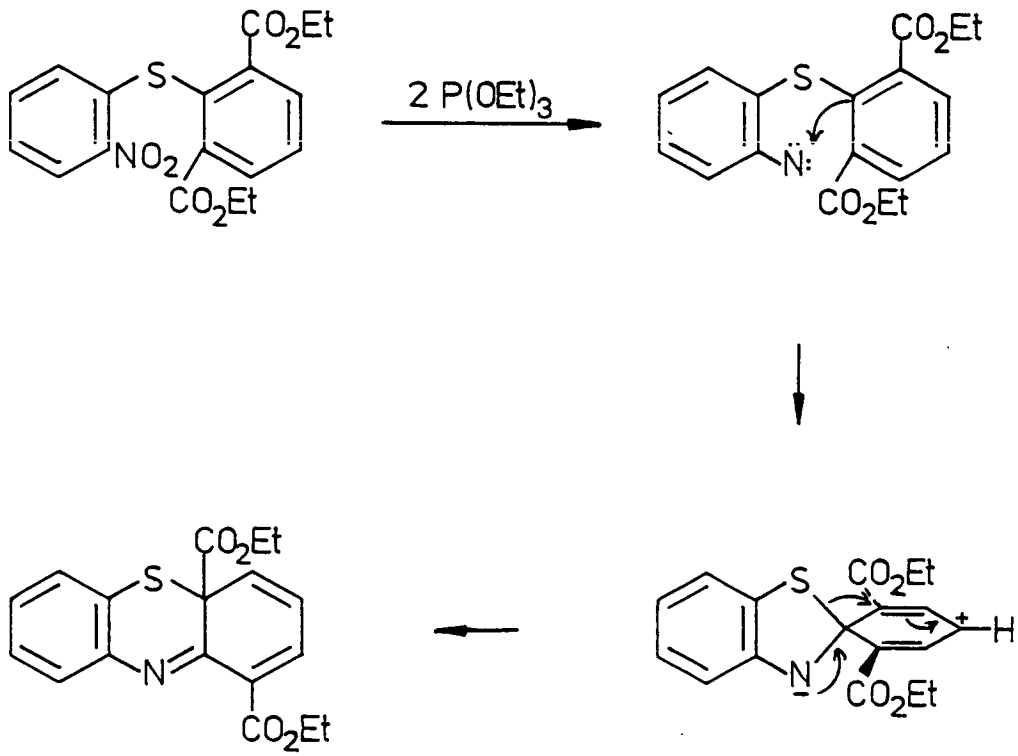
(97)

Scheme 47

Other substituted sulphides lend support to this mechanism, which is further substantiated by e.s.r. spectroscopic evidence in the unsubstituted case[104b].

If the ortho-positions in the phenyl ring under nitrene attack are "blocked" by substituents, then rearomatisation is prevented, so that the isolated product from deoxygenation of the 2,6-dicarbethoxy-substituted sulphide, for example, is a novel heterocyclic structure (98) (Scheme 48).

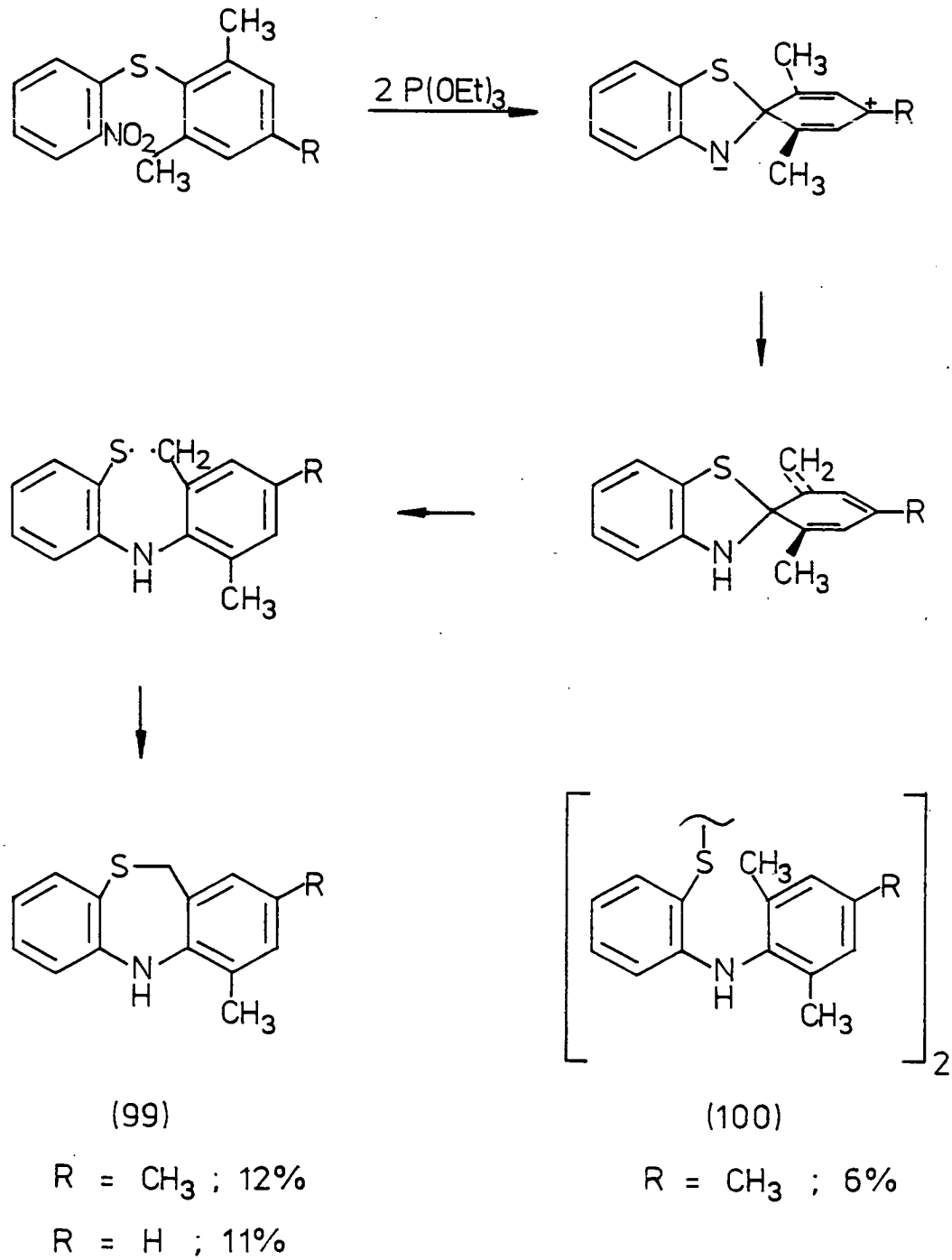
In the case of the 2,6-dimethyl- and 2,4,6-trimethylphenyl 2-nitrophenyl sulphides, this "blocked ortho effect" leads to



(98)

Scheme 48

formation of seven-membered ring thiazepines (99) (Scheme 49). A small amount of the disulphide (100) obtained from the 2,4,6-trimethyl substituted sulphide gives support to the diradical mechanism for thiazepine formation proposed by Cadogan and Kulik[105], as shown in Scheme 49.



(99)

R = CH_3 ; 12%

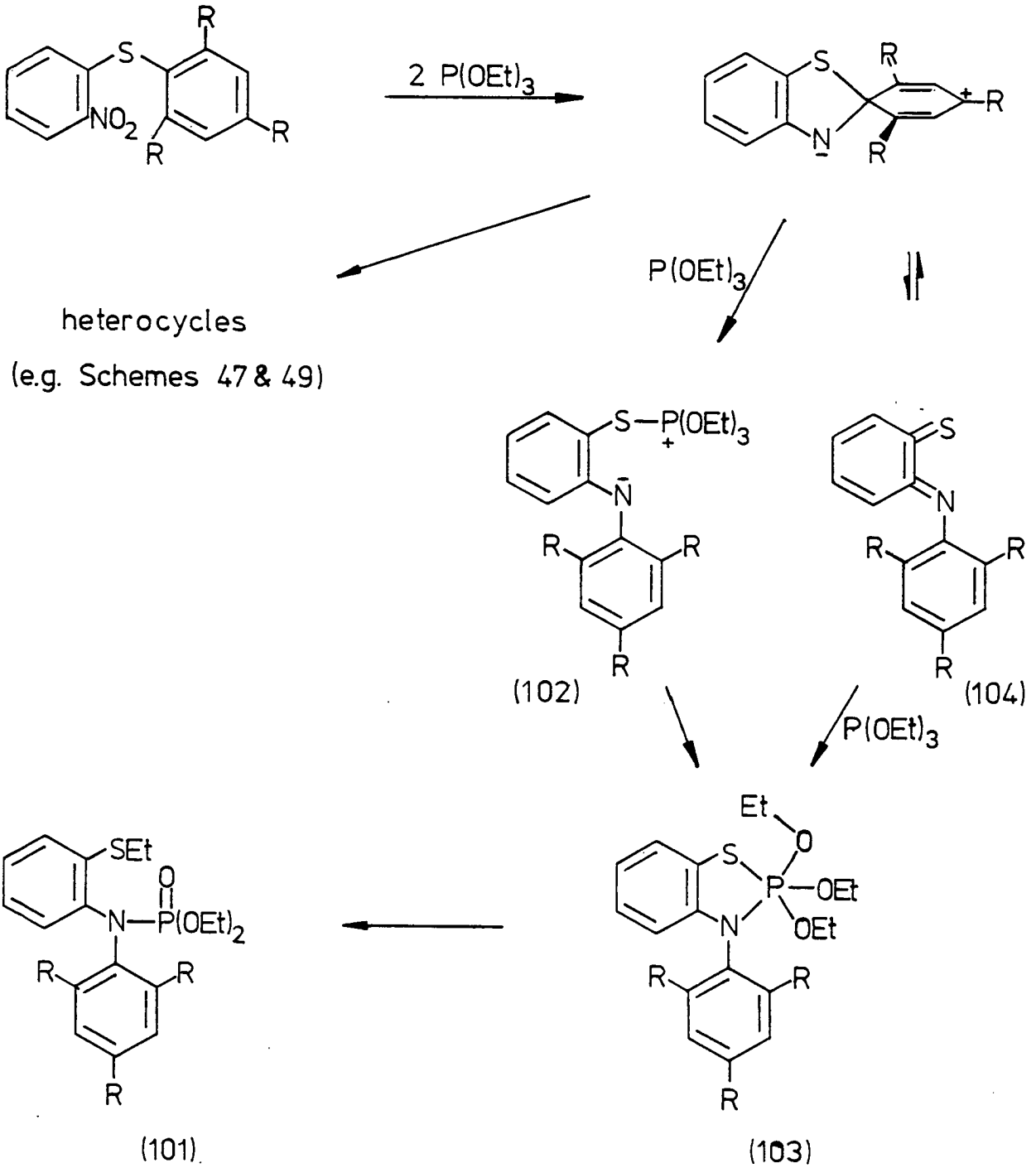
R = H ; 11%

(100)

R = CH_3 ; 6%

Scheme 49

However, as the low yields in Scheme 49 indicate, these heterocycles are only minor products. The major products from deoxygenation of ortho-blocked sulphides are phosphoramidates (101) (Scheme 50).



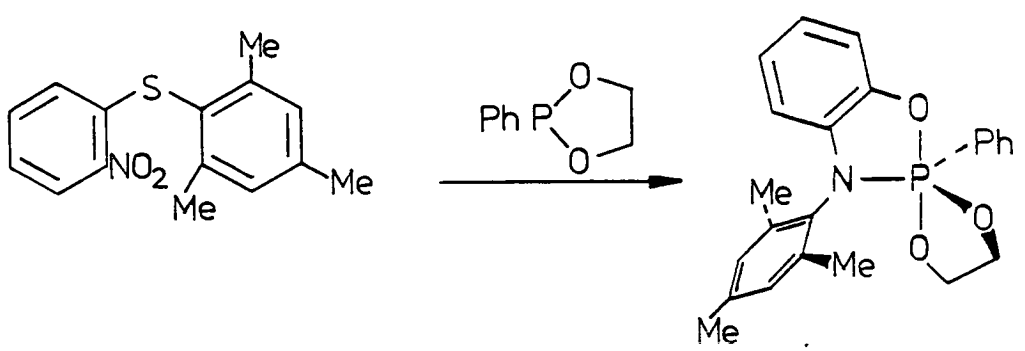
Scheme 50

With the ortho-positions blocked, a 1,2-sulphur shift becomes more hindered, thus increasing the lifetime of the spirodiene intermediate so that it can be trapped by phosphite rather than rearrange to give heterocyclic products. Trapping may occur either by nucleophilic attack by phosphite on sulphur, giving a zwitterionic species (102) which then

cyclises to a 1,3,2-benzthiazaphosph(v)ole (103), or alternatively by addition of phosphite to the thioquinone isomer (104) of the spirodiene to give the same phosph(v)ole. Intramolecular alkylation of the phosph(v)ole then leads to the isolated phosphoramidate (101), as shown in Scheme 50.

Later kinetic studies[106] by ^{31}P n.m.r. spectroscopy strongly suggest that various tervalent phosphorus esters do indeed react with nitro-diaryl sulphides to give an intermediate pentacoordinate phosphorane, but isomerise under the reaction conditions (boiling cumene at 153°C) to give amidates as the final isolated product.

Credence was given to this suggestion when use of the cyclic phosphorus ester, 2-phenyl-1,3,2-dioxaphospholan, increased the stability of the intermediate sufficiently to enable the spirobicyclic benzthiazaphosph(v)ole (105) to be isolated and its X-ray crystal structure determined[107]. (Scheme 51).



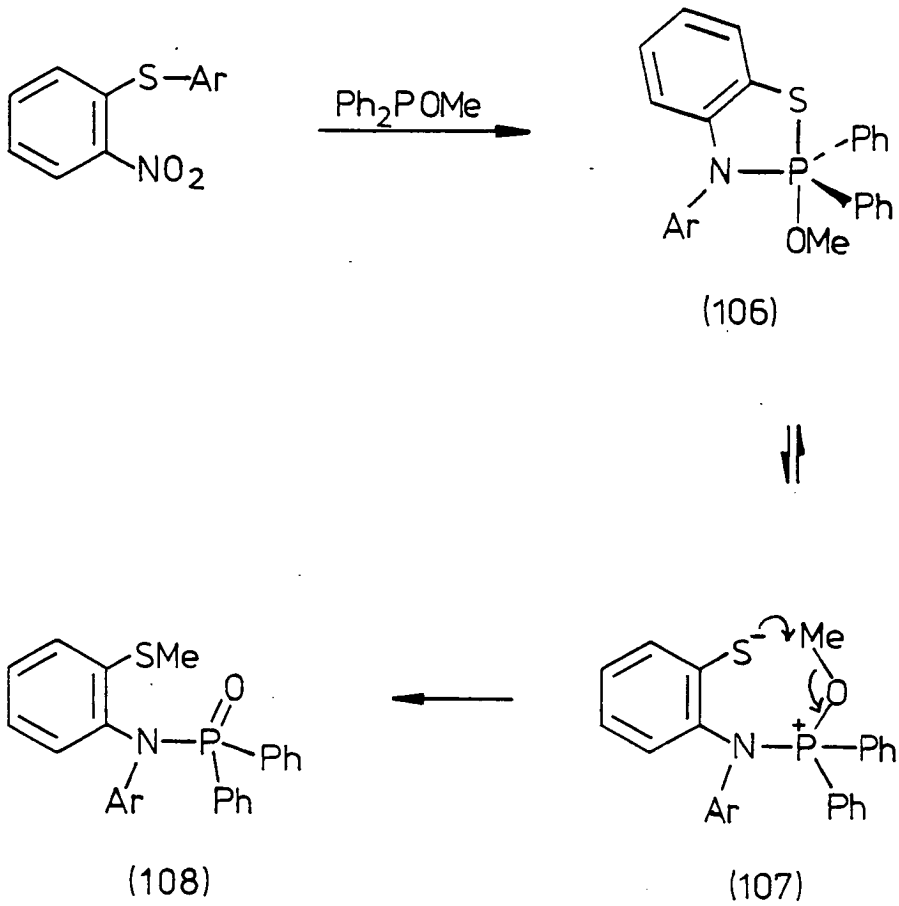
(105)

Scheme 51

The corresponding N-2,6-dimethylphenyl and N-2,6-dimethoxyphenyl analogues of (105) have also been isolated in high yield.

By carrying out deoxygenations under milder conditions in boiling toluene at 110°C using methyl diphenylphosphinite,

Cadogan and Tweddle[106] were able to isolate the first monocyclic benzthiazaphosph(v)oles (106) (Scheme 52).



Scheme 52

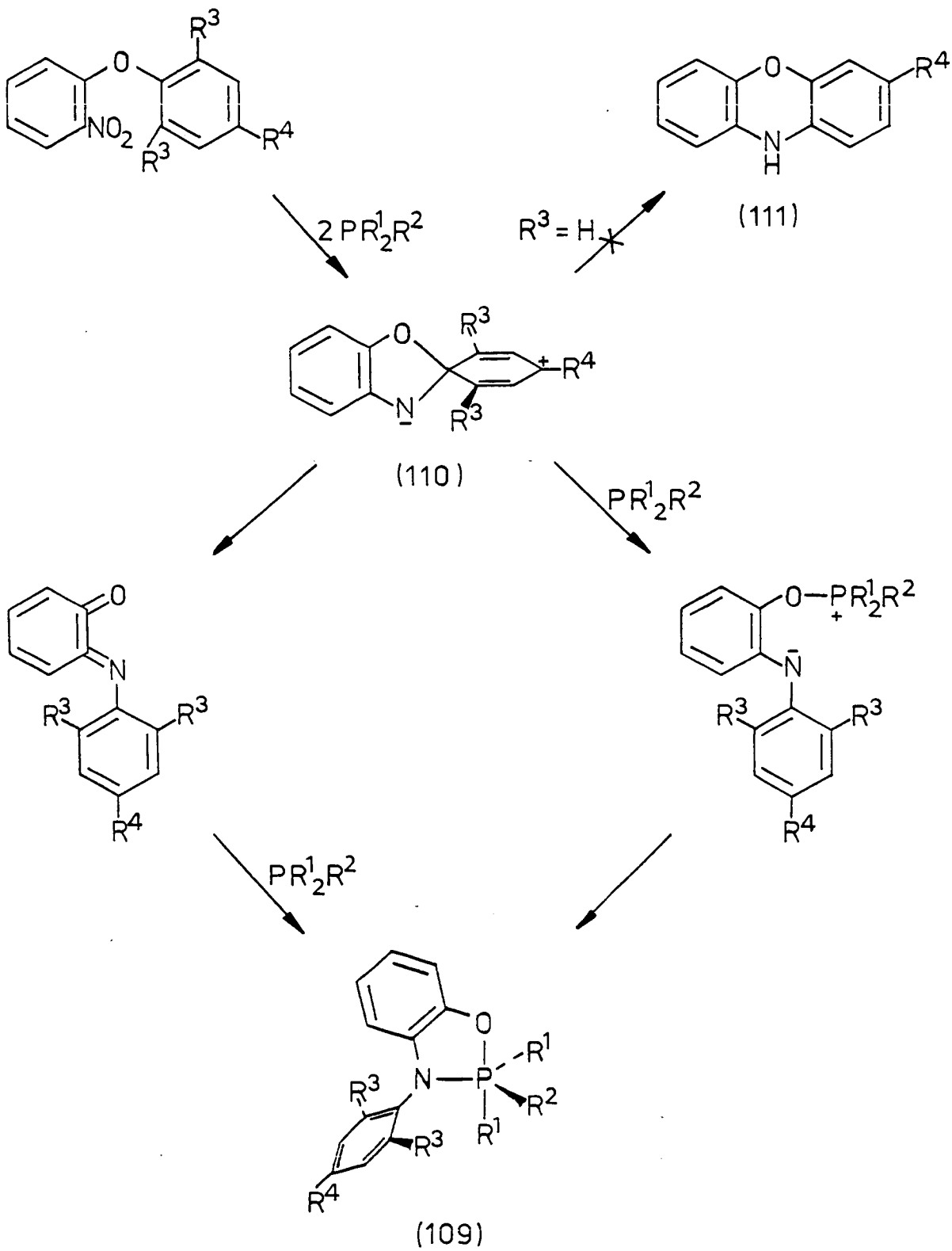
In contrast with their spirobicyclic analogues, which remain virtually unaffected, these monocyclic benzthiazaphosph(v)oles (106) exhibit ^{31}P n.m.r. chemical shift changes of more than 100 p.p.m. with changes in solvent polarity, indicating an equilibrium existing between the pentacoordinate structure and its isomeric quasiphosphonium betaine form (107). The isolated monocyclic phosphoranes were found to react as postulated previously (Scheme 50), rearranging at 153°C in boiling

cumene to their isomeric phosphinamidates (108); the observed first order kinetics are consistent with the formation of a quasiphosphonium betaine (107) as the rate determining step. Accordingly, deoxygenations carried out directly in boiling cumene using methyl diphenylphosphinite gave amidates (108) directly, rather than their pentacoordinate precursors (106).

2.7.2 Reaction of tervalent phosphorus reagents with 2-nitrodiaryl ethers: Formation of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

By analogy with the "unblocked" aryl 2-nitrophenyl sulphides which give phenothiazines on deoxygenation, the corresponding aryl 2-nitrophenyl ethers might be expected to give phenoxazines. In practice, however, non-phosphorus containing heterocycles such as phenoxazines were found in very low yield (1-5%), and only then from ethers having both ortho-positions "blocked"[108].

Instead, reaction of aryl 2-nitrophenyl ethers with tervalent phosphorus reagents has led to the isolation of a large number of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles (109) in yields of 12-95%. An analogous mechanism to the sulphide deoxygenations was proposed by Cadogan and his co-workers[108] (Scheme 53), but because of the oxygen atom's lesser tendency to migrate, the spirodienyl intermediate (110) is trapped by phosphite in preference to forming a phenoxazine (111). Thus the spirodienyl intermediate can regain its aromaticity either by undergoing direct nucleophilic attack by another molecule of phosphorus reagent to give the pentaco-ordinate phosphorane via a dipolar intermediate, or alternatively



Scheme 53

via the quinone imine isomer which can subsequently trap the phosphorus reagent to give the pentacoordinate product (109).

In comparison with the corresponding benzthiazaphosph(v)oles,

in which nucleophilic sulphur is readily alkylated intramolecularly, the benzoxazaphosph(v)oles are thermally stable, being formed in boiling cumene and isolated by vacuum distillation at temperatures up to 180°C. Exclusion of water from the reaction mixture, however, is essential to prevent hydrolytic decomposition of the phosph(v)oles to tetracoordinate phosphorus species, and ultimately to 2-hydroxydiphenylamines (see Chapter 4).

Tait[109] found that 2,6-disubstituted aryl 2-nitrophenyl ethers gave high yields of 1,3,2-benzoxazaphosph(v)oles with most tervalent phosphorus reagents, but that ethers without ortho blocking groups reacted better with phosphonites than with phosphites.

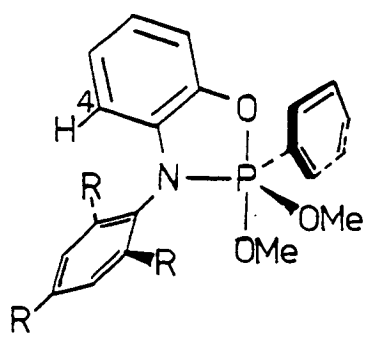
A possible explanation lies in the increased stability afforded to phosphonite derived phosphoranes by accommodating an alkyl or aryl ligand more readily in an equatorial position than an apicophilic alkoxy ligand, and also by reducing the likelihood of hydrolytic attack when fewer alkoxy ligands (good leaving groups) are present.

The assignment of a pentacoordinate trigonal bipyramidal structure to the 1,3,2-benzoxazaphosph(v)oles was based on examination of their hydrolysis products[108], and by analytical and spectroscopic techniques[110], as outlined below.

Thus, ^{31}P n.m.r. spectra showed chemical shifts of between -33 and -62 p.p.m., characteristic of the pentacoordinate state. These chemical shifts were relatively unaffected by changes in solvent polarity, excluding the possibility of the ring closed phosphorane existing in equilibrium with its open-chain zwitterionic tautomer.

A common feature of all the mass spectra was the direct loss from the parent ion peak of a fragment corresponding to the oxidised phosphorus moiety, $R^1_2R^2PO$, followed by facile loss of a further proton.

The ^1H n.m.r. spectra exhibited a characteristic complex doublet or multiplet at ca $\delta 6.0$, attributed to the aromatic proton at position 4 of the benzoxazaphosphole system (112) being shielded by the ring current of the pendant N-aryl ring. This large degree of shielding suggests that the N-aryl ring is restricted in its rotation and oscillates about a mean position orthogonal to the benzoxazaphosphole system, thus occupying a position of minimum steric interaction with both the heteroaromatic system and bulky exocyclic ligands such as the equatorial phenyl ligand in (112).



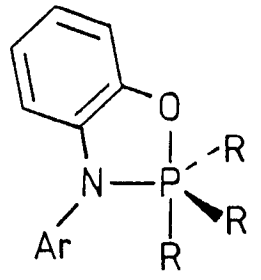
(112)

Variable temperature ^1H n.m.r. studies of 1,3,2-benzoxazaphosph(v)oles such as (112), derived from dimethyl phenylphosphonite, have shown that at low temperatures, intramolecular permutational isomerisation can be slowed down suffiently to observe separate apical and equatorial methoxy ligands. This enables calculation of the free energy of activation (ΔG^*) for interchange of apical and equatorial ligand positions. Such permutational isomerisation processes are a common feature

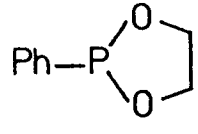
of pentacoordinate phosphorus chemistry, and the consequences of these and other intramolecular rotations are discussed in greater detail in the following chapter dealing with dynamic stereochemistry.

Finally X-ray crystallographic studies[111] have confirmed the geometry suggested by this spectroscopic evidence, and in particular, the orthogonality of the N-aryl group in the solid state, within a structure deviating only slightly from an ideal TBP.

TABLE 1

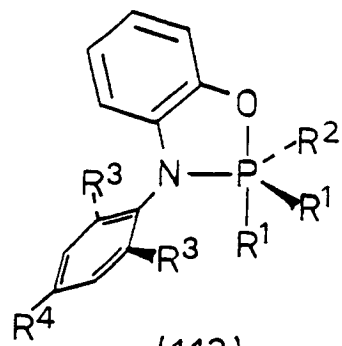


(113a-e)

Compound	N-Phenyl substituent	PR_3	T_c (°C)	ΔG^* (kJ mol^{-1})
113a	2,4,6-$(Me)_3$	$P(OMe)_3$	-71	-
b	2,4,6-$(Me)_3$	$PhP(OMe)_2$	-5	52.0
c	4-Me	"	-50	43.0
d	none	"	-59	40.9
e	2,4,6-$(Me)_3$		+175	96

3. Variable Temperature N.M.R. Studies of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

The temperature dependent n.m.r. spectra of a large number of the title compounds (113) have been studied by Cadogan, Grace and Tait[110], who concluded that restricted rotation of



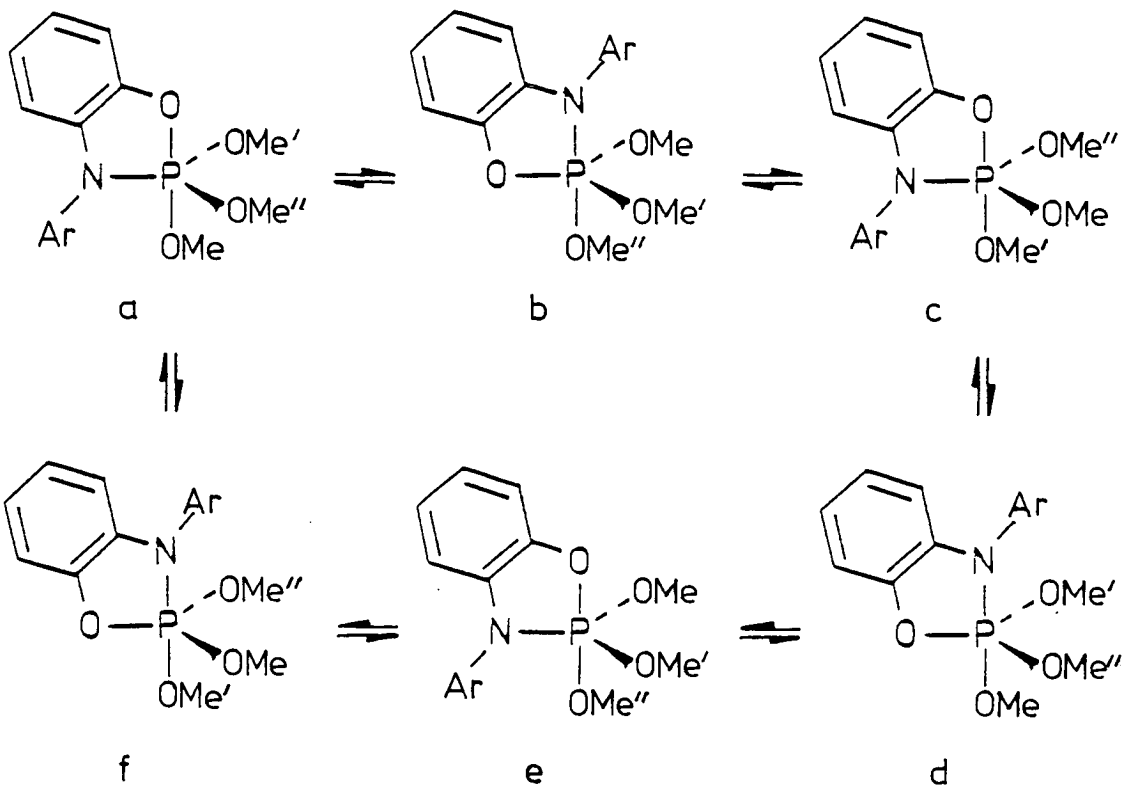
(113)

the N-aryl ring greatly influences the ease with which PI occurs. Since these studies had an important bearing on the content of this thesis, a detailed account is given in this chapter of some of the variable temperature n.m.r. experiments which led Cadogan et al. to form the above conclusion.

Firstly, the room temperature ^1H n.m.r. spectrum of the trimethyl phosphite derived benzoxazaphosph(v)ole (113a, Table 1) exhibited a sharp nine-proton phosphorus coupled doublet for the methoxy ligands, indicating rapid P.I.on the n.m.r. timescale. As the temperature of the probe was reduced, this signal split into two broad doublets below -80°C; the lower field doublet, being twice the intensity of the higher field doublet, was assigned to the two equatorial methoxy groups (J_{POMe} 14.5Hz), while the higher field signal's smaller coupling constant (J_{POMe} 10Hz) confirmed its assignment to the longer, weaker apical methoxy group. The low temperature

"frozen" geometry therefore has the hetero-ring spanning the apical-equatorial position, as would be expected.

Coalescence of apical and equatorial methoxy signals occurs at ca. -71°C, and the P.I. process responsible for this magnetic equivalence of three methoxy ligands is represented in Scheme 54 using the Turnstile notation, with the heterocyclic ring as the ligand pair.

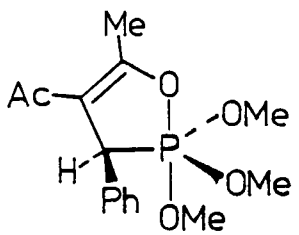


Scheme 54

The high energy TBPs in this pseudorotation cycle are 'b', 'd', and 'f', being energetically disfavoured by the nitrogen atom's lower apicophilicity compared with endocyclic oxygen, and the nitrogen atom's preference for the equatorial plane to maximise its π-donor ability. Any steric interaction between the orthogonal N-2,4,6-trimethylphenyl group and the exocyclic methoxy groups is likely to be minimal, and common

to all TBPs in Scheme 54.

Although ΔG^{*} cannot be easily obtained for the case of a 3-site exchange process (coalescence of three methoxy signals), the coalescence temperature of -71°C does bear comparison with the coalescence temperature of ca.-40°C observed for the methoxy ligands of the tetraoxyphosphorane (114)[112].

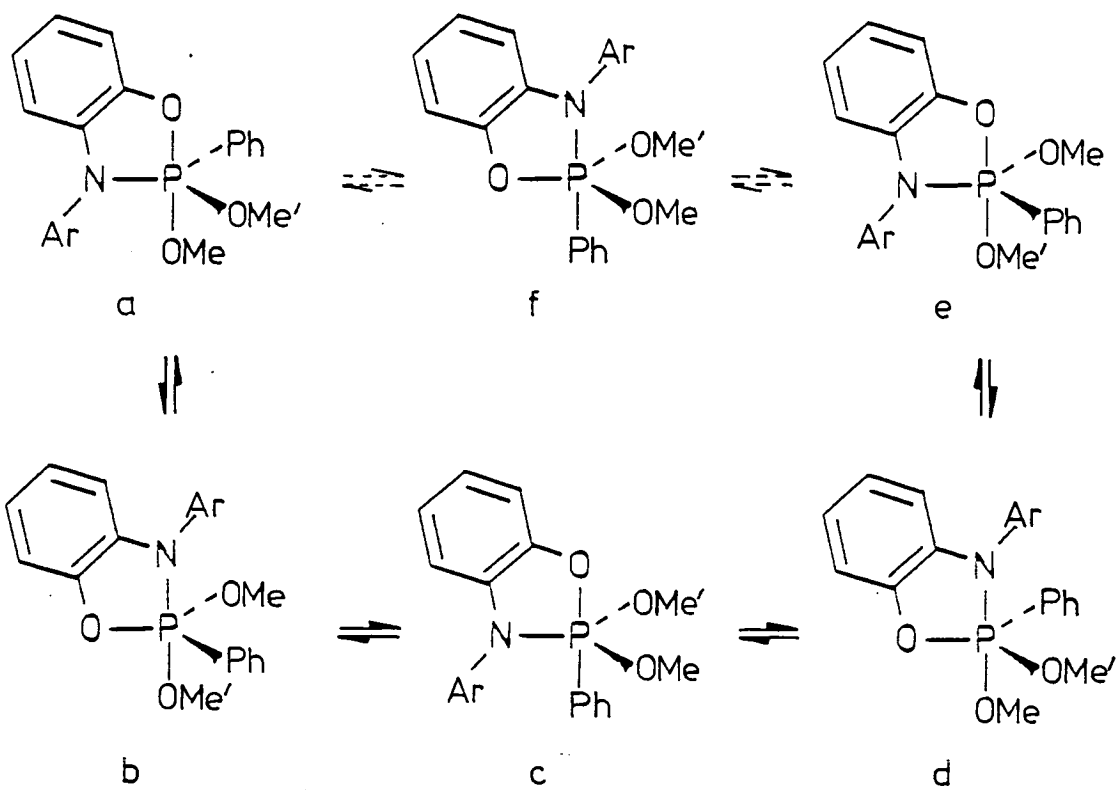


(114)

Assuming a similar frequency separation below coalescence for each phosphorane, then the higher coalescence temperature for (114) suggests a higher energy P.I. process due partly to the carbon atom's lower electronegativity compared with nitrogen, and partly to the additional steric strain associated with eclipsing of phenyl and methoxy groups when carbon is apical.

The above tetraoxyphosphoranes, having three identical exocyclic ligands, can only give rise to one possible high energy TBP (N apical) in a pseudorotation cycle (ignoring any much higher energy process which places the ring diequatorially). By substituting less electronegative exocyclic ligands in place of methoxy, however, the number of alternative high energy TBP structures increases, as do the activation energies required for P.I.

Thus, the ^1H n.m.r. spectra of 2,3-dihydro-2,2-dimethoxy-2-phenyl-3-(2,4,6-trimethylphenyl)-1,3,2-benzoxazaphosph(v)ole (113b, Table 1) showed an averaged $P(OMe)_2$ doublet signal at $+45^oC$ (J_{POMe} 12.3Hz), which broadened and split into two sharp 3-proton doublets as the temperature was reduced to -60^oC. Again, the higher field doublet was assigned to the apical methoxy group on the basis of its smaller coupling constant (J_{POMe} 10.8Hz). The coalescence temperature of -5^oC corresponds to a free energy of activation of 52 kJ mol^{-1} for the two-site exchange process outlined in Scheme 55.



(113b) : Ar = 2,4,6-trimethylphenyl [see Table 1]

(113c) : Ar = 4-methylphenyl ["]

(113d) : Ar = phenyl ["]

Scheme 55

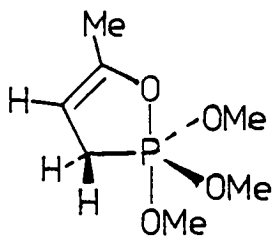
The ground state "frozen" TBPs observed in the low temperature n.m.r. spectra are structures 'a' and 'e' (Scheme 55), as apicophilicity considerations alone would predict. The process by which the separate apical and equatorial methoxy signals of 'a' and 'e' are made magnetically equivalent involves an intermediate high energy TBP cycle analogous to Scheme 54, but differing in the individual energy levels of each TBP. Thus the preferred energy pathway is likely to be via TBPs 'b', 'c', and 'd', rather than via the more direct, but higher energy TBP 'f' (Scheme 55) (TBP 'f' is doubly destabilised by having both amino and phenyl functions in apical positions). The free energy of activation will therefore correspond to the energy required to interconvert TBPs 'a' and 'e' via the three intermediate TBPs 'b', 'c' and 'd'; the highest energy TBP could either be TBP 'c' (phenyl apical), or more likely, TBPs 'b' and 'd', which have an amino function apical.

The large increase in coalescence temperature associated with substituting a phenyl ligand for a methoxy ligand in Schemes 54 and 55 (Ar = 2,4,6-trimethylphenyl) suggests there may be a large steric interaction between the P-phenyl ligand and N-aryl ring during P.I., which increases the activation energy barrier.

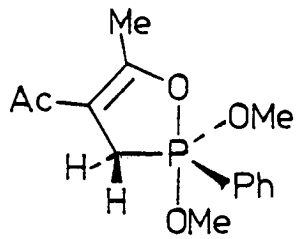
This was supported by observations on the N-4-methylphenyl analogue (113c, Table 1) which showed that, in the absence of the bulky ortho-methyl groups, the free energy barrier for equilibration of methoxy signals is reduced to 43.0kJ mol^{-1} (T_c = -50°C). (For comparison, ΔG^* = 52.0 kJ mol^{-1}; T_c = -5°C, when Ar = 2,4,6-trimethylphenyl). The corresponding

N-phenyl derivative (113d, Table 1) gave ΔG^{*} = 40.9 kJ mol^{-1}, and T_c = -59°C, in accord with the above trend.

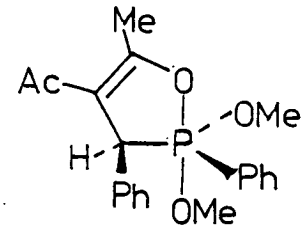
Similar observations have been reported by Gorenstein[50] when two bulky ligands interfere during a P.I. process. Thus, he reported identical free energy barriers for the unhindered tetraoxyphosphorane (115) and trioxyphosphorane (116), but observed a 50% increase in the free energy barrier when one of the ring methylene protons of (116) was replaced by a phenyl group (117). Gorenstein concluded that apical placement of



(115)



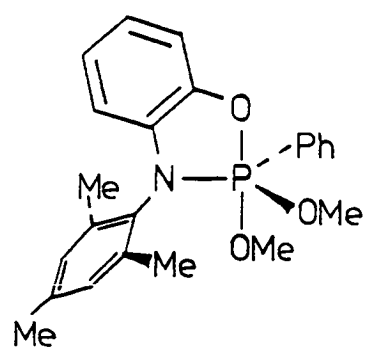
(116)



(117)

the exocyclic phenyl ligand in itself was not particularly unfavourable, but that steric interactions during P.I., exemplified by eclipsing of phenyl groups in (117), were of greater significance than considerations of apicophilicity alone.

Returning to the variable temperature n.m.r. spectra of the 1,3,2-benzoxazaphosph(v)oles, a further coalescence of signals was observed for the ortho-methyl groups of (113b).

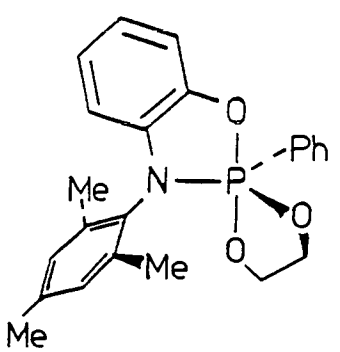


(113b)

The lower coalescence temperature measured for these ortho-methyl resonances (T_c = -32°C) compared with the P-methoxy resonances (T_c = -5°C) might at first be considered as an indication that free N-aryl rotation can occur, with a lower activation energy. When substituting T_cs into the equations to determine ΔG^*, however, it is found that this difference in values of T_c is balanced by the frequency separation term for exchanging signals ($\Delta\nu$), with the net result that the derived free energy barrier for equivalence of ortho-methyl signals is 50 kJ mol^{-1}, compared with 52 kJ mol^{-1} for the P-methoxy signals.

This close similarity in ΔG^* values suggested that the two different coalescences observed may in fact be linked by one and the same P.I. process (Scheme 55) in which the N-aryl ring remains restricted in an essentially orthogonal orientation to the heteroaromatic plane, and the apparent equivalence of ortho-methyl signals is a consequence of the rapid P-methoxy ligand interchange which averages the ortho-methyl environments.

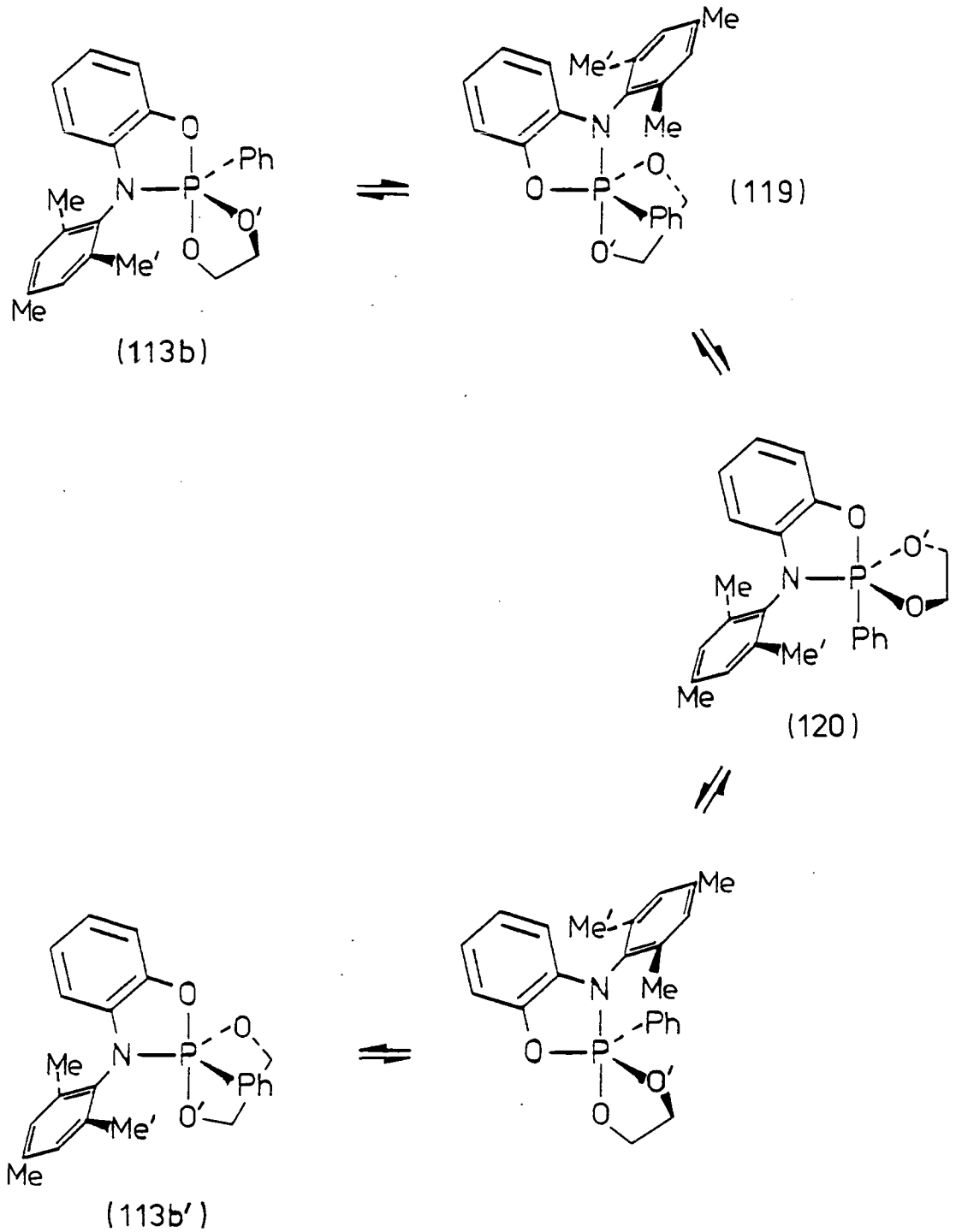
Confirmation that N-aryl rotation does not occur in the above cases arises from the variable temperature n.m.r. studies of the spiro-benzoxazaphosph(v)ole (113e, Table 1).



(113e)

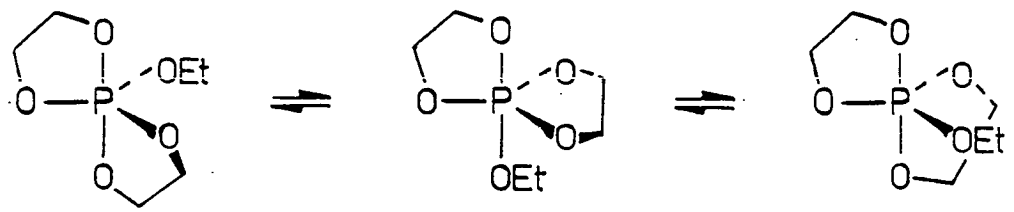
The ortho-methyl groups of (113e) resonate as two separate signals up to high temperature, but coalesce at +175°C to give a free energy of activation of 96 kJ mol^{-1}. These, and other spectral changes described below, can be rationalised by the P.I. process shown in Scheme 56. Thus, the dioxaphospholan ring protons resonate as a complex multiplet at room temperature, changing to a broad doublet as the temperature is lowered to -60°C. This spectral change may indicate rapid interchange of ring termini between apical and equatorial positions above ca. -60°C, by a process which would be expected to require a relatively low activation energy in order to place the N-aryl functions apical (119) (Scheme 56). Such a low energy process [(113b)⇌(119)] maintains different ortho-methyl environments (Me' anti to P-Ph), while partially averaging the ring methylene environments.

The high temperature coalescence of ortho-methyl signals, and the accompanied collapse of the dioxaphospholan ring signals to a broad mound at +192°C, can both be accounted for by a very much higher energy P.I. process requiring diequatorial ring placement as shown in TBP (120) (ΔG^{*} =96 kJ mol^{-1}). Having surmounted this high energy barrier to P.I. at elevated temperatures, an averaged environment is presented to both ortho-methyl groups and ring methylene protons through rapid interconversion of "ground state" TBPs (113b) and (113b').



Scheme 56

A similarly high activation energy was observed by Denney et al.[113] for the oxyphosphorane shown in Scheme 57, where the observed coalescence of ring methylene proton signals at +172°C corresponds to a free energy barrier of ca. 92 kJ mol^{-1}.



Scheme 57

In summary, these dynamic n.m.r. studies of 1,3,2-benzoxazaphosph(v)oles by Cadogan et al. have led to the following conclusions:

(i) The relatively low free energy barrier (ΔG^{*}=ca.40-50 kJ mol^{-1}) to P.I. in the monocyclic phosphoranes is markedly affected by steric influences of substituents in the pendant N-aryl ring.

(ii) A very much higher free energy barrier (ΔG^{*}=ca.90 kJ mol^{-1}) to P.I. exists in spirobicyclic phosphoranes, indicative of diequatorial placement of a five-membered ring in the highest energy intermediate TBP structure.

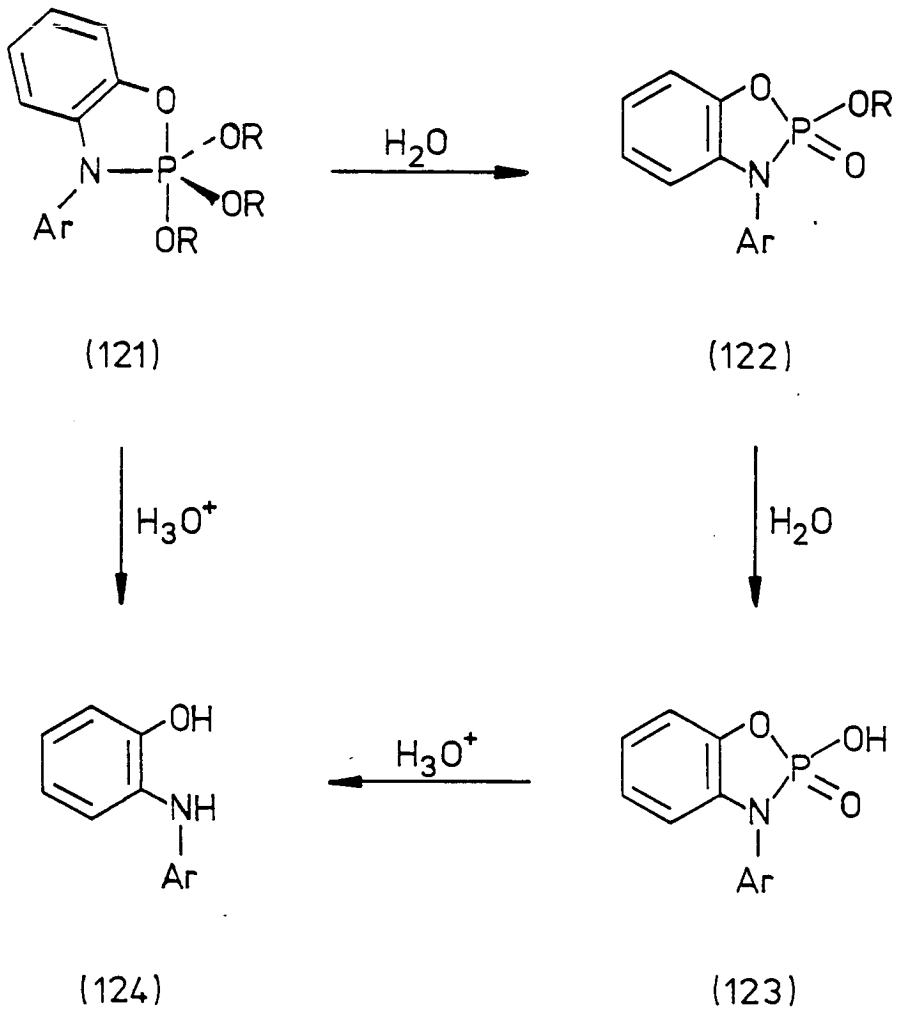
(iii) Free rotation of the N-aryl function does not occur over the range of temperatures observed, indicating that such rotation is severely restricted by steric interactions which constitute a free energy barrier of >90 kJ mol^{-1}.

4. Hydrolysis Reactions of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

It was noted in an earlier chapter (2.7.2) that these 1,3,2-benzoxazaphosph(v)oles can be very susceptible to hydrolysis, and indeed are sometimes difficult to obtain free from hydrolytic impurities, despite rigorous efforts to exclude moisture during their preparation[108].

Initial hydrolysis studies by Tait[109], arising from chromatographic separation of some of the minor products formed in the preparation of these phosphoranes, suggested that step-wise degradation of the pentacoordinate structure can occur, depending on the severity of the hydrolysis conditions. Thus, the 2,2,2-trialkoxy phosphoranes (121) may partially hydrolyse during attempted recrystallisation to give a 2-alkoxy-3-aryl-2,3-dihydro-2-oxo-1,3,2-benzoxazaphosph(v)ole (122), as shown in Scheme 58. An interesting feature of these cyclic phosphoramidates is that, like their pentacoordinate precursors, their ^{1}H n.m.r. spectra exhibit a marked shielding of one of the aromatic protons, indicating that sterically induced orthogonality of the two ring systems is also prevalent in these compounds[110].

Left open to normal atmospheric conditions, loss of the 2-alkoxy ligand can be induced, leading to the cyclic 2-hydroxy product (123). An example of such a compound [(123); Ar = 2,6-dimethylphenyl] has been shown to possess distorted tetrahedral geometry at phosphorus by X-ray crystallographic analysis[111].

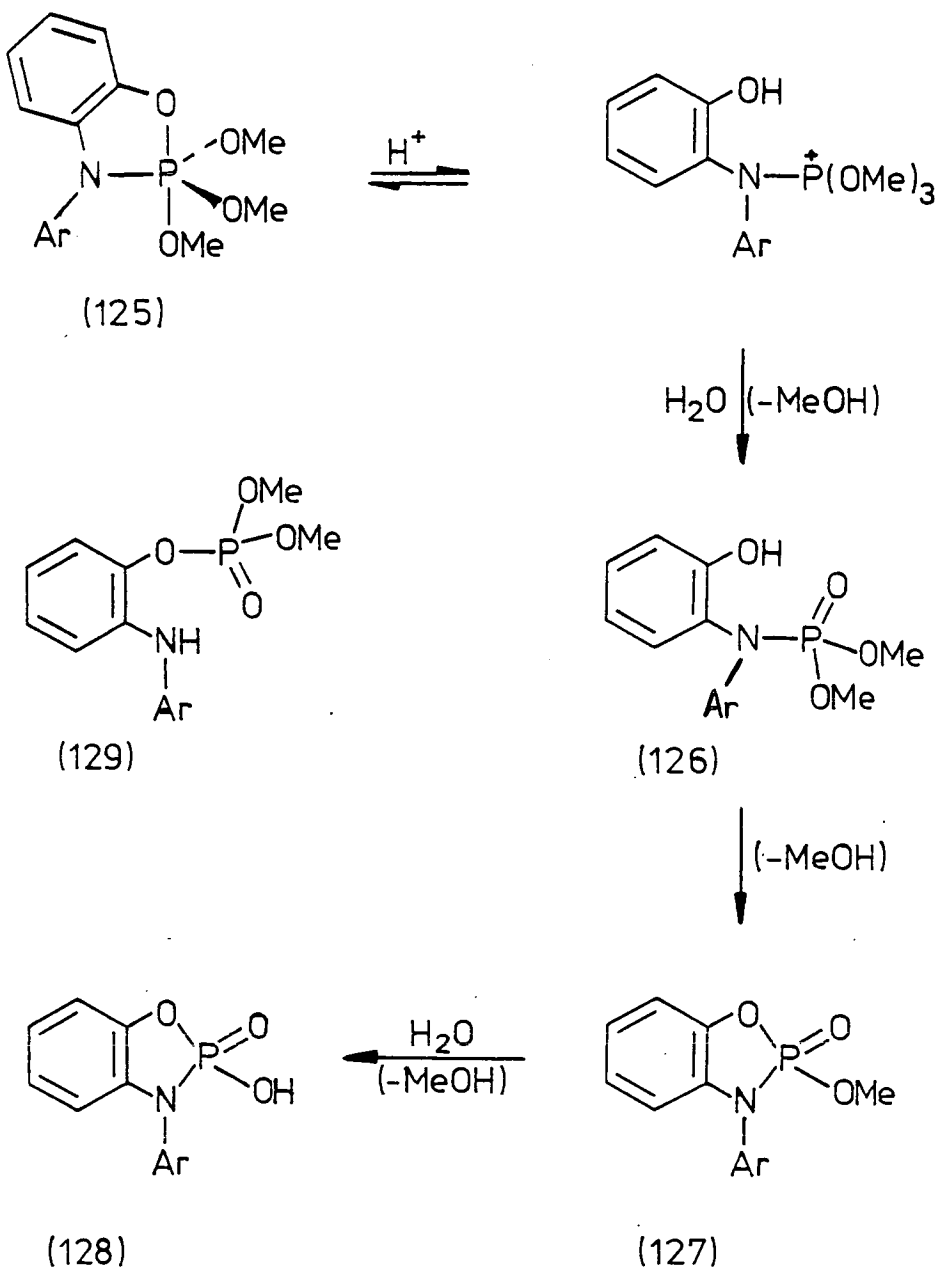


Scheme 58

Complete hydrolysis with the loss of the phosphorus moiety as an acid leads to the formation of 2-hydroxydiphenylamines (124), also known as 2-anilinophenols. This is readily achieved by refluxing the benzoxazaphosph(v)ole or its partial hydrolysis products in dilute ethanolic hydrochloric acid (Scheme 58).

A more detailed study by Cadogan and Grace[114] monitored the hydrolysis of the 2,2,2-trimethoxy-phosph(v)ole (125) under neutral to slightly acidic conditions by ^1H n.m.r. spectroscopy.

This suggested the intermediate formation of an acyclic phenolic ester (126) as the first step in the hydrolysis (Scheme 59). Subsequent ring closure with loss of methanol affords the cyclic phosphoramidate (127), which can then lose a further molecule of methanol to give the isolated cyclic hydroxy monoester (128).

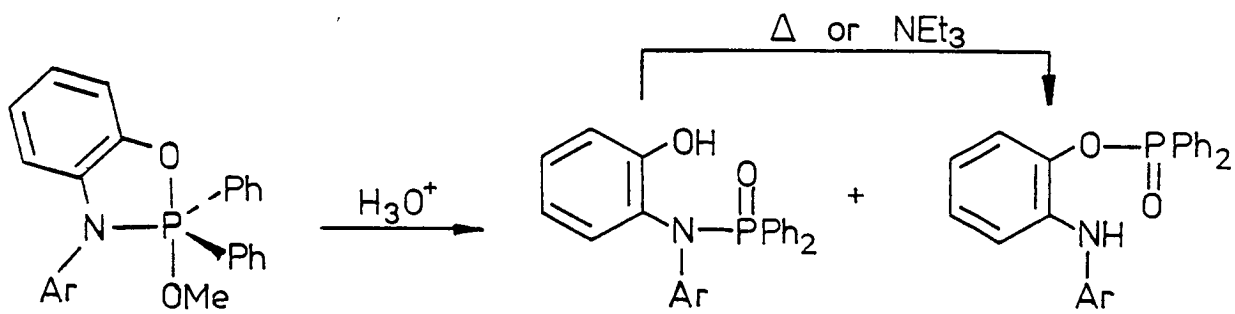


(125) (129) (126) (128) (127)

Scheme 59 Ar = 2,4,6-trimethylphenyl

Although the possible formation of an intermediate acyclic phosphate (129), rather than its isomeric acyclic phosphoramidate (126), cannot be ruled out, evidence from mild acid hydrolysis of related 1,3,2-benzoxazaphosph(v)oles strongly supports the acyclic phosphoramidate structure (126).

Thus, the hydrolysis of phosphoranes derived from methyl diphenylphosphinite (130) in aqueous dioxan containing toluene-4-sulphonic acid gives the N-(2-hydroxyphenyl)-P,P-diphenyl-N-arylphosphinic amides (131) in 94-96% yield, together with small yields (2-4%) of the corresponding isomeric 2-aryl-aminophenyl diphenylphosphinates (132) (Scheme 60).



Ar = 4-methylphenyl

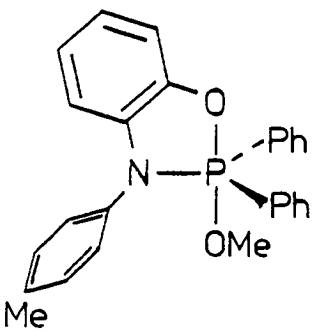
Ar = 2,4,6-trimethylphenyl

Scheme 60

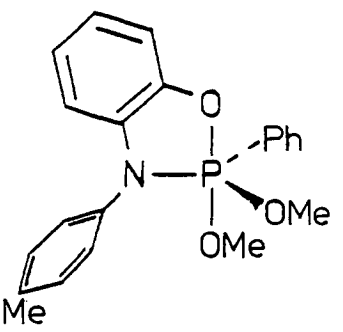
While the minor product does not convert to the major product under the reaction conditions, either heat or base catalysis (Scheme 60) can convert the first formed phosphinic amide (131) to the diphenylphosphinate[114] (132).

Mechanistic studies by Cadogan and Tweddle[115] into the effects of phosphorane structure and reaction pH on the types

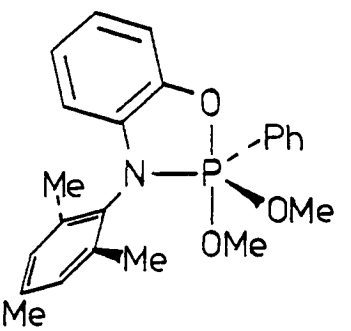
of hydrolysis product obtained, have included the acidic, basic, and neutral hydrolysis reactions of the three differing phosphoranes (133), (134), and (135). These reactions are considered in detail in the following sub-sections.



(133)



(134)

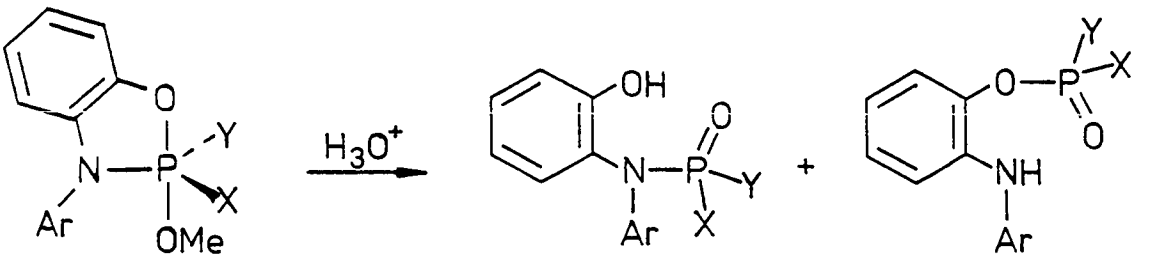


(135)

4.1 Acidic hydrolysis

Hydrolysis reactions were generally monitored by ^{31}P n.m.r. spectroscopy after injecting concentrated hydrochloric acid into an n.m.r. tube containing the phosphorane dissolved in dry dioxan. All the phosphoranes studied, with the exception of the N-2,4,6-trimethylphenyl case (135), gave two products (Scheme 61), the major one being an acyclic phenol (136), with a lesser quantity of an acyclic amine (137), in accord with previously observed acidic hydrolyses[114].

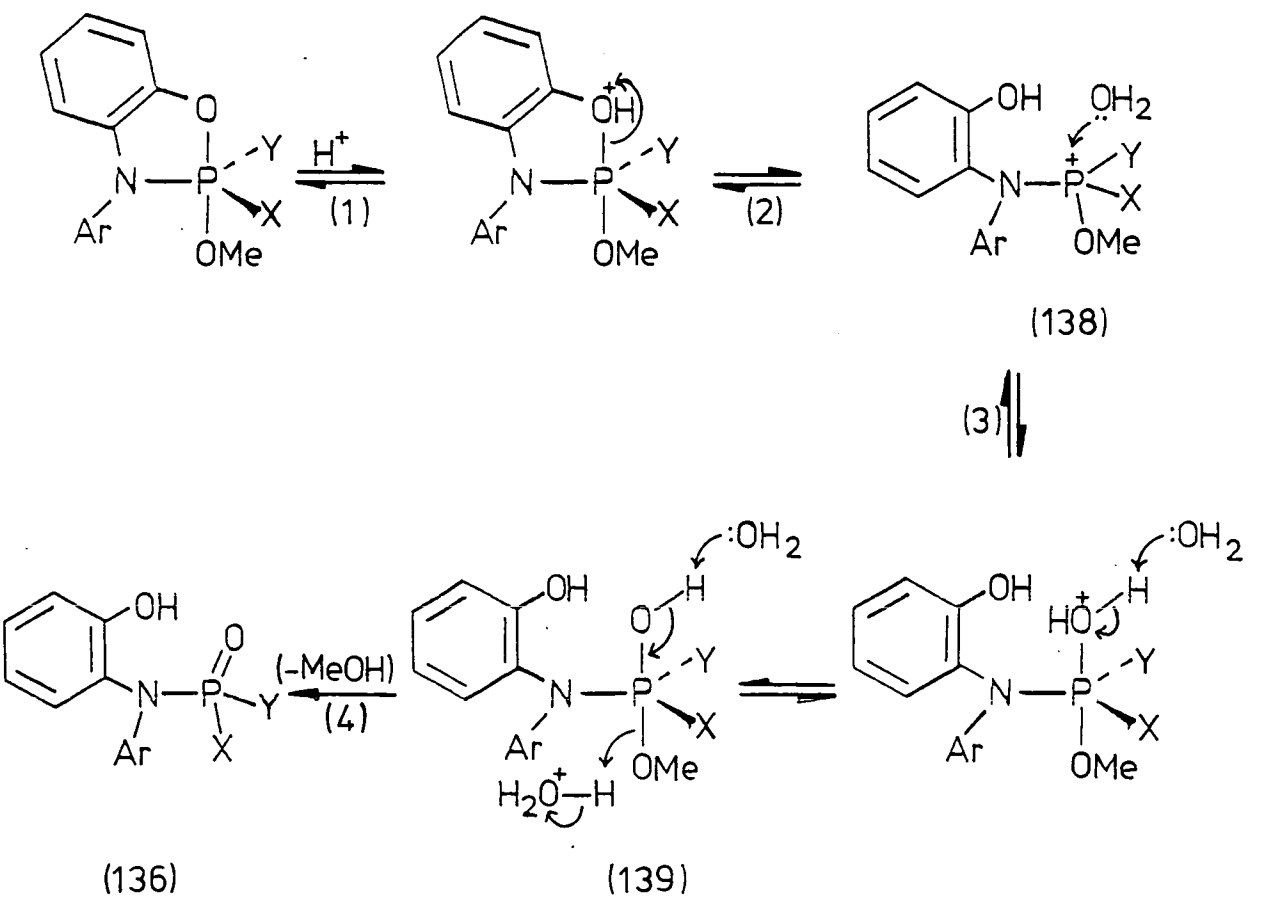
The general mechanism and step wise reaction sequences



(136) (137)

Scheme 61

shown in Scheme 62 can rationally account for the observed reaction products, and at the same time illustrate the widely accepted rules governing reaction at pentacoordinate and tetracoordinate phosphorus centres.



(136) (139)

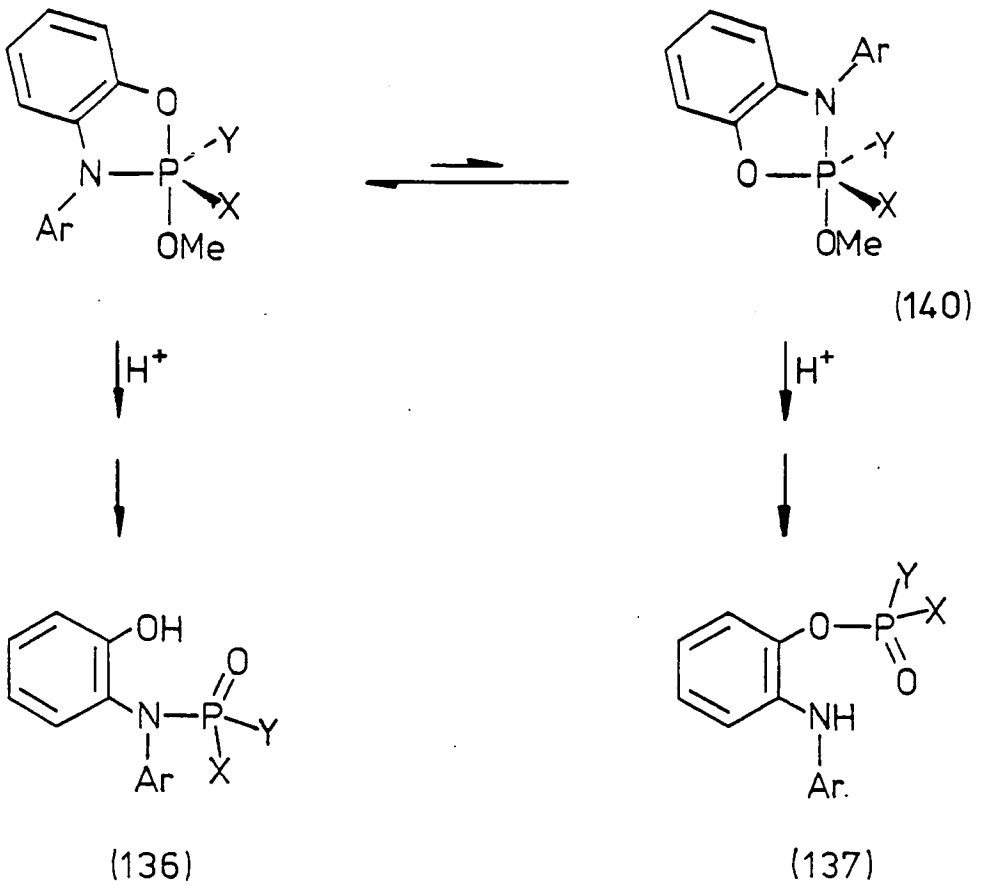
Scheme 62

In step (1), protonation occurs at the position of highest partial negative charge, in this case, at the apical ring oxygen atom. Step (2) then proceeds with endocyclic ring cleavage to give a quasi-phosphonium centre (138). [The alternative protonation of the apical methoxy ligand in step (1) with subsequent loss of methanol would be disfavoured by an increase in ring strain on forming a cyclic phosphonium ion in step (2)].

Step (3) involves attack by water at the "hard" tetrahedral phosphonium centre, opposite the most electronegative group (methoxy) to give a TBP intermediate free to pseudorotate to its lowest energy form (139). Hydroxyphosphoranes are inherently unstable species, and step (4) occurs readily with apical loss of the best leaving group (methoxy) to give the final isolated major product, an acyclic phenol (136).

Isomerisation of this acyclic phenol to the minor isolated product (137) only occurs under basic conditions[114], and hence is unlikely to occur under these acidic hydrolysis conditions. A more likely mechanism for formation of the acyclic amine product involves hydrolysis of the small proportion of the starting phosphorane which may exist as the higher energy TBP isomer (140), as a result of permutational isomerisation. By analogy with Scheme 62, this TBP may first be protonated on the apical endocyclic nitrogen atom to eventually give the acyclic amine (137) (Scheme 63).

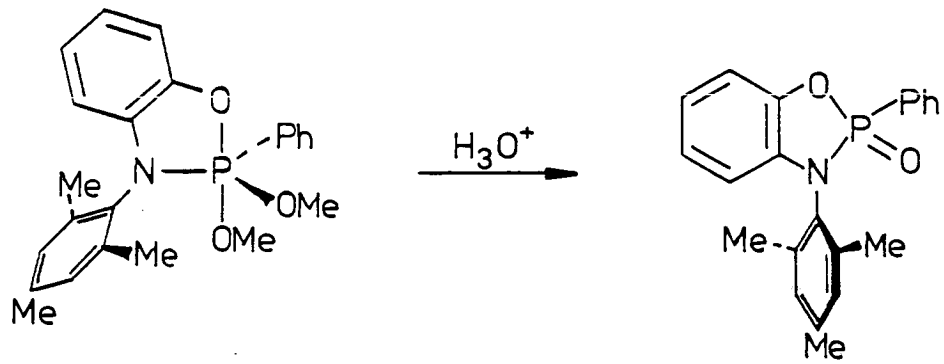
The strength of the acid used in hydrolysis can affect the ratio of major to minor product obtained, reflecting the different basicities of oxygen and nitrogen. Thus, the phosphorane (133) gave a 90% yield of acyclic phenol (136)



Scheme 63

(X=Y=Ph; R=4-methylphenyl) alone using toluene-4-sulphonic acid, but the stronger, less selective hydrochloric acid gave major to minor products in the ratio 7:3.

The previously mentioned exception which does not give acyclic hydrolysis products is the N-2,4,6-trimethylphenyl substituted 1,3,2-benzoxazaphosph(v)ole (135), which gives a cyclic phosphonamidate (141) on acidic hydrolysis (Scheme 64). A possible explanation may lie in the increased steric crowding around the nitrogen atom as its hybridisation changes from sp^2 to sp^3 on forming an acyclic product; this crowding would be particularly exacerbated by the presence of two ortho-methyl groups. Therefore, the acyclic phenol product may form, but rapidly cyclise to (141) with relief of steric



(135) (141)

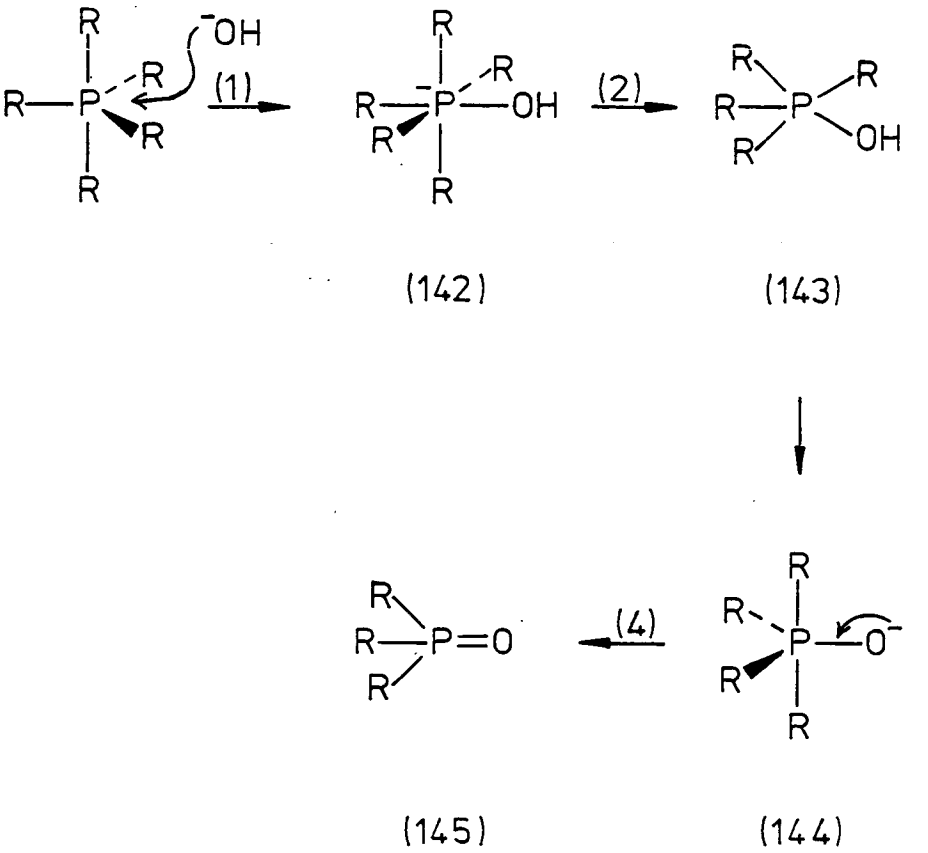
Scheme 64

crowding. Alternatively, protonation and loss of the apical methoxy ligand leading to the cyclic phosphonium centre may be preferred to increased steric crowding at nitrogen. Hydrolysis of the cyclic phosphonium ion with apical loss of the remaining methoxy group would then give the cyclic phosphonamidate (141) directly.

4.2 Basic hydrolysis.

Using ^{31}P n.m.r. spectroscopy to monitor hydrolysis of 1,3,2-benzoxazaphosph(v)oles in aqueous dioxan buffer solutions (pH 13.3), Cadogan and his co-workers[114,115] were able to rationalise the various reaction product types according to the general basic hydrolysis mechanism shown in Scheme 65.

Step (1) occurs with nucleophilc attack by ^-OH at the phosphorus centre to give a hexacoordinate intermediate (142). Attack occurs in the equatorial plane and, providing steric interactions allow access, will occur opposite the most electronegative equatorial ligand to minimise electrostatic repulsion.



Scheme 65

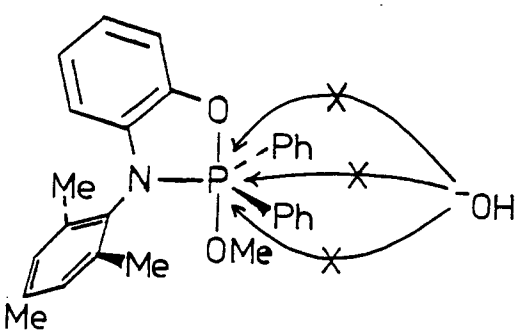
In step (2) the hexaco-ordinate intermediate loses the ligand adjacent to the greatest number of electronegative ligands, to give the most stable topomer of the hydroxy-phosphorane (143).

Deprotonation of the hydroxyphosphorane in step (3) will be followed by pseudorotation if required, in order to give the most stable topomer of the phosphorane (144) which will have the oxygen anion equatorial.

Finally, the phosphorane intermediate (144) will collapse in Step (4), generally via apical loss of the best leaving group, to give the final tetracoordinate product (145).

Applying this general mechanism to some of the 1,3,2-

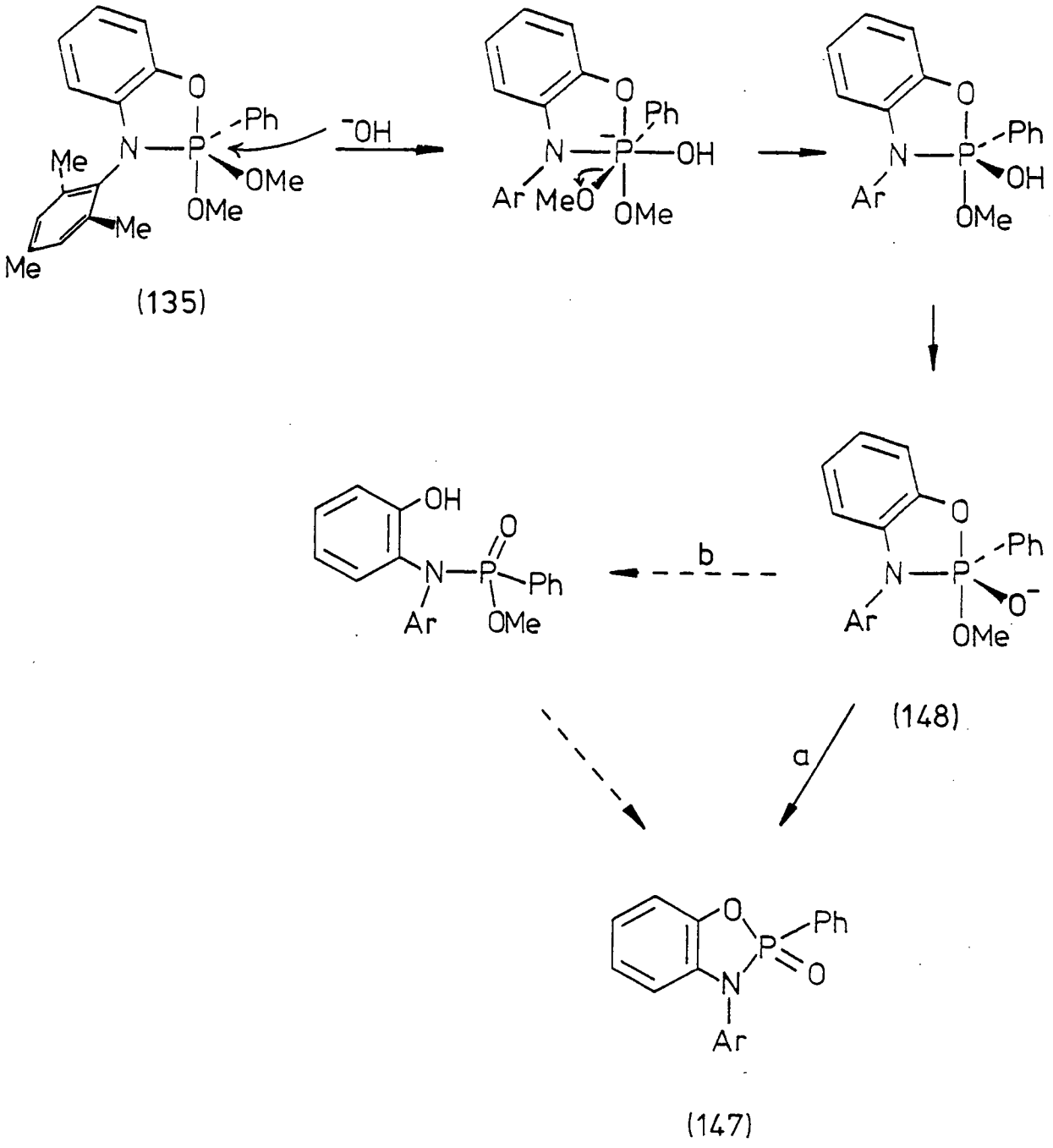
benzoxazaphosph(v)oles already examined under acidic hydrolysis conditions, Cadogan et al. were able to satisfactorily account for all of the various hydrolysis products observed. Thus the phosphorane (133)[115] and its N-mesityl analogue[114] (146) were found to be unreactive towards basic hydrolysis, even at elevated temperatures.



(146)

This stability stems from the high degree of steric crowding which prevents attack by hydroxide ion on phosphorus. Considering (146) in particular, the most favourable position for attack would be expected to be opposite the nitrogen atom, but is hindered by the adjacent bulky equatorial phenyl ligands in this essentially "frozen" TBP structure. Alternative equatorial attack opposite the phenyl ligands is unlikely to occur, because of the low electronegativity and poor leaving group ability of the phenyl ligands, and also because of steric interactions between the phenyl ligands and the ortho-methyl groups of the N-aryl ring.

When one of the phenyl ligands is replaced by a less bulky and more electronegative methoxy ligand, the resultant phosphorane (135) is hydrolysed rapidly under basic conditions to give the cyclic phosphonamidate (147), in accord with the predicted mechanism shown in Scheme 66.



Ar = 2,4,6-trimethylphenyl

Scheme 66

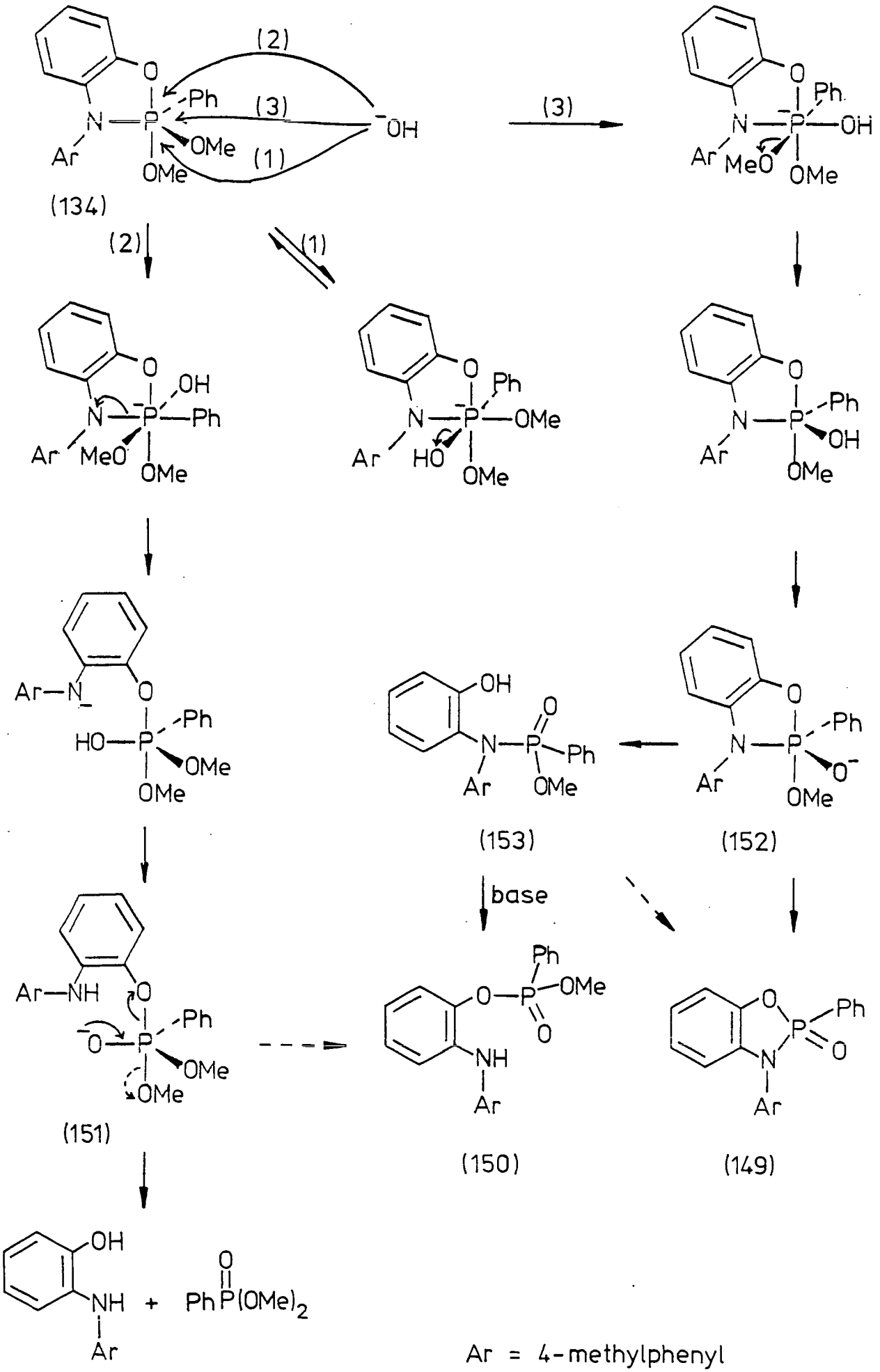
Attack from opposite the most electronegative equatorial ligand (methoxy) is still sterically hindered by adjacent phenyl and N-aryl ring systems, but the smaller methoxy ligand permits hydroxyl ion attack opposite nitrogen, leading to the

anionic phosphorane intermediate (148). As in the acidic hydrolysis of the same phosphorane (Scheme 64), the final cyclic phosphonamidate (147) could arise either directly from (148) by loss of the apical methoxy leaving group (route 'a', Scheme 66), or alternatively by fission of the endocyclic apical P-O bond to give an acyclic phenol (route 'b') which subsequently cyclises to relieve steric crowding around the sp^3 hybridised nitrogen atom.

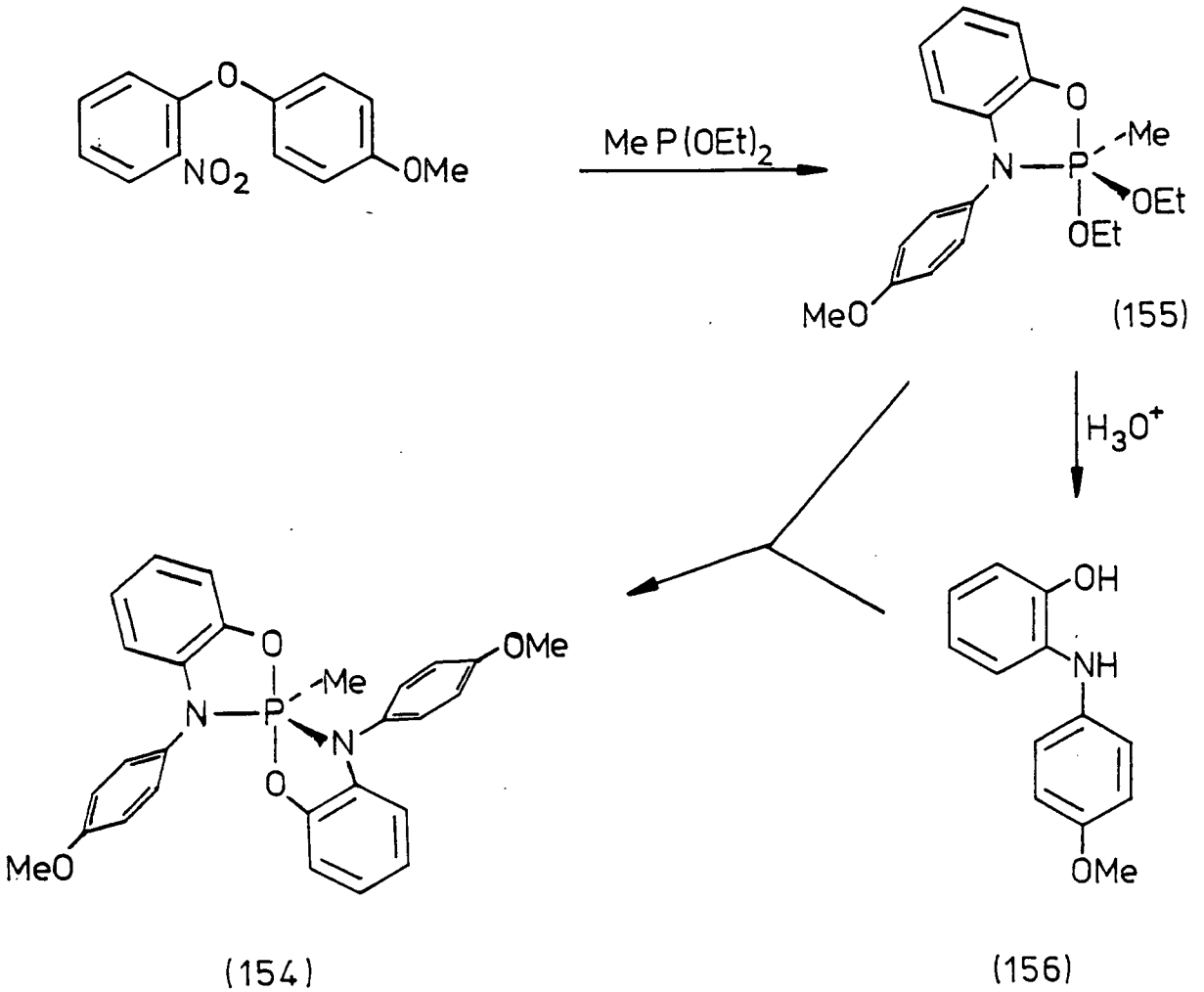
The large number of hydrolysis products observed for the third phosphorane studied (134) is a consequence of its less crowded structure, having no ortho-substituents in the N-aryl ring and only one bulky phenyl ligand in a more fluxional TBP. Thus hydroxide ion is capable of attacking in either of three positions, as shown in Scheme 67.

The hydrolysis products observed by ^{31}P n.m.r. spectroscopy comprise the cyclic phosphonamidate (149), dimethyl phenylphosphonate, and an acyclic product (150), in the ratio 1:1:3. Attack opposite the phenyl ligand [route (1)] is least favoured on steric and electronegativity grounds, and in any case would give a hexacoordinate intermediate which collapses by loss of hydroxyl ligand to reform the starting material (134).

Attack by route (2) is sterically more likely than for the "ortho-blocked" phosphoranes, and would lead to an acyclic anionic phosphorane intermediate (151) which would be expected to collapse by loss of the best apical leaving group (ArO) to give dimethyl phenylphosphonate plus an anilinophenol. If apical methoxy were to be the leaving group, a small amount of the acyclic amine product (150) would be formed.


(2)
(3)
(1)
Ph
OMe
OMe
OH
Ar
(134)
(3)
(2)
(1)
OH
Ph
OMe
MeO
HO
Ar—N
HO—P
Ar—NH
O⁻—P
(151)
(153)
(152)
base
(150)
(149)
NH
Ar
PhP(OMe)2
Ar = 4-methylphenyl

Scheme 67



(154) (156)

Scheme 68

Hydroxide attack opposite nitrogen is probably the most favoured overall [route (3)], from both steric and electronic considerations, leading to a deprotonated phosphorane intermediate (152) which might be expected to collapse to give a mixture of the cyclic phosphonamidate (149) and an acyclic phenol (153). Under the basic reaction conditions, rearrangement of this phenol to the isomeric acyclic amine product (150) is likely to occur.

4.3 Neutral hydrolysis

Hydrolysis reactions of 1,3,2-benzoxazaphosph(v)oles in neutral aqueous dioxan have given products which can be rationalised in terms of either mechanism, acidic or basic, described above, without invoking any additional reaction pathways[115]. Examples of neutral hydrolyses will not therefore be described here.

4.4 Miscellaneous hydrolysis reactions

An interesting mechanism involving a ligand exchange reaction between a phosphorane and its hydrolysis product has been proposed[108] to account for the formation of the spirophosphorane (154) in 20% yield from the deoxygenation of 4-methoxyphenyl 2-nitrophenyl ether using diethyl methylphosphonite (Scheme 68). Transesterification is postulated as occurring between the first formed monocyclic phosphorane (155), and its anilinophenol hydrolysis product (156).

SECTION II

EXPERIMENTAL

Abbreviations and Symbols

b.p.	boiling point
m.p.	melting point
t.l.c.	thin layer chromatography
g.l.c.	gas liquid chromatography
h.p.l.c.	high performance liquid chromatography
l.p.c.	low pressure chromatography
n.m.r.	nuclear magnetic resonance
s; d; t; q; m	singlet; doublet; triplet; quartet; multiplet
J	coupling constant
δ	chemical shift
p.p.m.	parts per million
br	broad
i.r.	infrared
ν	wavenumber (cm^{-1})
M^+	mass of molecular ion
m/e	mass to charge ratio
m^*	metastable peak
h; min	hours; minutes
mol	moles
mmol	millimoles

Instrumentation

Melting points of new compounds were obtained on a Kofler hot-stage microscope for stable compounds, and on a Gallenkamp melting point apparatus in a 'Parafilm'-sealed capillary tube for atmospherically unstable compounds. For other compounds, the Gallenkamp apparatus was normally used.

Microanalyses were carried out on a Perkin-Elmer Elemental Analyser 240 by Mr. J. Grunbaum, University of Edinburgh.

Infrared spectra were recorded on a Perkin-Elmer 157G Grating Infrared spectrophotometer. Unless otherwise noted, chloroform solution spectra were obtained, using matched cells with sodium chloride windows (path length 0.1 mm). Polystyrene film was used to give a reference peak, ν_{max} 1603 cm^{-1}. Major and characteristic minor peaks are given, and assigned if possible.

Proton (^{1}H) nuclear magnetic resonance spectra were recorded on a Varian EM360 spectrometer operating at 60MHz, or on a Varian HA100 instrument operating at 100MHz. Chemical shift values were recorded on the δ scale in p.p.m. relative to tetramethylsilane as internal standard (δ=0). Unless otherwise noted, the solvent used was deuteriochloroform. In particular spectra in which two distinct diastereomeric signals arise from one group, both resonances are recorded together, and the proportion of each isomer noted.

Phosphorus (^{31}P) n.m.r. spectra were obtained on a Varian XL100 instrument or on a JEOL FNM-FX60Q instrument. Chemical shift values were measured in p.p.m. on the δ scale

relative to 85% phosphoric acid as internal standard (δ=0); shifts to high frequency are positive, whereas shifts to low frequency are assigned negative values. All spectra were proton noise-decoupled and unless otherwise noted, deuteriochloroform was used as solvent. Mixtures of compounds were recorded by giving the percentage peak height in brackets following the chemical shift value of each peak.

Mass spectra and exact mass measurements were recorded on an A.E.I. MS902 spectrometer. The parent ion and major fragmentation peaks are given, together with the percentage peak heights and any metastable peaks in brackets. A V.G. Micromass 12 spectrometer, coupled to a Pye 104 Gas Chromatograph was used to obtain spectra by g.l.c./mass spectrometry.

Alumina (Laporte Industries, Type H) was used for column chromatography and dry column chromatography. For thin layer chromatography (t.l.c.), 5 x 200 mm glass plates covered by 0.3 mm alumina (Merck, Aluminium oxide G, type E), with added fluorescent indicator (M. Woelm, Eschwege, Germany), were used. Gas liquid chromatography (g.l.c.) was carried out on a Pye 104 Gas Chromatograph fitted with a flame ionisation detector; a 7 feet by 1/8 inch 1% SE30 column was found to be most useful. The technique of low pressure chromatography (l.p.c.) was employed for difficult separations, using a 15 x 1000 mm alumina column (Merck, aluminium oxide 90 active, 90μ). Analytical scale high performance liquid chromatography (h.p.l.c.) was carried out using a 5 x 250 mm alumina column (Spherisorb A5Y, 5μ).

Optical rotations were measured using a Perkin-Elmer 141 Polarimeter operating at 589.3 nm (sodium D line).

Solutions were made up in super-dry ethanol and inserted into a quartz cell, path length 1 dm, for measurement. Angles of rotation are expressed as specific rotations $[\alpha]_D^t$ or as molecular rotations $[M]_D^t$, as defined by Vogel[116].

2. Preparation of Materials

2.1 General Materials

(i) Solvents. Unless denoted 'dry' or 'super-dry', commercially available common solvents were used without further treatment.

Dry solvents: light petroleum (petrol, b.p. 40-60°) was redistilled and dried over sodium wire before use. Diethyl ether was dried over sodium wire before use, as were cyclohexane, tetrahydrofuran (THF), 1,4-dioxan, benzene, toluene and cumene. Dichloromethane and chloroform were passed through an alumina column (Activity I), stored over anhydrous calcium chloride and redistilled on to dry molecular sieve before use.

Super-dry solvents: these were prepared by heating the appropriate dry solvent under reflux for several hours with lithium aluminium hydride and distilling on to dry molecular sieve. This procedure was employed to obtain super-dry petrol, ether, dioxan, benzene, toluene and cumene. 'Super-dry' ethanol and 'genuine absolute' methanol were prepared as described by Vogel[117] and stored over dry molecular sieve.

(ii) Diethylamine and triethylamine were dried by storing over sodium hydroxide pellets.

(iii) 1,2-Ethanediol and sec-butanol were stored over anhydrous sodium sulphate and anhydrous magnesium sulphate respectively, and redistilled on to dry molecular sieve before use.

2.2 Aryl 2-Nitrophenyl Ethers

These compounds were prepared by the method of Wright and Jorgensen,[118] as exemplified in the following two cases:

(i) A mixture of 2-methoxyphenol (22.4 g, 0.18 mol), 1-chloro-2-nitrobenzene (23.7 g, 0.15 mol), potassium hydroxide pellets (8.4 g, 0.15 mol) and dimethyl sulphoxide (200 ml) was stirred at 90° for 24 h, under an atmosphere of nitrogen. The dark solution was poured into 2N hydrochloric acid (300 ml) containing ice chips (100 g) and stirred vigorously to induce crystallisation. The resulting solid was filtered off and recrystallised from methanol to give pale yellow crystals of 2-methoxyphenyl 2-nitrophenyl ether (27.3 g, 74%), m.p. 63.5-64.5° (lit.,[119] 63°).

(ii) 2-Nitrophenyl 2-tert-butylphenyl ether was prepared as an oil by the same method after heating for 46 h. When stirring failed to induce crystallisation, the dark oil was extracted into ether and dried over anhydrous magnesium sulphate. After distilling two low-boiling minor fractions, identified as unreacted starting materials by g.l.c. (2% SE30, 200°), the required product was distilled as a viscous orange oil (69%), b.p. 125-127°/0.1 mm (Found: C, 70.6; H, 6.0; N, 5.35. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%), ν_{max} 1530 and 1350 cm^{-1} (NO_2), δ 1.38 (9H, s, t-Bu), and 6.7-8.0 (8H, m, aromatic), m/e 271 (M^+, 83), 256 [83, m^*

241.8 (271→256)], 210 [23, m* 172.3 (256→210)], 196 (41) and 195 [100, m* 148.5 (256→195)].

The following compounds were also prepared by this method; 4-methoxyphenyl 2-nitrophenyl ether (69%), m.p. 75-78° (lit.,[120] 77°); 2-methylphenyl 2-nitrophenyl ether (80%), b.p. 127-133°/0.05 mm (lit.,[121] b.p. 125°/0.04 mm); 3-methylphenyl 2-nitrophenyl ether (65%), b.p. 122-132°/0.1 mm (lit., b.p.[121] 130°/0.01 mm); 2-naphthyl 2-nitrophenyl ether (76%), m.p. 59-60° (lit.,[122] 59.5-60.5°); 1-naphthyl 2-nitrophenyl ether[123] (67%), m.p. 57-59° (Found: C, 72.4; H, 4.2; N, 5.2. $C_{16}H_{11}NO_3$ requires C, 72.5; H, 4.2; N, 5.3%), ν_{max} 1530 and 1355 cm^{-1} (NO_2), δ6.7-8.2 (11H, m, aromatic), m/e 265 (M^+, 65), 143 (100), and 115 (48); 2-nitrophenyl 3-tert-butylphenyl ether (71%), b.p. 138-144°/0.2 mm (Found: C, 70.7; H, 6.45; N, 5.15. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%), ν_{max} 1530 and 1355 cm^{-1} (NO_2), δ1.28 (9H, s, t-Bu) and 6.7-8.0 (8H, m, aromatic), m/e 271 (M^+, 75), 256 (100), 195 (22), and 122 (77).

Thanks are due to D.S.B. Grace who prepared 4-methylphenyl 2-nitrophenyl ether and 2,4-dimethylphenyl 2-nitrophenyl ether, and to B.S. Tait who prepared 2,6-dimethylphenyl 2-nitrophenyl ether and 2,6-dimethoxyphenyl 2-nitrophenyl ether.

2.3 Tervalent Phosphorus Compounds

Trimethyl phosphite and tri-n-butylphosphine were dried over sodium wire and distilled on to dry molecular sieve under an atmosphere of dry nitrogen. Commercially available samples of phosphorus trichloride and dichlorophenylphosphine were used without further purification, as was diethyl methyl-

phosphonite, which was supplied by the Chemical Defence Establishment, Porton Down.

Dimethyl phenylphosphonite was prepared by reaction of dichlorophenylphosphine (71.6 g, 0.4 mol) with super-dry methanol (32 g, 1.0 mol) in the presence of triethylamine (102 g, 1.0 mol) and dry ether (650 ml), as detailed by D.S.B. Grace[124]. The product was obtained as a colourless oil (49.9 g, 73%), b.p. 90°/8.5 mm (lit.,[125] b.p. 101-102°/15 mm).

2-Phenyl-1,3,2-dioxaphospholan was prepared by the method of Mukaiyama et al.:[126] dichlorophenylphosphine (35.8 g, 0.2 mol) was reacted with 1,2-ethanediol (12.4 g, 0.2 mol) in the presence of triethylamine (40.4 g, 0.4 mol) in dry benzene (350 ml) to give 2-phenyl-1,3,2-dioxaphospholan as a colourless oil (29.6 g, 88%), b.p. 72-74°/0.3 mm (lit.,[126] b.p. 79-80°/0.8 mm).

Dimethylphenylphosphine was prepared by a modification of the method described by Kaplan and Thornton[127] for d^6-dimethylphenylphosphine. Thus, dichlorophenylphosphine (64.4 g, 0.36 mol) in dry ether (180 ml) was added very cautiously under a dry nitrogen atmosphere to a stirred solution of methyl magnesium iodide (ca. 0.9 mol) in ether (350 ml) maintained at -50°. After heating under reflux for 0.5 h, excess diethylamine was added to quench any unreacted Grignard reagent, and the reaction mixture was filtered through alumina to remove insoluble inorganic salts. The filtrate was evaporated and distilled in vacuo to give dimethylphenylphosphine as a colourless oil (30.3 g, 61%), b.p. 52-57°/5 mm (lit.,[128] b.p. 65°/8 mm).

Methylphenylchlorophosphine was prepared in an overall

yield of 26% in the following three-stage synthesis: (i) N,N-diethylaminophenylchlorophosphine was prepared from dichlorophenylphosphine and diethylamine by the method of Seidel and Issleib[129] in 78% yield, b.p.90-94°/0.35 mm (lit.,[130] b.p. 82-84°/0.05 mm). (ii) In an adaptation of the method of Wagner et al.,[131] ethereal methyllithium[132] was added slowly to a stirred solution of N,N-diethylaminophenylchlorophosphine in dry ether maintained at -78° under an atmosphere of dry nitrogen. After replacing the ether with dry benzene to facilitate precipitation of the lithium salts, the reaction mixture was filtered, the filtrate evaporated, and the yellow, pasty residue distilled to give a colourless oil identified as N,N-diethylaminomethylphenylphosphine (44%), b.p.76-80°/1.0 mm, ν_{max} (neat) 1430 (PPh), 1370, 1290 (PMe), 1180, 1020 and 925 cm^{-1}, δ 1.05 (6H, t, $PN(CH_2\underline{CH_3})_2$, J_{HH} 7Hz), 1.46 (3H, d, PMe, J_{PH} 6Hz), 2.96 (4H, dq, $PN(\underline{CH_2}CH_3)_2$, J_{HH} 7Hz, J_{PH} 10Hz), and 7.26 (5H, m, aromatic), ^{31}P δ+48.7, m/e 195 (M^+, 100), 180 [100, m^*166.2 (195→180)], 152 (40), 123 (70), 109 (70) and 104 [28, m^* 55.5 (195→104)]. (Since this aminophosphine appears to have been wrongly reported in the literature as having b.p.102-110°/0.2 mm, m.p. 70-74°[133], it was later prepared by an alternative route, from methylphenylchlorophosphine and diethylamine, to give a colourless oil, b.p. 63-65°/0.4 mm, with n.m.r. data identical to that of the above compound).

The aminophosphine was characterised by boiling under reflux in benzene with an equimolar quantity of sulphur. After 1 h, solvent was evaporated and the residue distilled to give N,N-diethylaminomethylphenylphosphine sulphide as a

colourless oil (100%), b.p.110-120°/0.1 mm (oven temperature) (Found: C, 57.9; H, 7.9; N, 6.3. $C_{11}H_{18}NPS$ requires C, 58.1; H, 8.0; N, 6.2%), ν_{max} (neat) 1435 (PPh), 1290 (PMe), 1105, 1020, 705, 695, and 680 cm^{-1} (P=S), δ 1.10 (6H, t, $PN(CH_2\underline{CH_3})_2$, J_{HH} 7Hz), 2.02 (3H, d, PMe, J_{PH} 13Hz), 3.03 (4H, dq, $PN(\underline{CH_2}CH_3)_2$, J_{HH} 7Hz, J_{PH} 12Hz), and 7.3-8.2 (5H, m, aromatic), ^{31}P δ+65.8, m/e 227 (30), 156 (42), 155 (44), 141 [21, m^* 127.4 (156→141)], and 72 [100, m^* 22.8 (227→72)]. (iii) Reaction of N,N-diethylaminomethylphenylphosphine with ethereal hydrogen chloride by the method of Duff and Shaw[134] gave methylphenylchlorophosphine (82%) b.p. 83-84°/9 mm (lit.,[135] b.p.66-67°/2 mm).

In an alternative synthesis of methylphenylchlorophosphine, dimethylamine and dichlorophenylphosphine were reacted by the method of Wagner *et al*[131] to give N,N-dimethylaminophenylchlorophosphine (80%), b.p.65-73°/0.18 mm (lit.,[131] b.p. 78°/2 mm), which was then reacted with methyllithium to give a colourless oil identified as N,N-dimethylaminomethylphenylphosphine (63%), b.p.69-71°/3 mm (lit.,[131] b.p. 66-70°/1 mm), δ1.42 (3H, d, PMe, J_{PH} 6Hz), 2.58 (6H, d, $PN(Me)_2$, J_{PH} 10Hz), and 7.3 (5H, m, aromatic).
(NB. This compound has also been wrongly reported in the literature as having b.p.102-110°/0.2 mm m.p.70-74°).[133a] Finally, methylphenylchlorophosphine was obtained in 68% yield on reaction of N,N-dimethylaminomethylphenylphosphine with hydrogen chloride.[134]

Methylphenylchlorophosphine was used to prepare several phosphinous acid esters by the general method described by Quin and Anderson.[136] Thus, sec-butanol (9.3 g, 0.125 mol) and

methylphenylchlorophosphine (15.8 g, 0.10 mol) were reacted under a dry nitrogen atmosphere at 0° in the presence of triethylamine (12.5 g, 0.125 mol) and dry ether (100 ml). Subsequent work-up gave sec-butyl methylphenylphosphinite as a colourless oil (15.4 g, 79%), b.p.73°/2.2 mm (Found: M^+, 196.100 709. $C_{11}H_{17}OP$ requires M, 196.101 697), δ (diastereomers, 1:1) 0.83 and 0.93 (3H, 2 x t, $CH_2\underline{CH_3}$, J_{HH} 7.5Hz), 1.14 and 1.24 (3H, 2 x d, $CH\underline{CH_3}$, J_{HH} 6Hz), 1.42 (3H, d, PMe, J_{PH} 6Hz), 1.3-1.8 (2H, m, $\underline{CH_2}CH_3$), 3.76 (1H, m, POCH), and 7.2-7.7 (5H, m, aromatic). ^{31}P δ+108.4 and +109.8. The phosphinite was boiled under reflux in dry benzene for 1 h with an equimolar quantity of sulphur. Evaporation of the solvent and distillation of the residue gave sec-butyl methylphenylphosphinothionate as a colourless oil (100%), b.p. 100-110°/0.2 mm (oven temperature) (Found: C, 57.9; H, 7.3. $C_{11}H_{17}OPS$ requires C, 57.9; H, 7.5%), ν_{max} (neat) 1440 (PPh), 1295 (PMe), 1115, 1030, 950 (P-O-C), 745, 710 and 695 cm^{-1} (P=S), δ (diastereomers, 1:1) 0.74 and 0.94 (3H, 2 x t, $CH_2\underline{CH_3}$, J_{HH} 7.5Hz), 1.01 and 1.33 (3H, 2 x d, $CH\underline{CH_3}$, J_{HH} 6Hz), 1.3-1.8 (2H, m, $\underline{CH_2}CH_3$), 1.96 (3H, 2 x d, PMe, J_{PH} 13.5Hz), 4.54 (1H, m, POCH), and 7.3-8.1 (5H, m, aromatic), ^{31}P δ+84.6, m/e 228 (M^+, 26), 173 (100, m^* 131.3 (228→173)], 172 (15), 157 [35, m^* 143.3 (172→157)], 156 (23), 155 (30), and 139 [20, m^* 111.7 (173→139)].

By the same method, reaction of super-dry methanol with methylphenylchlorophosphine gave methyl methylphenylphosphinite[137] (73%), b.p. 53°/3 mm, δ 1.46 (3H, d, PMe, J_{PH} 6Hz), 3.45 (3H, d, POMe, J_{PH} 13Hz), and 7.2-7.6 (5H, m, aromatic), ^{31}P δ+119.0. This was characterised as the phosphinothionate (100%), b.p.

80-90°/0.2 mm (oven temperature) (lit.,[138] b.p. 80-85°/0.4 mm). (Found: C, 51.8; H, 5.9. $C_8H_{11}OPS$ requires C, 51.6; H, 5.95%), ν_{max} (neat) 1440 (PPh), 1295 (PMe), 1110, 1035, 895 (P-O-C), 745, 715 and 690 cm^{-1} (P=S), δ[139] 1.98 (3H, d, PMe, J_{PH} 14Hz), 3.52 (3H, d, POMe, J_{PH} 14Hz), 7.50 (3H, m, aromatic), and 7.75-8.0 (2H, m, aromatic), ^{31}P δ+90.0, m/e 186 (M^+, 100), 171 (28), 156 [62, m^* 130.8 (186→156)], 141 [21, m^* 127.4 (156→141)], 139 (21).

Dimethyl phosphorochloridite was prepared by the method of Ramirez *et al.*[140] from phosphorus trichloride and trimethyl phosphite as a colourless fuming oil, b.p. 101-104°/760 mm (lit., b.p. 96-108°/760 mm).

The preparation of dimethyl 2,6-dimethoxyphenylphosphonite was adapted from a synthesis of dialkyl arylphosphonites described by Wolf *et al.*,[141] and developed in the following series of reactions: 1,3-dimethoxybenzene was reacted with phenyllithium[142] by the method described by Wittig[143] to give 2,6-dimethoxyphenyllithium. Subsequent addition of 1,2-dibromoethane to the organolithium reagent by the method of Lettre and Jahn[144] afforded 2,6-dimethoxybromobenzene (66%), m.p. 94-95° (lit.,[144] 94-95°), from which the Grignard reagent, 2,6-dimethoxyphenylmagnesium bromide, was prepared as a dark solution in dry THF by the method of Eade *et al.*[145] In an extension of the method of Petrov and Nifant'ev,[146] the Grignard solution (*ca* 0.15 mol) was added dropwise with vigorous stirring under a dry nitrogen atmosphere to a mixture of dimethyl phosphorochloridite (19.3 g, 0.15 mol), dry pyridine (30 ml) and dry ether (200 ml) maintained at a temperature of *ca* -60°. The precipitated salts were filtered off on a layer

of Celite, solvent was evaporated from the filtrate, and fresh dry ether was added to the residue to precipitate any remaining salts. After a further filtration, ether was removed and the residue distilled on Kugelrohr apparatus to give dimethyl 2,6-dimethoxyphenylphosphonite as a colourless oil (14.3 g, 42%), b.p. 90-100°/0.1 mm (oven temperature), δ3.66 (6H, d, 2POMe, J_{PH} 12Hz), 3.80 (6H, s, 2ArOMe), 6.4-6.65 (2H,m, aromatic), and 7.1-7.45 (1H, m, aromatic), ^{31}P δ+173.9. The phosphonite was characterised by reaction with sulphur to give glistening white needles of dimethyl 2,6-dimethoxyphenylphosphonothionate (100%), m.p. 95° (from petrol/ether) (Found: C, 46.0; H, 5.7. $C_{10}H_{15}O_4PS$ requires C, 45.8; H, 5.8%), ν_{max} (Nujol) 1430 (PPh), 1255 (ArO), 1110, 1025 (P-O-C), 725 and 680 cm^{-1} (P=S), δ 3.79 (6H, d, 2POMe, J_{PH} 14Hz), 3.82 (6H, s, 2ArOMe), 6.52 (2H, m, aromatic), and 7.30 (1H, m, aromatic), ^{31}P δ+85.2, m/e 262 (M^+, 100), 231 (13), 230 [7, m^* 201.9 (262→230)], 229 (16), 199 [16, m^* 171.4 (231→199)].

2.4 Optically Active Compounds

Sec-butanol was resolved by the lengthy procedure of Pickard and Kenyon[147] from the brucine salt of its hydrogen phthalate ester to give (+)-sec-butanol, b.p. 99.5°/760 mm, $[\alpha]_D^{22}$ +15.2°, $[M]_D^{22}$+11.25° (1% solution) (lit.,[147] b.p.99°/760 mm $[M]_D^{22}$ +10.77° (5% solution)). By the same method which was employed for racemic sec-butanol, the optically active alcohol was reacted with methylphenylchlorophosphine to give optically active sec-butyl methylphenylphosphinite (68%),

$[\alpha]_D^{22}$ +9.7° (0.5% solution). As in the case of racemic sec-butyl methylphenylphosphinite, the introduction of a chiral tervalent phosphorus atom gave rise to diastereomeric signals being observed in the ^1H and ^{31}P n.m.r. spectra.

Thanks are due to Dr.A.G.Rowley who had previously resolved sec-octanol by the method described by Vogel,[116] and kindly supplied a sample of (+)-sec-octanol, b.p.81-82°/15 mm, $[\alpha]_D^{18}$ +9.75° (lit.,[116] $[\alpha]_D^{17}$ +9.9°). This alcohol was similarly reacted with methylphenylchlorophosphine and triethylamine by the method of Quin and Anderson[136] to give optically active sec-octyl methylphenylphosphinite (50%), b.p. 128-133°/4.4 mm, δ1.42 (3H, d, PMe, J_{PH} 6Hz), 0.7-1.8 (16H, m, aliphatic), 3.82 (1H, m, POCH), and 7.1-7.9 (5H, m, aromatic), ^{31}P δ+107.9 and +109.5. The phosphinite was characterised as the phosphinothionate (81%), b.p. 110-115°/15 mm (oven temperature) (Found: C, 63.4; H, 8.9. $C_{15}H_{25}OPS$ requires C, 68.35; H, 8.9%), ν_{max} (neat) 1435 (PPh), 1290 (PMe), 1110 (P-O-C), 705 and 690 cm^{-1} (P=S), δ (diastereomers, 1:1) 0.7-1.8 (16H, m, aliphatic), 1.95 and 1.98 (3H, 2 x d, PMe, J_{PH} 13.5Hz), 4.62 (1H, m, POCH), 7.50 (3H, m, aromatic), and 7.8-8.1 (2H, m, aromatic), ^{31}P δ +84.6 m/e 284 (M^+, 5), 173 [100, m^* 105.4 (284→173)], 157 (9), 156 (9), 155 [14, m^* 138.9 (173→155)], and 139 (9).

3. Deoxygenation of Aryl 2-Nitrophenyl Ethers: Preparation of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

Technique. Due to the water-lability of these penta-coordinate oxazaphospholes, precautions were necessary to try to exclude moisture. Thus, all glassware was oven-dried

before use and the preparation, recrystallisation and subsequent reactions of all oxazaphospholes were performed under an atmosphere of dry nitrogen. Any procedure involving the handling of these labile species was carried out in a dry-box flushed with dry nitrogen.

General Method. A solution of the aryl 2-nitrophenyl ether (5 mmol) and tervalent phosphorus reagent (20 mmol) in super-dry cumene (40 ml) was boiled under reflux, in a dry nitrogen atmosphere, for a period of up to 70 h.

Cumene was removed by high-vacuum distillation into a liquid nitrogen trap. Several glass bulbs were then fitted to the reaction flask and the products separated by high-vacuum distillation using Kugelrohr apparatus. The first fraction, consisting of the oxide of the tervalent phosphorus reagent, was obtained as a colourless oil, b.p. ca.70-130°/ 0.1 mm (oven temperature). The residue was distilled to give a second fraction, b.p. ca. 130-180°/0.1 mm (oven temperature), which generally solidified to a hard, clear glass on cooling and was found to be the crude oxazaphosphole by n.m.r. examination. Purification was normally effected by trituration in the dry-box with dry petrol, and subsequent recrystallisation to give a white crystalline solid which was stored under dry nitrogen.

All boiling points given refer to the Kugelrohr oven temperature. Reaction times varied widely from the above general method; monitoring by t.l.c. (alumina, petrol-ether) and/or ^{31}P n.m.r. showed some reactions to be complete in several hours. In these cases the use of a lower boiling solvent such as super-dry toluene or benzene was often found to give cleaner reaction products. Some deoxygenation reactions

were performed on twice the scale described in the general method; such reactions are indicated by the use of 80 ml of solvent.

3.1 Reaction of dimethyl phenylphosphonite

(i) With 2,6-dimethylphenyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 70 h, solvent was removed and high-vacuum distillation gave the following fractions: (1) a colourless oil (b.p. 70-125°/0.1 mm) identified by its ^{1}H n.m.r. spectrum as dimethyl phenylphosphonate; (2) a hard, pale green glass (b.p. 140-165°/0.1 mm) which was identified by ^{1}H n.m.r. as 3-(2,6-dimethylphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole (3.61 g, 95%). This crude product was sublimed, then recrystallised from petrol-ether (1:1) to give white crystals of pure oxazaphosphole m.p. 107-109° (lit.,[108] 108-110°); n.m.r. and mass spectral data were in agreement with the literature values.[108]

(ii) With 2,6-dimethoxyphenyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 69 h, solvent and dimethyl phenylphosphonate were removed by distillation and the residue in the reaction flask distilled to give a pale green glass (b.p. 170-175°/0.02 mm) identified as 3-(2,6-dimethoxyphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole (3.50 g, 85%), m.p. (from ether) 131-134° (sealed tube, Gallenkamp) (Found: C, 63.7; H, 5.7; N, 3.4%; M^+, 413. 137 111. $C_{22}H_{24}NO_5P$ requires C, 63.9; H, 5.85; N, 3.4%; M, 413. 193 200), ν_{max} 1440 (PPh), 1310 (ArN), 1260 (ArO), 1120, 1020, and 975 cm^{-1} (P-O-C), δ3.35 br (6H, d, 2POMe, J_{PH} 12Hz), 3.64 (6H, s, 2ArOMe), 6.05 (1H, m, aromatic), and

6.5-7.8 (11H, m, aromatic), ^{31}P δ-41.6, m/e 413 (100), 382 (35), 367 (23), 261 (25), 227 [18, m^* 124.8 (413→227)], 226 (14), and 210 (37).

This oxazaphosphole decomposed to its hydrolysis products very rapidly, and great difficulty was encountered in obtaining samples of sufficient purity for characterisation.

(iii) With 2-methylphenyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 68 h, solvent and dimethyl phenylphosphonate were removed and the product distilled as a viscous, pale green oil (b.p. 145-160°/0.15 mm) which solidified on cooling and was identified as 2,3-dihydro-2,2-dimethoxy-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole (3.10 g, 84%), m.p. (from petrol) 99-99.5° (sealed tube, Gallenkamp) (Found: C, 68.4; H, 6.3; N, 3.6. $C_{21}H_{22}NO_3P$ requires C, 68.7; H, 6.0; N, 3.8%), ν_{max} 1440 (PPh), 1305 (ArN), 1265 (ArO), 1020, 970, and 925 cm^{-1} (P-O-C), δ2.22 (3H, s, ArMe), 3.16 (3H, d, POMe, J_{PH} 12Hz), 3.58 (3H, d, POMe, J_{PH} 12.5Hz), 5.96 (1H, m, aromatic), and 6.4-7.8 (12H, m, aromatic), ^{31}P δ-45.6, m/e 367 (M^+, 100), 336 (21), 181 [23, m^* 89.3 (367→181)], and 180 (87).

(iv) With 2,4-dimethylphenyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 65 h, solvent and dimethyl phenylphosphonate were removed and the product distilled as a viscous oil (b.p. 130-160°/0.05 mm) which crystallised slowly on cooling and was identified as 3-(2,4-dimethylphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole (3.02 g, 79%), m.p. (from petrol-ether) 123-124.5° (Found: C, 69.2; H, 6.35; N, 3.65. $C_{22}H_{24}NO_3P$ requires C, 69.3; H, 6.3; N, 3.7%), ν_{max} 1440 (PPh), 1305 (ArN), 1260 (ArO), 1130, 1020, 975, and 935 cm^{-1} (P-O-C), δ 2.14 (3H, s, ArMe),

2.30 (3H, s, ArMe), 3.13 (3H, d, POMe, J_{PH} 11.7Hz), 3.53 (3H, d, POMe, J_{PH} 12.7Hz), 5.93 (1H, m, aromatic), and 6.4-7.8 (11H, m, aromatic), ^{31}P δ-45.3, m/e 381 (M^+, 100), 350 (16), 335 (19), 195 [20, m^* 99.8 (381→195)], and 194 (66).

(v) With 2-methoxyphenyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 69 h, solvent and dimethyl phenylphosphonate were removed and the product distilled as a pale green viscous oil (b.p. 160-175°/0.15 mm) identified as 2,3-dihydro-2,2-dimethoxy-3-(2-methoxyphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole (2.85 g, 74%), m.p. (from petrol-ether) 111-112° (sealed tube, Gallenkamp) (Found: C, 65.5; H, 5.75; N, 3.75. $C_{21}H_{22}NO_4P$ requires C, 65.8; H, 5.8; N, 3.65%), ν_{max} 1440 (PPh), 1315 (ArN), 1265 (ArO), 1020, 975, and 920 cm^{-1} (P-O-C), δ3.36 (6H, d, 2POMe, J_{PH} 12Hz), 3.66 (3H, s, ArOMe), 6.08 (1H, m, aromatic), and 6.5-7.8 (12H, m, aromatic), ^{31}P δ-43.2 m/e 383 (M^+, 100), 352 (23), 337 (9), 197 [8, m^* 101.3 (383→197)], 196 (20), 182 (39), and 180 [42, m^* 84.6 (383→180)].

(vi) With 2-nitrophenyl 2-tert-butylphenyl ether. After reaction in cumene (40 ml) for 9 h, solvent and dimethyl phenylphosphonate were removed and the product distilled as a pale yellow glass (b.p. 140-150°/0.1 mm) identified as 2,3-dihydro-2,2-dimethoxy-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole (1.39 g, 68%), m.p. (from petrol) 115-119° (sealed tube, Gallenkamp) (Found: C, 70.6; H, 7.0; N, 3.5. $C_{24}H_{28}NO_3P$ requires C, 70.4; H, 6.9; N, 3.4%), ν_{max} 1440 (PPh), 1305 (ArN), 1265 (ArO), 1110, 1020, 970, and 930 cm^{-1} (P-O-C), δ 1.40 (9H, s, t-Bu), 3.09 (3H, d, POMe,

J_{PH} 11Hz), 3.89 (3H, d, POMe, J_{PH} 13.5Hz), 5.92 (1H, m, aromatic), and 6.4-8.0 (12H, m, aromatic), ^{31}P δ-47.3, m/e 409 (M^+, 100), 394 (12), 378 (20), 363 (37), 224 (10), 223 [15, m^* 121.6 (409→223)], 222 (10), 208 (22), and 180 (54).

3.2 Reaction of 2-phenyl-1,3,2-dioxaphospholan

(i) With 2-methylphenyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 24 h, solvent was removed and high-vacuum distillation gave the following fractions: (1) a colourless oil (b.p. 70-155°/0.2 mm) which formed a white, waxy solid on cooling, and was identified by its ^1H n.m.r. spectrum as 2-oxo-2-phenyl-1,3,2-dioxaphospholan; (2) a hard, pale yellow glass (b.p. 155-220°/0.2 mm) identified as the oxazaphosphole (2.43 g, 67%) by ^1H n.m.r. This crude product was triturated with dry ether and recrystallised from ether-dichloromethane to give 2,3-dihydro-3-(2-methylphenyl)-2-phenylspiro-{1,3,2-benzoxazaphosphole-2,2'-[1,3,2]dioxaphospholan}, m.p. 144-145° (sealed tube, Gallenkamp) (Found: C, 68.8; H, 5.5; N, 3.7. $C_{21}H_{20}NO_3P$ requires C, 69.0; H, 5.5; N, 3.8%), ν_{max} 1440 (PPh), 1305 (ArN), 1260 (ArO), 1020, 980, 950, and 930 cm^{-1} (P-O-C), δ (diastereomers, 1:1.7) 1.95 and 2.22 (3H, 2 x s, ArMe), 3.4-4.2 (4H, m, $2CH_2$), 5.92 (1H, m, aromatic), and 6.45-8.05 (12H, m, aromatic), ^{31}P δ-33.1 and -32.3, m/e 365 (M^+, 100), 199 (95), 181 (26), 180 (77), 141 (17), and 93 (33).

(ii) With 3-methylphenyl 2-nitrophenyl ether. A mixture of the nitro-compound (1.83 g, 8 mmol) and the cyclic phosphonite (5.38 g, 32 mmol) in cumene (65 ml) was reacted for 6 h. After removal of solvent and cyclic phosphonate, the product was distilled as a hard glass (b.p. 140-180°/0.1 mm) which

crystallised slowly on cooling and was identified as 2,3-dihydro-3-(3-methylphenyl)-2-phenylspiro-{1,3,2-benzoxazaphosphole-2,2'-[1,3,2]dioxaphospholan} (2.66 g, 91%), m.p. (from ether) 183-185° (Found: C, 68.7; H, 5.5; N, 3.7. $C_{21}H_{20}NO_3P$ requires C, 69.0; H, 5.5; N, 3.8%), ν_{max} 1440 (PPh), 1310 (ArN), 1260 (ArO), 1135, 1020, and 945 cm^{-1} (P-O-C), δ2.38 (3H, s, ArMe), 3.5-4.3 (4H, m, $2CH_2$), 6.04 (1H, m, aromatic), and 6.5-8.0 (12H, m, aromatic), ^{31}P δ-31.8, m/e 365 (M^+, 4), 199 (82), 184 [100, m^* 170.1 (199→184)], 183 (54), 141 (94), 124 [80, m^* 42.1 (365→124)], and 120 [48, m^* 78.2 (184→120)].

(iii) With 2-nitrophenyl 2-tert-butylphenyl ether. After reaction in cumene (40 ml) for 7 h, solvent and cyclic phosphonate were removed and the product distilled to give a white crystalline solid (b.p. 180-190°/.0005 mm) which was identified as 2,3-dihydro-2-phenyl-3-(2-tert-butylphenyl)spiro-{1,3,2-benzoxazaphosphole-2,2'-[1,3,2]dioxaphospholan} (1.79 g, 88%), m.p. (from ether-dichloromethane) 174-175° (Found: C, 70.6; H, 6.5; N, 3.4. $C_{24}H_{26}NO_3P$ requires C, 70.75; H, 6.4; N, 3.4%), ν_{max} 1440 (PPh), 1305 (ArN), 1260 (ArO), 1110, 1075, 1020, 970, 950, and 930 cm^{-1} (P-O-C), δ1.36 (9H, s, t-Bu), 3.4-4.1 (4H, m, $2CH_2$), 5.82 (1H, m, aromatic), and 6.5-8.1 (12H, m, aromatic), ^{31}P δ-31.0, m/e 407 (M^+ 100), 223 [15, m^* 122.2 (407→223)], 222 [8, m^* 221.0 (223→222)], 208 [30, m^* 194.0 (223→208)], and 180 (53).

(iv) With 2-nitrophenyl 3-tert-butylphenyl ether. After reaction for 7 h, cumene and cyclic phosphonate were removed, and the product distilled as a pale yellow oil (b.p. 170-180°/0.0005 mm). The oil crystallised to an off-white solid on

cooling and was identified as 2,3-dihydro-2-phenyl-3-(3-tert-butylphenyl)spiro-{1,3,2-benzoxazaphosphole-2,2'-[1,3,2]dioxaphospholan} (1.38 g, 68%), m.p. (from ether-dichloromethane) 164-165° (Found: C, 70.7; H, 6.5; N, 3.3. $C_{24}H_{26}NO_3P$ requires C, 70.75; H, 6.4; N, 3.4%), ν_{max} 1440 (PPh), 1310 (ArN), 1265 and 1260 (ArO), 1075, 1020, 990, 955, and 945 cm^{-1} (P-O-C), δ1.31 (9H, s, t-Bu), 3.4-4.3 (4H, m, $2CH_2$), 6.03 (1H, m, aromatic), and 6.5-8.1 (12H, m, aromatic), ^{31}P δ-32.2, m/e 407 (M^+, 78), 241 (100), and 226 [21, m^* 211.9 (241→226)].

3.3 Reaction of diethyl methylphosphonite

(i) With 2-nitrophenyl 2-tert-butylphenyl ether. After reaction for 24 h, cumene and the low-boiling diethyl methylphosphonate were removed by high-vacuum distillation, and the product distilled as a colourless viscous oil which turned reddish in colour on exposure to light. This oil could not be crystallised, but was redistilled and identified as 2,2-diethoxy-2,3-dihydro-2-methyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole (1.80 g, 96%), b.p. 135-140°/0.4 mm, ν_{max} 1310 (ArN), 1270 (ArO), 1115, 1025, 975, 945, and 925 cm^{-1} (P-O-C), δ0.90 br (6H, s, $2POCH_2\underline{CH_3}$), 1.30 (9H, s, t-Bu), 1.76 (3H, d, PMe, J_{PH} 17Hz), 3.76 br (4H, s, $2PO\underline{CH_2}CH_3$), 5.83 (1H, m, aromatic), and 6.4-7.6 (7H, m, aromatic), ^{31}P δ-35.6 br, m/e 375 (M^+, 100), 347 (16), 330 (41), 269 (35), 239 (24), 224 (32), and 208 (92) (Found: M^+, 375.196 765. $C_{21}H_{30}NO_3P$ requires M, 375.196 320).

(ii) With 2,4-dimethylphenyl 2-nitrophenyl ether. After reaction for 2 h, cumene and diethyl methylphosphonate were

removed and the product distilled as a viscous, pale green oil which slowly crystallised on storage. Rêdistillation gave an oily, low-melting solid which was identified as 3-(2,4-dimethylphenyl)-2,2-diethoxy-2,3-dihydro-2-methyl-1,3,2-benzoxazaphosph(v)ole (1.64 g, 95%), b.p. 120-130°/0.2 mm, ν_{max} 1315 (ArN), 1270 (ArO), 1110, 1025, and 980 cm^{-1} (P-O-C) δ0.88 (6H, t, $2POCH_2\underline{CH_3}$, J_{HH} 7Hz), 1.83 (3H, d, PMe, J_{PH} 17.5Hz), 2.12 (3H, s, ArMe), 2.32 (3H, s, ArMe), 3.66 (4H, m, $2PO\underline{CH_2}CH_3$), 5.86 (1H, m, aromatic), and 6.4-7.2 (6H, m, aromatic), ^{31}P δ-36.1, m/e 347 (M^+, 100), 319 [21, m^* 293.3 (347→319)], 302 (29), 274 [14, m^* 248.6 (302→274)], 273 (14), 195 [14, m^* 109.6 (347→195)], and 194 [59, m^* 193.0 (195→194)] (Found: M^+, 347.163 543. $C_{19}H_{26}NO_3P$ requires M, 347.165 021).

3.4 Reaction of sec-butyl methylphenylphosphinite

(i) With 2-nitrophenyl 2-tert-butylphenyl ether. After reaction for 66 h, cumene was removed and high-vacuum distillation gave the following fractions: (1) a colourless oil (b.p. 80-125°/0.25 mm), shown by its ^1H and ^{31}P n.m.r. spectra to be sec-butyl methylphenylphosphinate, ^{31}P δ(diastereomers, 1:1) +40.2 and +40.4; (2) a hard, pale orange glass (b.p. 125-150°/0.25 mm) identified as crude oxazaphosphole (1.33 g, 61%). The glass was triturated with dry petrol and recrystallised from a small quantity of additional petrol to give white needles of 2,3-dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole, m.p. 112.5-116° (sealed tube, Gallenkamp) (Found: C, 74.4; H, 7.9; N, 3.3. $C_{27}H_{34}NO_2P$ requires C, 74.5; H, 7.9; N, 3.2%), ν_{max} 1440 (PPh), 1305 (ArN),

1265 (ArO), 1160, 1110, and 1025 cm^{-1} (P-O-C), δ(diastereomers, 1:1) 0.18 and 0.41 (3H, 2 x t, $CH_2\underline{CH_3}$, J_{HH} 7.5Hz), 0.20 and 0.81 (3H, 2 x d, $CH\underline{CH_3}$ J_{HH} 6Hz), 0.56 and 1.12 (2H, 2 x m, $\underline{CH_2}CH_3$), 1.39 and 1.41 (9H, 2 x s, t-Bu), 2.31 (3H, 2 x d, PMe, J_{PH} 14Hz), 3.53 (1H, m, POCH), 5.85 (1H, m, aromatic), and 6.35-7.8 (12H, m, aromatic), ^{31}P δ-28.6 and -29.0, m/e 435 (M^+, 28), 379 [100, m^* 330.2 (435→379)], 362 (25), and 208 [98, m^* 114.5 (379→208)].

(ii) With 2,6-dimethylphenyl 2-nitrophenyl ether. After reaction for 64 h, cumene and sec-butyl methylphenylphosphinate were removed, and the product distilled as a pale green oil (b.p. 135-150°/0.2 mm) which crystallised on cooling and was identified as 3-(2,6-dimethylphenyl)-2,3-dihydro-2-methyl-2-phenyl-2-sec-butoxy-1,3,2-benzoxazaphosph(v)ole (1.58 g, 78%), m.p. (from petrol) 123-125° (Found: C, 73.9; H, 7.5; N, 3.3%; M^+, 407.198 974. $C_{25}H_{30}NO_2P$ requires C, 73.7; H, 7.4; N, 3.4%; M, 407.201 406), ν_{max} 1440 (PPh), 1305 (ArN), 1265 (ArO), 1120, 995, and 960 cm^{-1} (P-O-C), δ(diastereomers, 1:1) 0-1.3 br (8H, m, sec-Bu), 1.6-2.2 br (3H, s, PMe), 2.2-2.3 (6H, 4 x s, 2ArMe), 3.3-3.9 (1H, m, POCH), 5.84 (1H, m, aromatic), and 6.35-7.85 (11H, m, aromatic), ^{31}P δ-31.9 br, m/e 407 (M^+, 57), 351 [100, m^* 302.7 (407→351)], 334 (37), 195 [27, m^* 108.3 (351→195)], and 194 (93).

3.5 Reaction of methyl methylphenylphosphinite

(i) With 2,6-dimethoxyphenyl 2-nitrophenyl ether. After reaction for 92 h, cumene was removed and high-vacuum distillation gave the following fractions: (1) a colourless oil (b.p. 85-110°/0.2 mm), shown by its n.m.r. spectra to be

methyl methylphenylphosphinate; (2) a pale yellow glass (b.p. 170-175°/0.2 mm) identified as 3-(2,6-dimethoxyphenyl)-2,3-dihydro-2-methoxy-2-methyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole (1.75 g, 88%), m.p. (from ether-dichloromethane) 136-143° (sealed tube, Gallenkamp) (Found: C, 66.4; H, 6.1; N, 3.6%; M^+, 397.141 700. $C_{22}H_{24}NO_4P$ requires C, 66.5; H, 6.1; N, 3.5%; M, 397.144 286), ν_{max} 1440 (PPh), 1305 (ArN), 1260 (ArO), 1120, 1025, and 970 cm^{-1} P-O-C), δ2.21 (3H, d, PMe, J_{PH} 16Hz), 2.32 (3H, d, POMe, J_{PH} 10.8Hz), 3.67 (3H, s, ArOMe), 3.77 (3H, s, ArOMe), 6.00 (1H, m, aromatic), 6.4-6.8 (5H, m, aromatic), and 7.15-7.75 (6H, m, aromatic), ^{31}P δ-24.5, m/e 397 (M^+, 100), 383 (24), 366 [39, m^* 337.4 (397→366)], 245 [16, m^* 151.2 (397→245)], 227 [8, m^* 129.8 (397→227)], 226 (8), and 210 (32).

(ii) With 2-methoxyphenyl 2-nitrophenyl ether. After reaction for 69 h, cumene and methyl methylphenylphosphinate were removed and the product distilled as an orange glass (b.p. 160-170°/0.2 mm) identified as 2,3-dihydro-2-methoxy-3-(2-methoxyphenyl)-2-methyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole (1.49 g, 81%), m.p. (from ether-dichloromethane) 126-131° (sealed tube, Gallenkamp) (Found: C, 68.4; H, 6.0; N, 3.9%, M^+, 367.132 409. $C_{21}H_{22}NO_3P$ requires C, 68.7; H, 6.0; N, 3.8%, M, 367.133 732), ν_{max} 1440 (PPh), 1310 (ArN), 1265 (ArO), 1120, 1025, and 970 cm^{-1} (P-O-C), δ (diastereomers, 1:1.4), 2.18 and 2.20 (3H, 2 x d, PMe, J_{PH} 15.5Hz), 2.28 and 2.38 (3H, 2 x d, POMe, J_{PH} 11Hz), 3.64 and 3.77 (3H, 2 x s, ArOMe), 6.03 (1H, m, aromatic), and 6.4-7.8 (12H, m, aromatic), ^{31}P δ-26.1 and -25.3, m/e 367 (M^+, 100), 336 [37, m^* 307.6 (367→336)], 197 [6, m^* 105.7 (367→197)], 196 (17), 182 (43), and 180 (37).

3.6 Reaction of dimethylphenylphosphine

(i) With 2,6-dimethoxyphenyl 2-nitrophenyl ether. After reaction for 2 h, cumene was removed, and the dark residue distilled to give the following fractions: (1) a white crystalline solid (b.p. 90-110°/0.1 mm, partly sublimed) which was recrystallised from ether-dichloromethane and identified as dimethylphenylphosphine oxide, m.p. 115-116° (lit.,[148] 115-119°); (2) a dark orange glass (b.p. 160-170°/0.1 mm) identified as 3-(2,6-dimethoxyphenyl)-2,3-dihydro-2,2-dimethyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole (1.09 g, 57%), m.p. (from ether-dichloromethane) 141-159° (unreliable; sealed tube, Gallenkamp) (Found: C, 69.1; H, 6.3; N, 4.1%; M^+, 381.147 051. $C_{22}H_{24}NO_3P$ requires C, 69.3; H, 6.3; N, 3.7%; M, 381.149 372), ν_{max} 1440 (PPh), 1305 (ArN), 1290 (PMe), 1265 (ArO), 1120, 1030, 970 and 935 cm^{-1} (P-O-C), δ 1.50 br (6H, d, 2PMe, J_{PH} ca.10Hz), 3.79 (6H, s, 2ArOMe), 5.86 (1H, m, aromatic), 6.3-6.7 (5H, m, aromatic), and 7.2-7.9 (6H, m, aromatic), ^{31}P δ-42.0, m/e 381 (M^+, 74), 366 (16), 350 [10, m^* 321.5 (381→350)], 245 (100), 230 [16, m^* 215.9 (245→230)], 213 (21), 210 (21), and 199 (51).

In a replicate experiment, the mother liquors from recrystallisation of the oxazaphosphole were chromatographed on alumina. Elution with methanol gave a white solid which was identified as 2-(2,6-dimethoxyanilino)phenol, m.p. 159-160° (lit.,[108] 159-160°). ^1H n.m.r. spectra of the oxazaphosphole indicated gradual decomposition of the pentacoordinate species to a mixture of the anilinophenol and dimethylphenylphosphine oxide.

3.7 Reaction of dimethyl 2,6-dimethoxyphenylphosphonite

(i) With 4-methylphenyl 2-nitrophenyl ether. After reaction for 21 h, cumene was removed and high-vacuum distillation gave the following fractions: (1) a colourless oil (b.p. 130-150°/0.1 mm) which solidified on cooling and was recrystallised from ether to give dimethyl 2,6-dimethoxyphenylphosphonate, m.p. 70-72°, δ 3.80 (6H, d, 2POMe, J_{PH} 12Hz), 3.86 (6H, s, 2ArOMe), 6.4-6.65 (2H, m, aromatic), and 7.2-7.6 (1H, m, aromatic), ^{31}P δ+18.9; (2) a yellow glass (b.p. 160-180°/0.03 mm) which was identified as 2-(2,6-dimethoxyphenyl)-2,3-dihydro-2,2-dimethoxy-3-(4-methylphenyl)-1,3,2-benzoxazaphosph(v)ole (1.07 g, 50%), m.p. (from petrol-dichloromethane) 132-134° (Found: C, 64.7; H, 6.1; N, 3.25%; M^+, 427.154 000. $C_{23}H_{26}NO_5P$ requires C, 64.6; H, 6.1; N, 3.3%; M, 427.154 849), ν_{max} 1430 (PAr), 1310 (ArN), 1260 and 1250 (ArO), 1110, 1020, 970, and 925 cm^{-1} (P-O-C), δ 2.36 (3H, s, ArMe), 3.25 (6H, d, 2POMe, J_{PH} 13Hz), 3.58 (6H, s, 2ArOMe), 6.10 (1H, m, aromatic), 6.4-6.8 (5H, m, aromatic), and 7.1-7.3 (5H, m, aromatic), ^{31}P δ-41.7, m/e 427 (M^+, 100), 396 [14, m^* 367.2 (427→396)], 381 (19), 246 (47), 213 (51), 199 (100), and 110 (51).

4. Deoxygenation of Aryl 2-Nitrophenyl Ethers: Preparation of Mixtures Containing 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

4.1 Reaction of dimethylphenylphosphine

(i) With 2-methoxyphenyl 2-nitrophenyl ether. After reaction in toluene for 22 h, solvent and dimethylphenylphosphine oxide

were removed by high-vacuum distillation. The residue was distilled as an orange oil (b.p. 175-190°/0.1 mm) which solidified to a glass on cooling and was identified by its n.m.r. spectra as mainly 2,3-dihydro-3-(2-methoxyphenyl)-2,2-dimethyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole (0.87 g, 50%), δ 1.58 br (6H, d, 2PMe, J_{PH} 9Hz), 3.86 (3H, s, ArOMe), 5.90 (1H, m, aromatic), and 6.3-7.9 (12H, m, aromatic), ^{31}P δ-42.5. This crude product contained minor impurities and could not be crystallised, hence it was redistilled into several fractions. Pure oxazaphosphole could still not be obtained from these fractions, however, due to their high solubility even in petrol, which prevented crystallisation.

As in the case of 3-(2,6-dimethoxyphenyl)-2,3-dihydro-2,2-dimethyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole (see section 3.6), this oxazaphosphole was observed to decompose in deuteriochloroform solution to dimethylphenylphosphine oxide and the corresponding anilinophenol.

(ii) With 2-methylphenyl 2-nitrophenyl ether. After reaction in toluene for 36 h, solvent and dimethylphenylphosphine oxide were removed by high-vacuum distillation. The residue was distilled as an orange oil (b.p. 155-165°/0.1 mm) which solidified to a glass on cooling and was identified as mainly 2,3-dihydro-2,2-dimethyl-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole (0.91 g, 60%) (Found: M^+, 335.144 374. $C_{21}H_{22}NOP$ requires M, 335.143 894), δ 1.20 br (3H, d, PMe, J_{PH} 8Hz), 1.80 br (3H, d, PMe, J_{PH} 10Hz), 2.33 (3H, s, ArMe), 5.76 (1H, m, aromatic), and 6.2-7.8 (12H, m, aromatic), ^{31}P δ-44.7. The crude product was triturated with dry petrol to give a pale green solid shown by ^{31}P n.m.r. (petrol-$(CD_3)_2CO$,

δ-48.4) to be pure oxazaphosphole. Deuteriochloroform solutions of this solid, however, always showed rapid decomposition of the oxazaphosphole to the corresponding anilinophenol and phosphine oxide. The instability of the pentacoordinate species was further illustrated by the failure to obtain a pure recrystallised sample and an acceptable melting point.

4.2 Reaction of sec-butyl methylphenylphosphinite

(i) With 2-methoxyphenyl 2-nitrophenyl ether. After reaction for 71 h, cumene and sec-butyl methylphenylphosphinate were removed by high-vacuum distillation. The residue was distilled as a pale green oil (b.p. 150-170°/0.1 mm) which solidified to a glass on cooling and was identified by its n.m.r. spectra as mainly 2,3-dihydro-3-(2-methoxyphenyl)-2-methyl-2-phenyl-2-sec-butoxy-1,3,2-benzoxazaphosph(v)ole (1.49 g, 73%), δ (diastereomers, 2:1) 0-1.4 (8H, m, aliphatic), 2.20 (3H, d, PMe, J_{PH} 15Hz), 3.4 (1H, m, POCH), 3.75 and 3.80 (3H, 2 x s, ArOMe), 6.05 (1H, m, aromatic), and 6.3-8.0 (12H, m, aromatic), ^{31}P δ-28.6 and -28.4 (major isomers), -28.5 and -28.3 (minor isomers).

Redistillation of the crude oxazaphosphole failed to remove a minor impurity, believed to be an acyclic phosphinate (^{31}P δ+43.2), and this redistilled sample could not be crystallised due to its high solubility, even in dry petrol.

(ii) With 2-nitrophenyl 2-tert-butylphenyl ether. After reaction for 66 h, cumene and sec-butyl methylphenylphosphinate were removed by high-vacuum distillation and the residue distilled to give an orange oil (b.p. 170-190°/1.0 mm) which

hardened to a glass on cooling. ^{1}H n.m.r. analysis of this material (1.39 g) showed it to be an equal mixture of two compounds, which were not separated by redistillation. Thus, the mixture was recrystallised from a generous amount of dry petrol to give a first crop of white crystals, identified as 2-(2-tert-butylanilino)phenyl methylphenylphosphinate, m.p. 104-105° (Found: C, 72.6; H, 6.95; N, 3.6. $C_{23}H_{26}NO_2P$ requires C, 72.8; H, 6.9; N, 3.7%), ν_{max} 3470 and 3400 br (NH), 1445 (PPh), 1310 (ArN), 1180 (P=O), 1130, 1105, and 925 cm^{-1} (P-O-C), δ 1.43 (9H, s, t-Bu), 1.89 (3H, d, PMe, J_{PH} 14Hz), 6.13 br (1H, s, NH), and 6.5-8.0 (13H, m, aromatic), ^{31}P δ+43.3, m/e 379 (M^+, 100), 208 [41, m^* 114.2 (379→208)], 193 [11, m^* 179.1 (208→193)], and 180 [9, m^* 85.5 (379→208)].

After several days, a second crop of white crystals was obtained. This was identified as 2,3-dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole by comparison of its ^{1}H n.m.r. spectrum with that of a previously prepared sample (see section 3.4(i)).

5. Deoxygenation of Aryl 2-Nitrophenyl Ethers: Preparation of Decomposition Products of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles

5.1 Reaction of dimethyl phenylphosphonite

(i) With 3-methylphenyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 65 h, solvent and dimethyl phenylphosphonate were removed by high-vacuum distillation. The residue was distilled as a dark orange oil (b.p. 145-250°/0.1

mm) which solidified to a glass on cooling, and was identified by its n.m.r. spectrum as crude cyclic phosphonamidate (1.41 g, 44%). Purification by trituration and recrystallisation from dry ether gave white crystals of 2,3-dihydro-3-(3-methylphenyl)-2-oxo-2-phenyl-1,3,2-benzoxazaphosph(v)ole (0.26 g), m.p. 122-125°, δ 2.32 (3H, s, ArMe), and 6.7-8.1 (13H, m, aromatic), ^{31}P δ+29.4, m/e 321 (M^+, 100) (Found: M^+ 321.091 239. $C_{19}H_{16}NO_2P$ requires M, 321.091 861).

In a replicate experiment, monitoring of the reaction showed the presence of the expected pentacoordinate oxazaphosphole (^{31}P δ(cumene $-C_6D_6$) -46.1), but this could not be isolated on subsequent distillation. Analysis of an intermediate fraction by n.m.r. and g.l.c./mass spectrometry showed it to be a mixture of the above cyclic phosphonamidate and a compound tentatively assigned as an acyclic hydrolysis product (δ 3.84 (3H, d, POMe, J_{PH} 11Hz), ^{31}P δ+18.9, m/e 353 (M^+)).

(ii) With 2-nitrophenyl 3-tert-butylphenyl ether. After reaction in cumene (80 ml) for 65 h, solvent and dimethyl phenylphosphonate were removed by high-vacuum distillation and the residue distilled to give a dark red viscous oil (2.59 g) (b.p. 150-215°/0.1 mm). Analysis by n.m.r. showed this to be a mixture, the major components of which were tentatively assigned as the pentacoordinate oxazaphosphole (15%, ^{31}P δ-44.9) and the cyclic phosphonamidate (56%, ^{31}P δ+29.4). Further fractionation of this mixture failed to isolate any pure component, as crystallisation could not be induced on attempted trituration of each fraction.

(iii) With 1-naphthyl 2-nitrophenyl ether. After reaction in cumene (80 ml) for 69 h, solvent and dimethyl phenylphosphonate were removed by high-vacuum distillation, and the residue distilled as a fluorescent yellow oil (b.p.170-180°/0.02 mm). This oil crystallised to a bright yellow, waxy solid (1.89 g) on cooling, but darkened rapidly, even in the absence of light and under an atmosphere of nitrogen. Recrystallisation from petrol-benzene gave a yellow solid which similarly darkened on storage. Analysis by n.m.r. and mass spectrometry suggested that the yellow solid was a non-phosphorus containing aromatic compound with a molecular weight of 233.

In a replicate experiment, the residue from the distillation was chromatographed on alumina, but the eluted yellow solution once again darkened rapidly, preventing identification of the reaction product.

Similarly, the reactions of 1-naphthyl 2-nitrophenyl ether with (1) diethyl methylphosphonite and (2) 2-phenyl-1,3,2-dioxaphospholan, and the reaction of 2-naphthyl 2-nitrophenyl ether with dimethyl phenylphosphonite all yielded unstable yellow-green products which decomposed rapidly, even when stored in darkness in the dry-box. Thus, the products of these reactions could not be isolated or identified, although ^{31}P n.m.r. spectra did indicate the presence of a small amount of a pentacoordinate oxazaphosphole in the reaction of 1-naphthyl 2-nitrophenyl ether with diethyl methylphosphonite (^{31}P δ-35.4), and of 2-naphthyl 2-nitrophenyl ether with dimethyl phenylphosphonite (^{31}P δ-47.9).

5.2 Reaction of dimethylphenylphosphine

(i) With 4-methoxyphenyl 2-nitrophenyl ether. Monitoring of the reaction in toluene indicated the presence of an oxazaphosphole after 48 h (^{31}P δ(toluene $-C_6D_6$) -48.1). Hence toluene and dimethylphenylphosphine oxide were distilled from the reaction mixture and the residue distilled to give a dark yellow oil (0.74 g) (b.p. 140-180°/0.15 mm). T.l.c. showed this oil to be a mixture, which was analysed by l.p.c. Eluting first with petrol and gradually increasing the polarity of the eluent with ether, the following compounds were isolated in very low yield:

(1) fine, off-white needles identified by comparison with some previously reported data[109] as 2,4'-dimethoxydiphenylamine, m.p. (from petrol) 65-70°, ν_{max} 3410 (NH), 1295 (ArN), 1120, and 1030 cm^{-1} (CO), δ3.80 (3H, s, ArOMe), 3.90 (3H, s, ArOMe), 5.90 br (1H, s, NH), and 6.7-7.3 (8H, m, aromatic), m/e 229 (M^+, 100), 214 [57, m^* 200.0 (229→214)], and 183 [30, m^* 156.5 (214→183)] (Found: M^+, 229.110 639. $C_{14}H_{15}NO_2$ requires M, 229.110 272);

(2) glistening straw-coloured crystals identified as 3-methoxyphenoxazine, m.p. 85-88°, ν_{max} (Nujol) 3400 (NH), and 1030 cm^{-1} (CO), δ3.67 (3H, s, ArOMe), 4.90 br (1H, s, NH), 6.25 (4H, m, aromatic), and 6.50 (3H, m, aromatic), m/e 213 (M^+, 100), 198 [71, m^* 184.1 (213→198)], and 170 [21, m^* 146.0 (198→170)] (Found: M^+, 213.080 347. $C_{13}H_{11}NO_2$ requires M, 213.078 973).

The other two compounds isolated could not be assigned unambiguously: (1) fine, dark yellow needles, m.p. 170°, with a molecular formula of $C_{19}H_{15}NO_2$, as indicated by accurate

mass; (2) a yellow solid, m.p. 135°, with a molecular formula of $C_{19}H_{16}N_2O_2$.

5.3 Reaction of tri-n-butylphosphine

(i) With 4-methoxyphenyl 2-nitrophenyl ether. ^{31}P n.m.r. monitoring of the reaction in cumene showed a gradual increase in the signal due to tri-n-butylphosphine oxide until the phosphine and phosphine oxide signals were of equal intensity. At this time (4 h), all of the nitro-compound had reacted; no other signals had been observed in the ^{31}P n.m.r. spectra. Thus, cumene and some unreacted phosphine were distilled from the reaction mixture, the remainder of which was analysed by dry column chromatography. The column was developed with petrol-ether (1:1) and the following compounds isolated:

(1) a pale yellow oil (0.93 g) identified by its n.m.r. spectra as unreacted tri-n-butylphosphine;

(2) a pale oil (b.p. 130-150°/0.1 mm) which solidified on cooling and was identified as 3-methoxyphenoxazine (0.26 g, 24%) by comparison of its ^1H n.m.r. and mass spectra with those of an authentic sample (see section 5.2 (i));

(3) a yellow solid (0.08 g) identified by mass spectrometry as the same compound of molecular formula $C_{19}H_{16}N_2O_2$ which was isolated previously (see section 5.2 (i));

(4) a dark solid (2.35 g) identified by its n.m.r. spectra as tri-n-butylphosphine oxide.

6. Miscellaneous Reactions

6.1 Preparation of 2-(2-methylanilino)phenol

By the method of Schmitt et al.,[149] o-toluidine and catechol were condensed in the presence of anhydrous zinc chloride and xylene. After reacting for 48 h, work-up and distillation gave a pale green oil (b.p. 110-120°/0.05 mm) which slowly solidified and was recrystallised from petrol to give an off-white solid identified as 2-(2-methylanilino)phenol (1.62 g, 9%), m.p. 61-63° (lit.,[149] 63°).

6.2 Preparation of 2-(2-tert-butylanilino)phenol

(i) Deoxygenation of 2-nitrophenyl 2-tert-butylphenyl ether. In the manner of previous deoxygenation reactions, 2-nitrophenyl 2-tert-butylphenyl ether (5.42 g, 0.02 mol) and trimethyl phosphite (9.92 g, 0.08 mol) were boiled under reflux in cumene for 70 h. After removal of the lower boiling fractions, the dark residual oil was dissolved in a mixture of ethanol and water (4:1) (100 ml) containing concentrated hydrochloric acid (20 drops), and stirred under reflux for 14 h. The hydrolysed product was extracted into ether, washed with water (3 x 100 ml) and dried over anhydrous magnesium sulphate. Evaporation of the solvent and distillation of the residue gave a viscous orange oil (2.84 g) (b.p. 180-210°/0.1 mm) which was shown by t.l.c. to comprise a multi-component mixture. A solid which slowly crystallised from this oil was filtered off and recrystallised from cyclohexane to give fine white needles identified as phenoxazine (0.14 g), m.p. and mixed m.p. 156-157° (lit.,[150] 156°), by comparison of

its i.r. spectrum with that of an authentic sample.[151]

The remainder of the viscous oil was analysed by l.p.c. and, although several minor components of the mixture were eluted, only the following compounds could be isolated: (1) a pale orange solid which, on recrystallisation, gave additional phenoxazine (0.18 g) (total yield, 9%); (2) elution with ether-ethyl acetate gave the final component as a dark oil. This was distilled to give a pale yellow viscous oil (b.p. 120-140°/0.05 mm) which darkened rapidly on exposure to light and was identified as 2-(2-tert-butylanilino)phenol (1.06 g, 22%) (Found: C, 79.4; H, 8.1; N, 6.3%, M^+, 241.146 215. $C_{16}H_{19}NO$ requires C, 79.6; H, 7.9; N, 5.8%; M, 241.146 656), ν_{max} 3600, 3460, and 3260 cm^{-1} (OH and NH), δ 1.45 (9H, s, t-Bu), 5.6 br (2H, s, OH and NH), and 6.6-7.6 (8H, m, aromatic), m/e 241 (M^+, 100), 226 [63, m^* 211.9 (241→226)], 211 [28, m^* 197.0 (226→211)], 210 (42), and 185 [23, m^* 142.0 (241→185)].

(ii) Reaction of 2-tert-butylaniline with catechol. In an attempt to prepare 2-(2-tert-butylanilino)phenol by a shorter and more direct route, 2-tert-butylaniline and catechol were condensed by the method of Schmitt et al.[149] After reacting for 19 h and initial work-up, the dark, viscous product was chromatographed on alumina. Elution with ether gave a greyish solid which was recrystallised from ethanol to give glistening plates identified as carbazole (0.2 g, 1.5%), m.p. 244-246° (lit.,[150] 247-248°), by comparison of its i.r. spectrum with that of an authentic sample.[151]

Elution with ethyl acetate gave a green oil (b.p. 130-140°/0.1 mm) which slowly crystallised on cooling and was

identified as 2-anilinophenol (2.9 g, 20%), m.p. 68-69° (lit.,[152] 69-70°).

(iii) Reaction of 2-aminophenol with 2-tert-butylphenol. In a further attempt to prepare 2-(2-tert-butylanilino)phenol by the method of Schmitt et al.,[149] 2-aminophenol and 2-tert-butylphenol were reacted for 42 h. After work-up, distillation of the reaction mixture gave a first fraction identified as unreacted 2-tert-butylphenol, b.p. 38°/0.1 mm. The dark residue was sublimed, then recrystallised from benzene to give glistening straw-coloured plates identified as 2,2'-dihydroxydiphenylamine (2.50 g, 12%), m.p. 128.5-129.5° (Found: C, 71.4; H, 5.5; N, 6.95%; M^+, 201.078 589. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%; M, 201.078 973), ν_{max} 3600 and 3380 cm^{-1} (OH and NH), δ 6.42 br (1H, s, NH), 6.5-7.0 (6H, m, aromatic), 7.1-7.3 (2H, m, aromatic), and 8.33 br (2H, s, 2OH), m/e 201 (M^+, 100), 172 (21), and 108 [21, m^* 58.0 (201→108)].

7. Variable Temperature N.M.R. Studies on 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

7.1 General procedure. The oxazaphosphole (ca 40 mg) was dissolved in an appropriate solvent (0.4 ml; dry dichloromethane for low temperatures, diphenyl ether for high temperatures) in a 5 mm n.m.r. tube. The sample temperature was adjusted in the spectrometer probe using a Varian temperature control unit and allowed to stabilise before spectra were recorded on either a Varian HA-100 instrument (250 Hz sweep-

width), or a Varian XL-100 instrument (mainly for ^{31}P n.m.r. spectra). Where separation of a single peak (or doublet) into several peaks (or doublets) was observed, the coalescence temperature (T_c) refers to that temperature at which the separate peaks (or doublets) merged to become just indistinguishable. On the HA-100 instrument, the exact temperature was then found in the usual way from calibration against the chemical shift difference between the alkyl and hydroxy protons of a methanol sample (or ethenediol at higher temperatures). On the XL-100 instrument, direct measurement of the temperature was obtained from a thermocouple inserted directly into the probe. In general, coalescence temperatures were quoted within a range of ± 2 to $\pm 10^{\circ}$, depending on the clarity of the spectral changes being observed.

For equally populated two-site exchange processes, the free energy of activation (ΔG^*) was calculated by a combination of (1) the simplified Gutowsky-Holm equation[153] for the situation at the coalescence temperature:

$2\pi\tau\Delta\nu = \sqrt{2}$, where τ is half the lifetime of either site, and $\Delta\nu$ is the chemical shift difference (Hz) between the separated signals, and (2) the Eyring equation[154]:

$$k' = \frac{\sigma kT}{h} \exp\ (-\Delta G^*/RT)$$

where k' is the rate constant for the exchange process, T is the coalescence temperature ($^{\circ}K$), σ is the transmission coefficient (1.0), and other symbols are conventional.

Thus, $k' = \frac{\pi\Delta\nu}{\sqrt{2}}$ and hence:

$$G^* = RT \ln \left(\frac{\sigma kT \sqrt{2}}{\pi \Delta \nu h}\right)$$

$$= 19.1445\ T_c \left(9.9722 + \log \frac{T_c}{\Delta \nu}\right)\ J\ mol^{-1}$$

A transmission coefficient of unity was chosen to enable direct comparison of free energy values with those of the majority of other workers in this field, and because high energy trigonal bipyramidal structures are usually regarded as transition states rather than intermediates in any pseudorotation pathway[44].

Oxazaphospholes bearing like σ-substituents in the N-aryl ring were found to exhibit equally populated exchanging signals below the coalescence temperature, and the spectral changes observed for one such oxazaphosphole are described in section 7.2. Data obtained from the spectra of other such oxazaphospholes is listed in Table 2, and a full description and analysis of these spectra will be given in the appropriate chapter of the Discussion section.

For the coalescence of unequally populated peaks (or doublets), the free energy of activation was determined by the method of Shanan-Atidi and Bar-Eli,[155] which has been shown to best approximate the results of complete line shape analysis[156]. This method involves utilising the integral traces of major and minor signals to obtain the equilibrium constant for, and hence the free energy difference between, the two exchanging states. This enables calculation of the population difference (ΔP), and hence the variable, $\frac{X}{2\pi}$, from the relationship plotted by Shanan-Atidi and Bar-Eli. Thus, the free energy of activation for conversion of the major signal

to the minor is given by the expression:

$$\Delta G_A^{\ddagger} = RT \text{ in } \left(\frac{kTX}{h\Pi\Delta\nu(1-\Delta P)}\right)$$

$$= 19.1445\ T_c\ [10.6198+\log\ (\frac{X}{2\pi(1-\Delta P)})+\log\frac{T_c}{\Delta\nu}]\ J\ mol^{-1}$$

and the free energy of activation for the reverse process is given by:

$$\Delta G_B^{\ddagger} = 19.1445\ T_c\ [10.6198+\log\ (\frac{X}{2\pi(1+\Delta P)})+\log\ \frac{T_c}{\Delta\nu}]\ J\ mol^{-1}$$

Unequally populated exchanging signals were observed only in the variable temperature spectra of oxazaphospholes bearing a single σ-substituent in the N-aryl ring, and the spectral charges observed for one such example are described in section 7.3. Data obtained from the spectra of other singly σ-substituted oxazaphospholes is listed in Table 3, while a full description and analysis of these spectral features will be given in the Discussion section.

7.2 Variable temperature ^{1}H n.m.r. studies on 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles bearing like σ-substituents.

(i) 3-(2,6-Dimethylphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole. At +28°, the ^{1}H n.m.r. spectrum showed the following signals, δ ($CDCl_3$) 2.14 (6H, s, 2ArMe), 3.38 br (6H, d, 2POMe, J_{PH} 12Hz), 5.91 (1H, m, aromatic), and 6.4-7.8 (11H, m, aromatic). Variable temperature spectra of solutions in dichloromethane were recorded. At +45°, a sharp doublet (J_{POMe} 12Hz) resonating at δ 3.4 was observed

due to the magnetically equivalent methoxy ligands. This signal gradually broadened to a low hump as the temperature was lowered, being replaced by two sets of doublets at ca -35°, which gradually sharpened to two sharp three-proton doublets at ca -60°. The high-field doublet (J_{POMe} 10.7Hz) was assigned to the apical methoxy ligand in accord with its lower coupling constant as compared with the low-field doublet (J_{POMe} 14Hz), assigned to the equatorial methoxy ligand. The temperature at which these doublets coalesced was accurately measured as $-15\pm5^{\circ}$. Thus, with $\Delta\nu$ = 96Hz, ΔG^{*}=51.4±1.1 kJ mol^{-1} for the exchange of equatorial and apical methoxy ligands.

A further spectral change was observed when the σ-methyl resonance (a sharp singlet at $+45^{\circ}$) broadened on cooling and at ca -60° had separated into two three-proton singlets. The coalescence temperature for this process was $-32\pm3^{\circ}$ which, with $\Delta\nu$=17Hz, gave ΔG^{*} =51.3±0.7 kJ mol^{-1} for the two-site exchange.

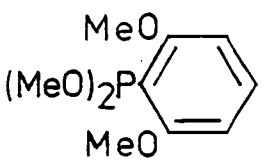
Data obtained from variable temperature studies of the above and other oxazaphospholes bearing like σ-substituents is listed in Table 2.

7.3 Variable temperature ^{1}H and ^{31}P n.m.r. studies on 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles bearing single σ-substituents.

(i) 2,3-Dihydro-2,2-dimethoxy-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole. At -127°, and ^{31}P n.m.r. spectrum of the oxazaphosphole consisted of two unequal singlets at δ-46.75 and δ-47.88 in the ratio of 5.5:1.

TABLE 2

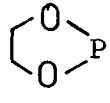
Variable temperature ^1H n.m.r.studies on 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles bearing like σ-substituents

N-Phenyl Substituent	$R^1_2R^2P$		T_c (°C)	Δν(Hz)	ΔG^* (kJ mol^{-1})
2,6-Me_2	$(MeO)_2PPh$	[a]	-15±5	96	51.4±1.1
		[b]	-32±3	17	51.3±0.7
2,6-$(OMe)_2$	$(MeO)_2PPh$	[a]	-17±5	96	51.0±1.1
		[b]	-36±3	20±1	50.1±0.8
2,6-$(OMe)_2$	Me_2PPh	[a]	-18±3	171±1	49.5±0.6
		[b]	-65±5	2±0.5	47.7±1.7
4-Me		[a]	-27±5	114±2	48.5±1.1
		[c]	-40±2	41±1	47.8±0.5

[a] From coalescence of PR^1_2 signals. [b] From coalescence of σ-NAr signals. [c] From coalescence of σ-PAr signals.

TABLE 3

Variable temperature n.m.r. studies on 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles bearing single σ-substituents.

N-Phenyl Substituent	$R^1R^2R^3P$	[b] T_c (°C)	Δν (Hz)	$\Delta G_A^{\ddagger}$ (kJmol^{-1})	$\Delta G_B^{\ddagger}$ (kJmol^{-1})	[h] $\Delta G_2^{\ddagger}$ (kJmol^{-1})	[a] ΔG (kJmol^{-1})
2-Me	$(MeO)_2PPh$	[d] -44±10	105±2	47.7±3.7	45.3±2.7	[c] >93	2.4
		[e] -58±5	17.5±0.5	48.0±2.6	45.7±1.7		
		[f] -60±5	46	45.9±2.4	43.5±1.5		
2,4-Me_2	$(MeO)_2PPh$	[d] -40±15	105±2	48.5±5.0	46.2±3.8	[c] >95.6	2.4
		[e] -55±4	17±1	48.7±2.5	46.4±1.5		
		[f] -57.5±7.5	41	46.6±3.2	44.2±2.2		
2-OMe	$(MeO)_2PPh$	[d] -30±5	98±5	[a] 48.2±1.2		[c] 97.4±2.7	0
		[e] -45±10	22±1	48.0±2.3			
		[f] -50±5	31	46.2±1.1			
2-t-Bu	$(EtO)_2PMe$	[d] -1±2	69±5	55.0±0.6			0
		[g] -20±2	18±1	53.9±0.6			
		[f] +5±2	70±2	56.3±0.6			
2,4-Me_2	$(EtO)_2PMe$	[d] -52±2	83±5	44.0±0.6			0
		[f] -59±2	40	43.8±0.5			
2-Me	 PPh	[e] +196±4	17.5±0.5	[c] 104.5±1.3	102.8±1.3		1.7
2-OMe	PhMePOMe	[d] +113±4	5.5±0.5	[c] 88.8±1.7	87.7±1.6		1.1
		[g] +125±4	10±0.5	89.7±1.5	88.5±1.5		
		[e] +125±4	9.5±0.5	89.8±1.6	88.7±1.5		
		[f] +146±6	33±1	90.3±1.9	89.2±1.8		

Footnotes to Table 3 :

a When $\Delta G=0$, then $\Delta G_A^{\ddagger} = \Delta G_B^{\ddagger} = \Delta G^*$ for equally populated exchanging signals.

b Unless denoted otherwise, solutions were in CH_2Cl_2.

c In Ph_2O.

d From coalescence of P-OR signals. e From coalescence of σ-NAr substituent signals.

f From coalescence of ^{31}P n.m.r. signals (solvent contains 20% $(CD_3)_2CO$).

g From coalescence of P-Me signals.

h $\Delta G_2^{\ddagger}$: free energy of activation for complete equilibration of P-OMe signals.

On warming, these signals coalesced and at -40° a sharp single line at δ-46.90 was observed. Thus, with T_c=-60±5° and Δν =46Hz the method of Shanan-Atidi and Bar-Eli gave $\Delta G_A^{\ddagger}$ =45.9±2.4 kJmol^{-1} for the process involved. The free energy difference (ΔG) between the major and minor signals was calculated as 2.4 kJ mol^{-1}.

The low temperature ^{1}H n.m.r. spectrum of the oxazaphosphole (-95°) similarly exhibited major and minor signals in the ratio of 5.4:1 for both apical and equatorial P-OMe doublets and the o-methyl group of the N-aryl ring. A coalescence occurred as the temperature was raised and at +28° a sharp averaged spectrum was observed, consisting of two phosphorus-coupled doublets due to the two partially equilibrated methoxy ligands, and a sharp singlet due to the o-methyl substituent. From the positions and coupling constants of the methoxy doublets in the spectrum at +28°, it was apparent that coalescence of the major equatorial P-OMe doublet with the minor apical P-OMe doublet (and vice versa) had occurred. These P-OMe coalescences gave T_c=-44±10°, Δν=105±2Hz, and hence $\Delta G_A^{\ddagger}$ =47.7±3.7 kJ mol^{-1}.

Similarly, from the coalescence of major and minor o-methyl signals, T_c =-58±5°, Δν= 17.5±0.5Hz, giving $\Delta G_A^{\ddagger}$ =48.0±2.6 kJ mol^{-1} for this equilibration process.

Coalescence of the partially equilibrated P-OMe signals was not observed for this oxazaphosphole, the energy barrier for such a process being calculated as greater than 93 kJ mol^{-1} ($\Delta G_2^{\ddagger}$). However, complete averaging of the environments of the P-OMe groups was observed in the case of the N-(2-methoxyphenyl) analogue, for which a free energy barrier of 97.4±2.7

kJ mol^{-1} was required (T_c = 157±10°; $\Delta\nu$ = 6.0±0.5Hz).

Data obtained from the variable temperature spectra of the above and other oxazaphospholes bearing single σ-substituents is summarised in Table 3.

The spectra of several other oxazaphospholes studied have not been tabulated, but are discussed fully in the appropriate chapter of the Discussion section.

8. The Reaction of Substituted 2-Anilinophenols with Tervalent Phosphorus Compounds: Preparation of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles and their Decomposition Products.

General method. A general synthesis of pentacoordinate phosphorus compounds reported by Trippett et al.[82] was investigated to determine the potential of such a method for the preparation of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

Thus, a tervalent phosphorus compound (2 mmol) in super-dry ether (10 ml) was stirred at -78° under an atmosphere of dry nitrogen, while a solution of a substituted 2-anilinophenol (2 mmol) in ether (4 ml) was added dropwise. N-Chlorodi-isopropylamine[157] (2 mmol) in ether (4 ml) was then slowly added to the reaction mixture, which was stirred for a further

0.5 h at -78°, and stirring continued overnight at room temperature. The fine white precipitate of amine hydrochloride was filtered off in the dry-box, ether evaporated from the filtrate, and the crude reaction product examined and purified further if necessary.

8.1 Reaction of 2-(2-tert-butylanilino)phenol with sec-butyl methylphenylphosphinite. After reaction in the presence of N-chlorodi-isopropylamine, the crude product was obtained as an opaque gum which slowly crystallised. This material was washed with super-dry petrol to give a white solid which was recrystallised from petrol and identified as 2,3-dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole (0.50 g, 57%), by comparison of its n.m.r. spectra with those of an authentic sample (see section 3.4(i)).

In a replicate experiment, monitoring of the reaction mixture by ^{31}P n.m.r. spectroscopy showed the presence of a mixture containing the oxazaphosphole and its acyclic hydrolysis products. Subsequent distillation of the crude product gave a pale yellow glass (b.p.140-160°/0.05 mm) which was recrystallised from petrol and identified by its n.m.r. spectra as 2-(2-tert-butylanilino)phenyl methylphenylphosphinate (0.28 g, 37%) (see section 4.2(ii)).

8.2 Reaction of 2-(2-methylanilino)phenol with dimethylphenylphosphine. In an attempt to prepare 2,3-dihydro-2,2-dimethyl-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole, which could be isolated only with great difficulty when

prepared by a deoxygenation reaction, 2-(2-methylanilino)-phenol and dimethylphenylphosphine were reacted in the presence of N-chlorodi-isopropylamine. A ^{31}P n.m.r. spectrum of the colourless filtrate from the reaction mixture showed a major signal at δ-50.9 (ether, C_6D_6), believed to be due to the required oxazaphosphole. However, on removal of the solvent, the filtrate turned dark green in colour, and n.m.r. analysis of this viscous oil showed it to be an approximately equal mixture of dimethylphenylphosphine oxide and 2-(2-methylanilino)phenol.

9. Preparation of Optically Active 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

9.1 2,3-Dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole.

(i) Reaction of 2-nitrophenyl 2-tert-butylphenyl ether with optically active sec-butyl methylphenylphosphinite. In the manner of previous deoxygenation reactions, the nitro-compound and phosphinite were boiled under reflux in cumene for 67 h. After distilling the lower boiling solvent and optically active sec-butyl methylphenylphosphinate ($[\alpha]_D^{22}$ +6.6° in 1% ethanol solution), the crude product was obtained as an orange glass (1.05 g, 48%), which was triturated and recrystallised from dry petrol to give white crystals of optically active 2,3-dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole, identified by comparison of its n.m.r. spectra with those of the corresponding racemic

oxazaphosphole (see section 3.4(i)). The ^{31}P n.m.r. spectrum of the optically active oxazaphosphole showed the expected two equally intense signals at δ-28.6 and -29.0 due to diastereoisomerism arising from the chiral centres at carbon and phosphorus.

Attempts to separate these diastereomers by fractional crystallisation failed: recrystallisation from a generous amount of petrol gave several crops, which n.m.r. analysis showed to contain equal amounts of each isomer.

(ii) Reaction of 2-(2-tert-butylanilino)phenol with optically active sec-butyl methylphenylphosphinite. By the method of Trippett et al.[82] (see section 8), the anilinophenol and optically active phosphinite were reacted in the presence of N-chlorodi-isopropylamine to give a colourless glass (b.p. 160-180°/0.1 mm) which was triturated with petrol to give a white solid (0.35 g), identified by its ^{31}P n.m.r. spectrum as mainly the required oxazaphosphole, but also containing a small amount of acyclic hydrolysis products at δ+43.3 and +43.5. Attempted fractional crystallisation of this solid from a generous amount of petrol gave equal amounts of each oxazaphosphole diastereomer, but now with the acyclic phosphinate at δ+43.3 as the major product.

9.2 Reaction of 2-(2-tert-butylanilino)phenol with optically active sec-octyl methylphenylphosphinite. By the method of Trippett et al.,[82] the anilinophenol (0.96 g, 4 mmol) and phosphinite (1.01 g, 4 mmol) were reacted in the presence of N-chlorodi-isopropylamine (0.54 g, 4 mmol). A ^{31}P n.m.r. spectrum of the filtrate from the reaction mixture indicated

the presence of the required oxazaphosphole at δ-30.5 and -31.2 (ether - C_6D_6), but after work-up these signals had almost disappeared. The dark green viscous oil which remained was distilled to give the following fractions: (1) a viscous, reddish oil (b.p.150-170°/0.2 mm) identified by its n.m.r. spectra as crude sec-octyl methylphenylphosphinate; (2) a pale glass (b.p.190-210°/0.2 mm) which was recrystallised from petrol-cyclohexane to give a white solid identified as 2-(2-tert-butylanilino)phenyl methylphenylphosphinate (0.40 g, 26%), by comparison of its n.m.r. spectra with those of an authentic sample (see section 4.2(ii)).

10. Separation of the Diastereomers of 2,3-Dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

Following the failure of fractional crystallisation to provide a separation of the optically active diastereomers (see section 9.1), various chromatographic techniques were investigated in an attempt to separate the enantiomeric pairs of diastereomers present in the racemic oxazaphosphole mixture. The following account outlines the techniques employed and the observations made.

(a) H.p.l.c. Using a 25 cm alumina analytical column and 25% water saturated solvents, two closely separated peaks were eluted using fairly non-polar eluants such as (1) 0.1% n-propanol in hexane or (2) 0.75% ethyl acetate in hexane.

Less well resolved peaks, also believed to be due to the required diastereomers, were obtained using a silica column with solvents having a 10% saturation of buffer solution of pH 10, which hopefully reduces acid-catalysed hydrolysis of the pentacoordinate species on the column.

Financial considerations, coupled with the reduced column efficiency generally encountered on scaling up, weighed against the use of a preparative scale h.p.l.c. column.

(b) Combined l.p.c./h.p.l.c. In a first experiment using a 90μ alumina l.p.c. column, ether was used to rapidly elute a sample of oxazaphosphole solution (ca 100 mg). The major product fraction (as indicated by the U.V. detector of the l.p.c. apparatus) was evaporated and identified by its ^{31}P n.m.r. spectrum as a mixture of the required diastereomers. Thus, subsequent samples of oxazaphosphole were eluted at a slower rate using 2-10% ether in petrol, and collected as consecutive 25 ml fractions in an automatic fraction collector. These fractions were evaporated and analysed by h.p.l.c. on the 25 cm alumina column, eluting with 0.75% ethyl acetate in hexane (25% water saturated). A regular gradation in the diastereomer ratio was observed in the series of fractions, indicating that some degree of separation was indeed being achieved. For example, the ratio of the second isomer to the first (as measured by peak heights) changed from 0.8 to 4.8 over four consecutive fractions.

However, on repeating this process several more times to optimise conditions and check the accountancy, the following observations were made:

(1) the partially separated fractions from a slowly eluted sample of racemic oxazaphosphole (370 mg) were recombined and evaporated to give only a very small quantity of the required diastereomers (9 mg), identified by their n.m.r. spectrum.

(2) Faster eluted samples were isolated from the column in higher yield, but never above 10%.

(3) Continued elution with a more polar solvent, such as ethyl acetate-ether, gave a large, broad product peak. Analysis of the evaporated product by t.l.c. and n.m.r. spectroscopy revealed that the bulk of the oxazaphosphole originally injected had decomposed (presumably by hydrolysis on the column) to give a mixture of 2-(2-tert-butylanilino)-phenol and an acyclic hydrolysis product.

These observations led to the conclusion that the degree of decomposition increases with the length of time on the column, thus working against an efficient separation. Furthermore, since no single pure isomer had been isolated even in the slowest elution time, it was decided that l.p.c. is unsuitable for the required separation.

(c) H.p.l.c. The above decomposition prompted reinvestigation of the original h.p.l.c. experiments. Thus, for each injection of oxazaphosphole onto the 25 cm alumina column, the desired diastereomers were eluted first with 0.75% ethyl acetate in hexane (25% water saturated). Then, the column was flushed out with ether (25% water saturated) to elute any of the more polar hydrolysis products. In each case, ether eluted a far greater amount of hydrolysis products then oxazaphosphole, confirming the suspicion gained from the

l.p.c. work.

Using a standard solution of oxazaphosphole, conditions were varied to try to reduce the degree of decomposition: (1) the water content of the solvent system was varied between 0 and 100%, but this had no effect on the ratio of oxazaphosphole to hydrolysis products. (This justified the use of a 25% water saturation to optimise resolution). (2) The degree of hydrolysis was similarly unaffected by replacing the 25% water saturation with 25% saturation of a buffer solution of pH 10.

The conclusion to be drawn from these facts would appear to be that hydrolysis is occurring by a catalytic effect on the surface of the alumina.

Having failed to find a method of preventing decomposition occurring on the column, a final attempt was made to effect a complete separation of diastereomers on the alumina h.p.l.c. column by the laborious method of "peak cutting". The following procedure was carried out: the maximum injection size which gave acceptable resolution was determined as being 10µl, containing 1 mg of oxazaphosphole. As each peak was eluted through the detector (eluent 0.75% ethyl acetate in hexane), it was collected in a separate flask and stoppered. Three fraction cuts were taken containing (1) mainly the first isomer, (2) a mixed fraction, and (3) mainly the second isomer.

By repeating this process many times, evaporating the solvent from each of the collected cuts, and reinjecting a small sample of each concentrated cut for analytical purposes, a stage was eventually reached whereby the second isomer was

isolated in a virtually pure state, as confirmed by its chromatogram and ^{31}P n.m.r. spectrum. Unfortunately, the first isomer could not be isolated free from minor amounts of the second isomer.

Despite the isolation of one isomer, however, the method of separation remains highly unsatisfactory, due mainly to hydrolysis on the column. Moreover, the separation of one isomer of the corresponding optically active oxazaphosphole (to obtain an optically pure pentacoordinate phosphorus centre) in sufficient quantity to enable measurement of an optical rotation is obviously impractical by the method employed above.

11. Some Hydrolysis Reactions of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles

The hydrolysis of several oxazaphospholes was studied at various pH values. Acidic hydrolyses were performed in solutions containing aqueous toluene-4-sulphonic acid or hydrochloric acid, while aqueous dioxan buffer solutions of pH 7.2 and 13.3[158] were used for neutral and basic hydrolyses respectively.

11.1 2,3-Dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole.

(i) Acidic hydrolysis. The oxazaphosphole (0.18 g) was dissolved in dry ether (10 ml) and two drops of 2N aqueous hydrochloric acid were added. The mixture was stirred at

room temperature for 4 h, after which time ^{31}P n.m.r. spectroscopy showed no remaining oxazaphosphole and a single product peak. The ethereal layer was washed with water (2 x 10 ml), dried over anhydrous magnesium sulphate, and solvent evaporated to give a pale brown oil. Trituration with dry petrol and recrystallisation from petrol-ether gave a fluffy, white solid identified as N-(2-hydroxyphenyl)-P-methyl-P-phenyl-N-(2-tert-butylphenyl)phosphinic amide (0.11 g, 71%), m.p.114-116° (sealed tube, Gallenkamp) (Found: C, 72.7; H, 6.8; N, 3.7%; M^+, 379.169251. $C_{23}H_{26}NO_2P$ requires C, 72.8; H, 6.9; N, 3.7%; M, 379.170107), ν_{max} 3400 br (OH), 1440 (PPh), 1300 (ArN), 1150 (P=O), 1080, and 975 cm^{-1}, δ 1.38 (9H, s, t-Bu), 1.71 (3H, d, PMe, J_{PH}14Hz), 6.60 (2H, m, aromatic), 6.9-7.7 (11H, m, aromatic), and 11.19 (1H, s, OH), ^{31}P δ+43.5, m/e 379 (M^+, 100), and 208 [55, m^* 114.2 (379→208)].

(ii) Thermal and base-catalysed rearrangement of N-(2-hydroxyphenyl)-P-methyl-P-phenyl-N-(2-tert-butylphenyl)-phosphinic amide. The phosphinic amide can be most readily distinguished from its isomer, 2-(2-tert-butylanilino)phenyl methylphenylphosphinate, by n.m.r. spectroscopy. Thus, to a deuteriochloroform solution of the phosphinic amide contained in an n.m.r. tube, was added a slight excess of an authentic sample of the isomeric phosphinate. The ^1H n.m.r. spectrum of the mixture showed the P-methyl and t-butyl signals of the phosphinate resonating at lower field than those of the phosphinic amide; the ^{31}P n.m.r. spectrum showed two closely spaced signals at δ+43.5 (phosphinic amide) and δ+43.3 (phosphinate). Several drops of triethylamine were

added to the tube, and the spectral changes monitored. The phosphinic amide signals decreased as those of the phosphinate increased, until after 2 h, only the phosphinate signals remained. This base-catalysed rearrangement was confirmed by enhancement of the resultant ^{31}P n.m.r. signal on addition of authentic phosphinate.

Similarly, an approximately equal mixture of the phosphinic amide and phosphinate was boiled under reflux at 80^{o} in a cyclohexane-petrol mixture. Monitoring of the near-saturated solution over 1 h by ^{31}P n.m.r. spectroscopy indicated a gradual isomerisation towards a single product. Overnight cooling then gave an off-white solid identified by its n.m.r. spectra as 2-(2-tert-butylanilino)phenyl methylphenylphosphinate.

11.2 2,3-Dihydro-2,2-dimethoxy-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole.

(i) Acidic hydrolysis. The oxazaphosphole (0.35 g) was dissolved in dioxan (5 ml) containing several drops of aqueous toluene-4-sulphonic acid, and the solution stirred at room temperature. T.l.c. (petrol) indicated that no oxazaphosphole remained after 10 minutes; solvent was therefore evaporated and the residue dissolved in chloroform, washed with 1% aqueous sodium bicarbonate (2 x 10 ml) and water (3 x 10 ml), and dried over anhydrous magnesium sulphate. The solution was filtered and evaporated to a pale green viscous oil which was triturated and recrystallised to give a white solid identified as 2,3-dihydro-2-oxo-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole (0.24 g, 77%),

m.p. (from petrol-dichloromethane) 149-150° (Found: C, 72.6; H, 6.1; N, 3.8%; M^+, 363.140952. $C_{22}H_{22}NO_2P$ requires C, 72.7; H, 6.1; N, 3.85%; M, 363.138808), ν_{max} 1445 (PPh), 1270 (P=O), 1130, 1020, and 980 cm^{-1}, δ1.49 (9H, s, t-Bu), 6.1-6.4 (2H, m, aromatic), and 6.8-7.8 (11H, m, aromatic), ^{31}P δ+31.3, m/e 363 (M^+, 100), 348 [28, m^* 333.6 (363→348)], 332 (11), and 132 (14).

In solution, this cyclic phosphonamidate slowly isomerises to an equilibrium mixture of two rotational stereoisomers; thus, in the ^1H n.m.r. spectrum of a freshly dissolved sample, the t-butyl signal at δ1.49 was observed to decrease as a singlet at δ0.94 gradually increased, the remainder of the spectrum being unchanged. Similarly, over a period of several days, a minor peak in the ^{31}P n.m.r. spectrum (δ +31.5) was observed to increase to an equilibrium ratio of ca 1.5:1 in favour of the original peak (δ+31.3.).

The ultimate product of hydrolysis was prepared by dissolving the oxazaphosphole (0.28 g) in 20% aqueous ethanol (10 ml) containing concentrated hydrochloric acid (3 drops). The reaction mixture was boiled under reflux in an atmosphere of nitrogen for 17 h; ethanol was evaporated and the residue extracted into ether, washed with water, and dried over anhydrous magnesium sulphate. Evaporation of ether and distillation of the residue gave a colourless oil (b.p.130-140°/0.3 mm, oven temperature) identified as 2-(2-tert-butylanilino)phenol (0.19 g, 100%), by comparison of its n.m.r. and mass spectra with those of an authentic sample (see section 6.2).

(ii) Basic hydrolysis. The oxazaphosphole (162 mg) was

dissolved in aqueous dioxan buffered to pH 13.3 (20 ml). After stirring at room temperature for 24 h, solvent was evaporated and the residue dissolved in chloroform, washed with water, and dried over anhydrous magnesium sulphate. Evaporation of chloroform gave a dark green oil (155 mg) identified by its n.m.r. spectra as an approximately 2:1 mixture of the cyclic phosphonamidate and unreacted oxazaphosphole. No anilinophenol was detected in this slow hydrolysis reaction.

11.3 2,3-Dihydro-2,2-dimethoxy-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole.

(i) Acidic hydrolysis. The oxazaphosphole (114 mg) was dissolved in dioxan (5 ml) containing several drops of aqueous toluene-4-sulphonic acid, and stirred at room temperature. T.l.c. (ether-petrol) indicated that no oxazaphosphole remained after 30 minutes; the solution was therefore evaporated and the residue dissolved in chloroform, washed with water, and dried over anhydrous magnesium sulphate. Filtration and evaporation of the chloroform left a dark oil, tentatively identified as an anilinophenol. Subsequent distillation gave a pale, viscous oil (b.p.110-120°/0.15 mm, oven temperature) which was confirmed as 2-(2-methylanilino)phenol by comparison of its n.m.r. and mass spectra with those of an authentic sample (see section 6.1).

In a replicate experiment, anhydrous magnesium sulphate was added after 5 minutes stirring in an attempt to isolate an intermediate hydrolysis product. After work-up, the product was examined by n.m.r. spectroscopy and tentatively

identified as a 2:1 mixture of 2-(2-methylanilino)phenol and 2,3-dihydro-3-(2-methylphenyl)-2-oxo-2-phenyl-1,3,2-benzoxazaphosph(v)ole. The latter assignment was based on the observation of two signals of equal intensity in the ^{31}P n.m.r. spectrum (δ+29.2 and +30.0), and two corresponding methyl signals in the ^{1}H n.m.r. spectrum (δ1.82 and 2.36), by analogy with the two rotational stereoisomers observed in solution spectra of the corresponding 2-tert-butyl-substituted cyclic phosphonamidate (see section 11.2(i)). Further repeated reactions, however, failed to isolate the desired cyclic phosphonamidate.

11.4 3-(2,6-Dimethoxyphenyl)-2,3-dihydro-2-methoxy-2-methyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole.

(i) Basic hydrolysis. The oxazaphosphole (52 mg) was stirred at room temperature in aqueous dioxan buffered to pH 13.3 (15 ml). After 22 h, the solution was evaporated to dryness and the dark green residue dissolved in deuteriochloroform; n.m.r. spectra indicated a mixture of anilinophenol (70%) and unreacted oxazaphosphole (30%). However, when this solution was washed with water, dried, and redissolved in deuteriochloroform, its ^{1}H n.m.r. spectrum was completely different; no anilinophenol or oxazaphosphole was present, and the major product was tentatively assigned as the corresponding acyclic phosphinic amide. (Thus, the absence of a buffer solution during aqueous work-up may effect hydrolysis by a different mechanism on any unreacted oxazaphosphole).

In a replicate experiment, the oxazaphosphole was stirred for 5 h at 110° in aqueous dioxan buffered to pH 13.3. Solvent

was evaporated and the residue examined both before and after aqueous work-up; in each case, only a single product was present, identified as 2-(2,6-dimethoxyanilino)phenol by comparison of its ^{1}H n.m.r. spectrum with that of an authentic sample (see section 3.6(i)).

11.5 2-(2,6-Dimethoxyphenyl)-2,3-dihydro-2,2-dimethoxy-3-(4-methylphenyl)-1,3,2-benzoxazaphosph(v)ole.

(i) Neutral hydrolysis. The oxazaphosphole (0.43 g), dissolved in aqueous dioxan buffered to pH 7.2 (0.4 ml), was placed in a 5 mm n.m.r. tube and its hydrolysis at 30° monitored by ^{31}P n.m.r. spectroscopy. After 30 minutes, a single product peak was observed (δ+19.2) and the spectrum remained unchanged after a further 45 minutes. Thus, solvent was evaporated and the residue dissolved in deuteriochloroform to show the same peak in its ^{31}P n.m.r. spectrum. The ^{1}H n.m.r. spectrum of this solution identified the products of neutral hydrolysis as dimethyl 2,6-dimethoxyphenylphosphonate (55%) and 2-(4-methylanilino)phenol (45%), by comparison with the known n.m.r. spectra of these compounds (see section 3.7(i)). In a replicate experiment, enhancement of the ^{31}P n.m.r. signal (δ+19.2) was observed on the addition of authentic phosphonate to the reaction mixture.

(ii) Basic hydrolysis. Although fairly insoluble, a small quantity of oxazaphosphole was dissolved in aqueous dioxan buffered to pH 13.3 (1 ml) in an n.m.r. tube. Monitoring by ^{31}P n.m.r. spectroscopy showed hydrolysis to be occurring slowly; after 67 h at 30° some oxazaphosphole remained (δ-41.5). However, the major product (δ+20.0) was confirmed as dimethyl

2,6-dimethoxyphenylphosphonate by peak enhancement with an authentic sample, while a minor product (δ+15.6) was also detected. In a second experiment, hydrolysis was performed at 80°, and after 1 h only the two product peaks were observed, in the same ratio as above. The ^{31}P n.m.r. spectrum remained unchanged after a further 10 h, hence solvent was evaporated to give an orange oil identified as a mixture of dimethyl 2,6-dimethoxyphenylphosphonate (47%), 2-(4-methylanilino)phenol (40%), and an unidentified minor product (13%, ^{31}P δ+15.6), by analysis of its ^{1}H n.m.r. spectrum.

(iii) Acidic hydrolysis. In the course of several experiments, the oxazaphosphole was dissolved in dioxan containing either aqueous hydrochloric acid or toluene-4-sulphonic acid in varying quantities. The reactions were monitored by ^{31}P n.m.r. spectroscopy over several days; many product peaks were observed, each varying in intensity with time. Furthermore, different peaks were observed after work-up than before work-up.

In common with the neutral and basic hydrolyses, however, the n.m.r. spectra of these acidic reaction mixtures showed the presence of both the phosphonate and anilinophenol.

Attempts to prepare the corresponding cyclic phosphonamidate from this oxazaphosphole also gave multi-component mixtures of acidic hydrolysis products.

12. Flash Vacuum Pyrolysis of 2,3-Dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole.

A sample of the oxazaphosphole (ca 50 mg) was pyrolysed by Dr.H.McNab, University of Edinburgh. The white solid was vapourised over a period of 30 minutes (inlet temperature 120°), with pyrolysis being performed at 700°/0.02 mm. After cooling, dry nitrogen was admitted to the system and the brown oily product dissolved in deuteriochloroform. Comparison of its n.m.r. spectra with those of an authentic sample identified the single product as 2-(2-tert-butylanilino)phenyl methylphenylphosphinate.

13. X-Ray Crystallographic Analysis of 2,3-Dihydro-2-oxo-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole.

Recrystallisation of the cyclic phosphonamidate from cyclohexane-petrol gave crystals suitable for an X-ray crystallographic study, kindly undertaken by Dr.R.O.Gould, University of Edinburgh.

The solution was based on 1729 independent intensities having values at least three times as large as their standard deviations. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included in expected positions (C-H = 1.1Å) but not refined. At convergence, R = 0.058 (5.8%). Crystals were triclinic, space group $P\bar{1}$,

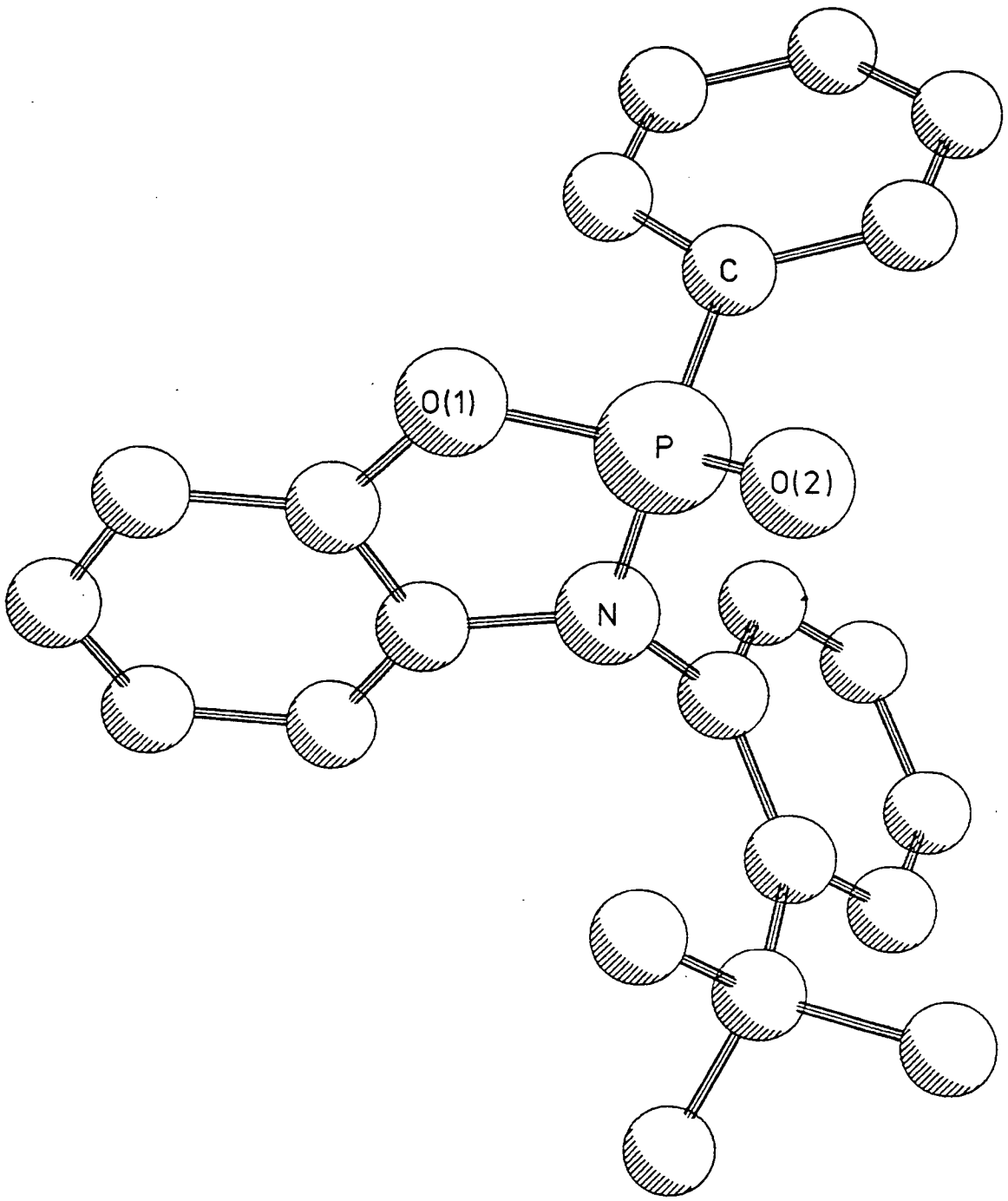


FIGURE 1: Stereoprojection of crystal structure of 2,3-dihydro-2-oxo-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

with cell dimensions: a = 9.342, b = 9.672, c = 12.042Å; α = 67.88, β 80.02, γ = 71.97°. The cell volume is 956Å^3, and the density calculated for two molecules per unit cell is 1.262 g cm^{-3}.

A stereoprojection of the molecule is shown in Figure 1, and the parameters about the phosphorus atom are listed in Table 4.

TABLE 4

Bond Angles (°) about Phosphorus		Bond Lengths (Å) to Phosphorus	
O(1) - P - O(2)	116.4	P - O(1)	1.620
O(1) - P - N	94.7	P - O(2)	1.465
O(1) - P - C	105.3	P - N	1.675
O(2) - P - N	108.6	P - C	1.788
O(2) - P - C	112.6		
N - P - C	108.6		

The standard deviations of bonds are about 0.005Å and of angles about 0.3°. Thus, the phosphorus atom has very nearly tetrahedral geometry, the only large distortion being that caused by the five-membered ring. Within experimental error, the nitrogen atom is planar, indicating sp^2 hybridisation. The hetero ring is almost coplanar with its fused benzene ring (interplanar angle 3.4°), and this entire ring system is essentially perpendicular to the other rings of

the system, the interplanar angles being: hetero to P-phenyl, 89.5°; hetero to N-phenyl, 84.8°. The angle between the planes of the two phenyl rings is 60°. This geometry places the tertiary butyl group at about the maximum possible distance from the P-phenyl ring.

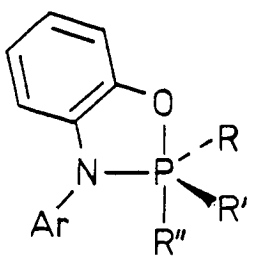
SECTION III

DISCUSSION

DISCUSSION

Programme of Research

The reduction of aryl 2-nitrophenyl ethers by tervalent phosphorus reagents has been used by Cadogan et al.[108] to prepare a range of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)-oles (157) in which the N-aryl group is symmetrically substituted.



(157)

The lability of these pentacoordinate compounds in the presence of water has been studied in some detail[114,115], as has the steric influence of the pendant N-aryl system on the ease of permutational isomerisation[110].

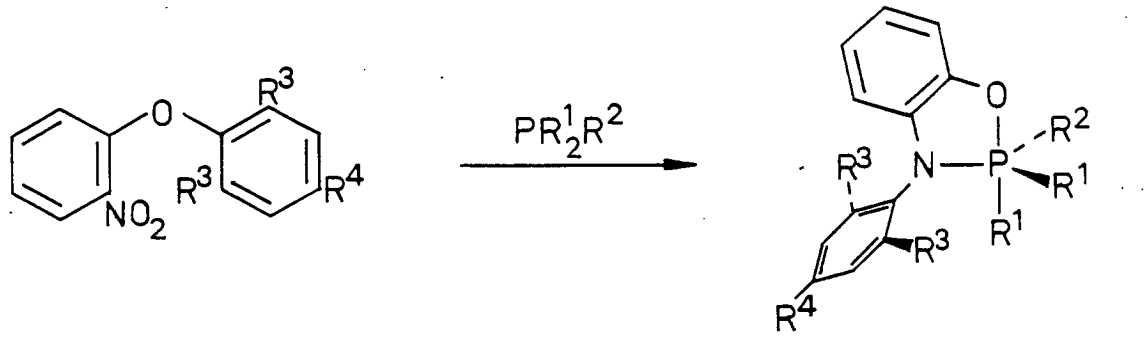
The research work described in this thesis has been devoted to continuing studies of the chemistry of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles. It was decided to extend the scope of the reaction by introducing less electronegative exocyclic ligands to the benzoxazaphosphole, and by incorporating asymmetrically substituted N-aryl groups. The effect of this asymmetry on the barriers to intramolecular rotation was particularly investigated using variable temperature n.m.r. spectroscopy, leading to a study

of chirality in the system, and to the attempted isolation and separation of a chiral monocyclic pentacoordinate phosphorus compound. Finally, the hydrolysis of several of these pentacoordinate benzoxazaphospholes was investigated to test a general theory which rationalises observed acid and base catalysed reaction products in terms of competing stereoelectronic factors.

1. Preparation of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphos-ph(v)oles and Their Decomposition Products

1.1 Introduction

Previous studies in this laboratory[108] into the reaction of aryl 2-nitrophenyl ethers with four equivalents of tervalent phosphorus reagent have given rise to a series of novel pentacoordinate benzoxazaphospholes by reaction of aryl 2-nitrophenyl ethers with four equivalents of tervalent phosphorus reagent (Scheme 69).



Scheme 69

The trigonal bipyramidal structure of the benzoxazaphospholes with an orthogonal N-aryl group as depicted in Scheme 69 was assigned on the evidence of hydrolysis products[108] and spectroscopic analysis[110], which have already been described in the Introduction (Chapter 2.7.2).

The properties and spectral analyses of the new pentacoordinate benzoxazaphospholes described in the Experimental section generally support these earlier observations.

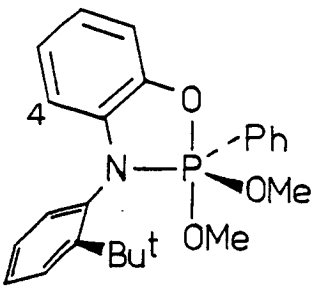
An improved procedure was employed, however, for the isolation stage in the preparation of these new phosphoranes. Thus, instead of using conventional small scale high-vacuum distillation apparatus, advantage was taken of the ease of operation , and hence the reduced possibility of atmospheric hydrolysis, afforded by the Kugelrohr bulb to bulb distillation technique. When combined with vacuum release in a nitrogen filled dry-box, this technique proved to be an extremely reliable and robust method of handling moisture-sensitive compounds. Consequently, benzoxazaphospholes prepared by the general method described in the Experimental section were normally obtained free from any hydrolysis by-products.

Yields were calculated on the basis of the final distillate which usually cooled to a hard, transparent glass. The purity of this fraction was checked by n.m.r. spectroscopy, but variations in yield tended to reflect the difficulties encountered in the separation of close boiling fractions, rather than any mechanistic change in the reaction pathway. As a rule, the closer the boiling point ranges of the final two fractions, the greater was the benzoxazaphosphole yield loss incurred in obtaining a crude glass of sufficient purity to allow trituration and recrystallisation. A detailed account of the characterisation of a typical 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)ole is given below.

1.2 Reaction of dimethyl phenylphosphonite with 2-nitrophenyl 2-tert-butylphenyl ether

After reaction in boiling cumene for 9 hours and removal of the lower boiling fractions, the product was obtained in

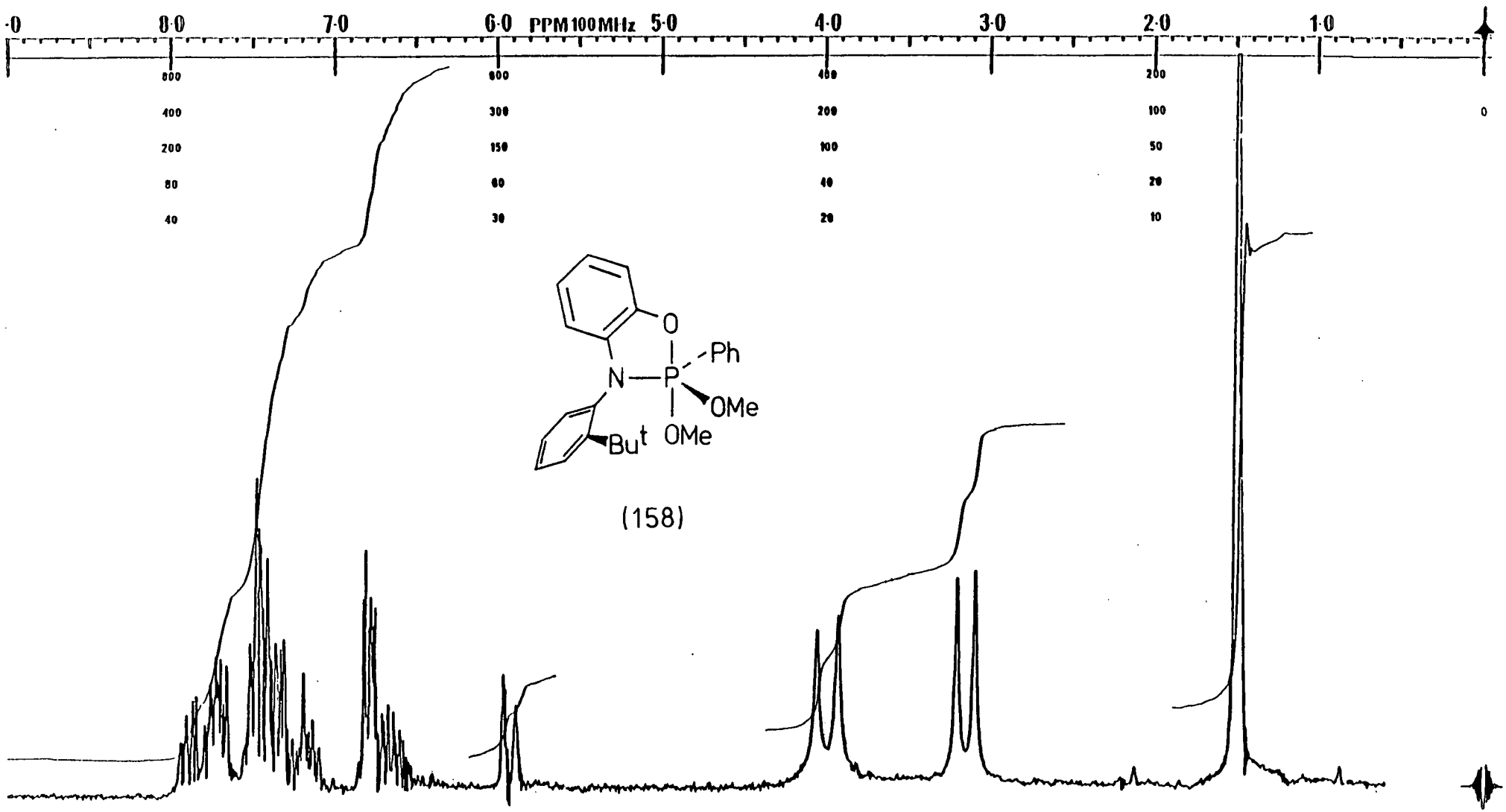
68% yield on Kugelrohr distillation, and identified as 2,3-dihydro-2,2-dimethoxy-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole (158). The structure and stereochemistry of (158) was based on the following spectral, analytical and chemical evidence.



(158)

The observed ^{31}P n.m.r. chemical shift at δ-47.3 is characteristic of pentacoordinate phosphorus compounds in general[159], and is also consistent with the chemical shifts of the corresponding N-phenyl and N-(2,4,6-trimethylphenyl) analogues (δ-45.0 and δ-46.7 respectively)[108]. Elemental analysis gave a carbon, hydrogen, and nitrogen content consistent with the empirical formula $C_{24}H_{28}NO_3P$. This was confirmed by mass spectroscopy which showed a molecular ion peak at m/e 409 (100%) and a metastable peak (m^* 121.6) consistent with the loss of dimethyl phenylphosphonate (409→223). Strong fragment peaks were also observed at m/e 378 (20%) and 363 (37%) due to the respective loss of methoxy and methyl groups.

Characteristic bands were observed in the i.r. spectrum corresponding to aryl-heteroatom stretching modes, viz. 1440 (PPh), 1310 (ArN) and 1265 cm^{-1} (ArO), in addition to several strong bands between 1150 and 900 cm^{-1} which were assigned to P-O-C stretching modes.



(158)

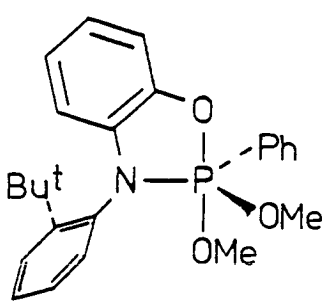
FIGURE 2: ^{1}H n.m.r. spectrum of 2,3-dihydro-2,2-dimethoxy-2-phenyl-3-(2-tert-butylphenyl)-benzoxazaphosph(v)ole (158).

The ^1H n.m.r. spectrum of (158) shown in Figure 2 illustrates various features characteristic of this class of phosphorane, and resonances were assigned as: δ1.40 (9H, s, t-Bu), 3.09 (3H, d, POMe, J_{PH} 11Hz), 3.89 (3H, d, POMe, J_{PH} 13.5Hz), 5.92 (1H, m, aromatic) and 6.4-8.0 (12H, m, aromatic). The multiplet or complex doublet resonating upfield from the other aromatic protons at δ5.92 was assigned to the C-4 proton in the benzoxazaphosphole ring. The strong shielding experienced by this proton is ascribed to ring current effect of the N-aryl ring when in its preferred orthogonal orientation with respect to the heteroaromatic ring. This compares with a similarly strong shielding (δ5.91) in the corresponding N-(2,6-dimethylphenyl) derivative, and an H-4 resonance of δ 6.14 in the unsubstituted N-phenyl compound[110]. The shielding in (158) is therefore consistent with the notion of N-aryl rotation being restricted to oscillation about a mean orthogonal plane. In compounds where the ortho-positions are "blocked", however, steric interference between aromatic systems is particularly severe, with the result that N-aryl movement is even more constrained within an orthogonal plane. Consequently H-4 experiences a stronger ring current, and hence increased shielding, when bulky substituents occupy the ortho-positions.

The two P-OMe ligands resonate as apparently separate phosphorus-coupled doublets at all temperatures. This observation differs from the ^1H n.m.r. spectra of the corresponding benzoxazaphospholes in which the N-aryl group is symmetrically substituted (i.e. bearing like ortho-substituents). These symmetrically substituted compounds exhibit separate

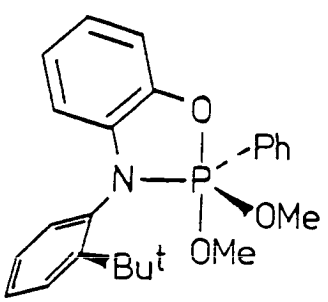
P-OMe signals at low temperature, but coalesce to an averaged 6-proton doublet at higher temperatures, indicating rapid positional exchange of ligands due to a regular P.I. process. The reason for the non-equivalence of P-OMe ligands in the ortho-t-butyl substituted benzoxazaphosphole is ascribed to the chirality introduced into the system by the presence of an asymmetric N-aryl group. This aspect is discussed in greater detail in Chapter 2.

With the N-aryl group restricted to an orthogonal plane (as indicated by the shielding of the 4-proton), the ortho-t-butyl substituent can lie in either a syn- or anti-configuration with respect to the bulky equatorial P-phenyl ligand. A consideration of molecular models shows the presence of severe steric crowding in the syn-configuration (159) and it seems likely that the most stable stereochemistry for this phosphorane will have the bulky tertiary butyl and P-phenyl groups in an anti-configuration (158).



(159)

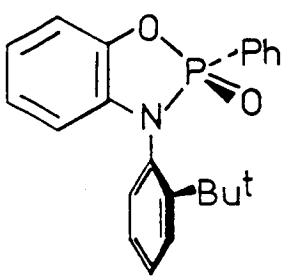
syn



(158)

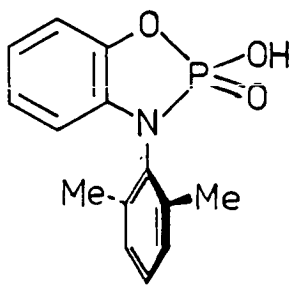
anti

No suitable crystals of the pentacoordinate phosphorane could be obtained to allow confirmation of this stereochemistry by X-ray analysis, but further indirect evidence came from the crystal structure of its cyclic phosphoramidate hydrolysis product, 2,3-dihydro-2-oxo-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole (160). Full details of the X-ray crystallographic analysis, including a stereoprojection of the structure (Figure 1), are given in the Experimental section, but essentially the structure possesses the anti-stereochemistry shown in (160). The geometry is



(160)

near tetrahedral at phosphorus, with a planar nitrogen atom indicating sp^2 hybridisation which maximises overlap of the perpendicular lone pair p-orbital with either an empty d-orbital on phosphorus, or the π-electron cloud of the adjacent fused benzene ring. Similar sp^2 hybridisation has been noted by Tait[111] in a related study of the cyclic phosphoramidate (161) and pentacoordinate phosphorane (162). The net effect of this anti-stereochemistry is to place the bulky tertiary butyl group as far as possible from the P-phenyl group.



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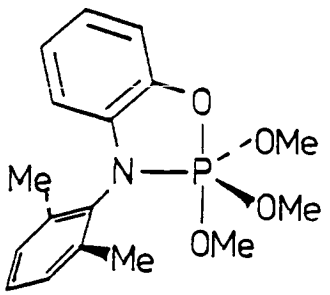
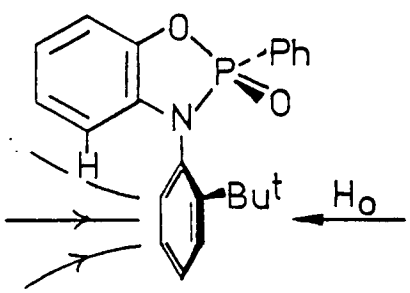


(162)

In order to relate the above stereochemistry to that of the original phosphorane (158), several features of the ^{1}H n.m.r. spectrum of the cyclic phosphonamidate are worthy of comment. Firstly, the aromatic proton in the 4-position of the phosphonamidate's heteroaromatic system (δ6.1-6.4) is less shielded than that in the corresponding phosphorane (δ5.92), indicating that sterically induced orthogonality of the pendant N-aryl system is not so pronounced in the tetracoordinate compound as in the corresponding pentacoordinate species. Similar observations have been made for symmetrically substituted phosphoranes and their tetracoordinate cyclic hydrolysis products[110].

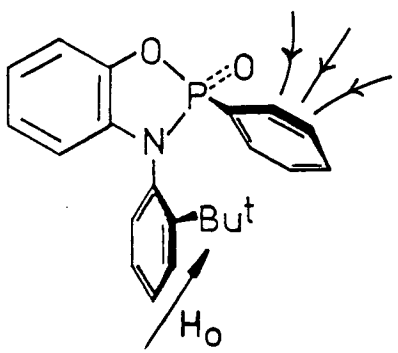
The second feature of note concerns the ortho-t-butyl substituent. In a freshly prepared solution of the cyclic phosphonamidate in deuteriochloroform, the t-butyl group resonated as a singlet (δ1.49), corresponding to the anti-configuration (160), but over a period of 7-10 days the intensity of this signal gradually decreased with the concomitant appearance of another singlet at δ0.94 to an equilibrium ratio of 1.5:1. Moreover, evaporation of the mother

liquors from recrystallisation of the original crude cyclic phosphonamidate gave an initial ^1H n.m.r. spectrum with signals at δ1.49 and δ0.94 in the ratio 0.75:1 respectively, but on standing for several days this gave the same equilibrium ratio of approximately 1.5:1 in favour of the signal at δ1.49. From these observations the minor equilibrium signal is ascribed to the sterically less favoured syn-isomer (163), in which the



(160)

anti



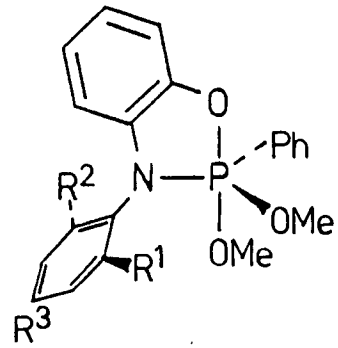
(163)

syn

t-butyl group is shielded by the ring current effect of the adjacent P-phenyl group, leading to an upfield shift to δ0.94. Since freshly dissolved crystals of the phosphonamidate show the anti-isomer signals once again, it is apparent that a fixed stereochemistry exists in the solid state, but in solution, a slow equilibrium is established between the syn- and anti-configurations.

The above spectral features show that despite restriction of N-aryl rotation being less severe in the tetracoordinate state, an anti-configuration is still the preferred stereochemistry. Therefore, it is reasonable to conclude that an anti-

TABLE 5



Compound	R^1	R^2	R^3	Yield (%)	$^{31}P\delta$ ($CDCl_3$)	M.p. (^oC)	Analysis (%)[a] C	H	N	$^1H\delta$ H-4 ($CDCl_3$)
164	OMe	OMe	H	85	-41.6	132-137	63.7	5.7	3.4	6.05
							63.9	5.85	3.4	
165	OMe	H	H	74	-43.2	111-112	65.5	5.75	3.75	6.08
							65.8	5.8	3.65	
166	Me	H	H	84	-45.6	99-99.5	68.4	6.3	3.6	5.96
							68.7	6.0	3.8	
167	Bu^t	H	H	68	-47.3	115-119	70.6	7.0	3.5	5.92
							70.4	6.9	3.4	
168	Me	H	Me	79	-45.3	123-124.5	69.2	6.35	3.65	5.93
							69.3	6.3	3.7	

a. Upper row, 'Found' values; lower row, 'Required' values.

configuration will also be preferred in the more crowded pentacoordinate structure of the original ortho-t-butyl substituted benzoxazaphosphole.

The preparation, characterisation and properties of all the other new benzoxazaphospholes studied are discussed in the appropriate sub-sections and tables below. The main objective of these sub-sections is to highlight significant trends and variations within the different classes of tervalent phosphorus reagents used to deoxygenate aryl 2-nitrophenyl ethers.

1.3 Reaction of dimethyl phenylphosphonite with aryl 2-nitrophenyl ethers

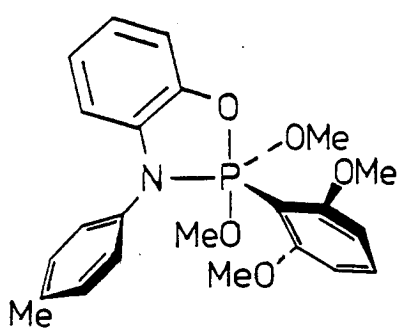
A range of predominantly asymmetrically substituted aryl 2-nitrophenyl ethers was reacted with dimethyl phenylphosphonite by the general method described in the Experimental section.

Table 5 lists the benzoxazaphospholes obtained in a pure state by this method, together with their yields, ^{31}P n.m.r. chemical shifts, melting points and elemental analyses.

Compounds (164-168) were all obtained as colourless, crystalline solids susceptible to hydrolytic degradation on exposure to the atmosphere, and hence were handled and stored in a dry-box flushed with dry nitrogen. The isolated yields generally reflect the ease of separation of the crude phosphorane fraction from the lower boiling dimethyl phenylphosphonite fraction.

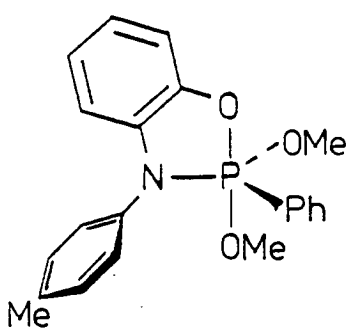
^{31}P N.m.r. chemical shifts ranged from -47.3 to -41.6

p.p.m. The higher chemical shifts associated with ortho-methoxy substituted compounds compared with the previously reported N-phenyl and N-(4-methoxyphenyl) derivatives[108] (δ-45.0) is tentatively ascribed to some contribution from the oxygen lone pair orbitals of the ortho-substituents towards the central phosphorus atom. Support for this suggestion comes from the observed chemical shifts of -41.7 p.p.m. for the dimethyl 2,6-dimethoxyphenylphosphonite derivative (169), compared with -44.7 p.p.m. for the corresponding benzoxazaphosphole (170) derived from dimethyl phenylphosphonite[108]. Electron releasing methyl and t-butyl ortho-



(169)

^{31}P δ-41.7



(170)

^{31}P δ-44.7

substituents in compounds (166-168), by comparison, give only a slight decrease in phosphorus chemical shift.

The final column of Table 5 records the ^{1}H n.m.r. chemical shift of the complex doublet or multiplet assigned to the highly shielded aromatic proton at position 4 of the benzoxazaphosphole system. Assuming that this shielding represents the proportion of time spent by the N-aryl group

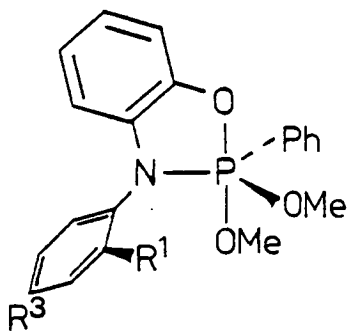
in the orthogonal plane due to steric constraints, a good correlation exists between the H-4 chemical shift and the size of the ortho-substituent. Thus, the bulky tertiary butyl group provides the greatest hindrance to N-aryl movement out of the orthogonal plane because of steric constraints imposed by the benzoxazaphosphole ring and the anti-P-phenyl ligand, and hence the large H-4 shielding (δ5.92) observed in the t-butyl derivative (167).

Both of the phosphoranes (164) and (165) bearing ortho-methoxy substituents, on the other hand, show least shielding of the 4-proton, reflecting the smaller bulk of this substituent and its ability to orientate the methyl part of the substituent to minimise steric interference, with the result that the N-aryl group has greater freedom to oscillate about the orthogonal plane.

The most important feature of the dimethyl phenylphosphonite derived phosphoranes listed in Table 5 has been the observation in low temperature n.m.r. spectra of diastereoisomers arising from the asymmetry conferred on the N-aryl ring by single ortho-substituents. Chapter 2 gives a detailed description of these temperature dependent spectra and their interpretation in terms of P.I. processes. It is pertinent at this stage, however, to consider only the lowest energy "frozen" structures identified by these dynamic n.m.r. studies, in order to discuss the effects of various steric interactions on the stereochemical structure and properties of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

Low temperature studies of the ^{1}H and ^{31}P n.m.r. spectra

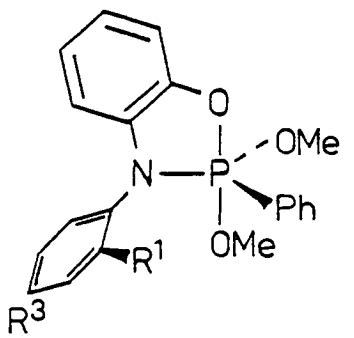
TABLE 6



a

anti

(major)



b

syn

(minor)

Compound	R^1	R^3	Isomer Ratio (a:b)
166	Me	H	5.5:1
168	Me	Me	5.5:1
165	OMe	H	1:1
167	Bu^t	H	∞

of several singly ortho-substituted benzoxazaphospholes have shown the presence of unequally populated diastereoisomeric forms (Table 6) corresponding to two possible orientations of the orthogonal N-aryl ring.

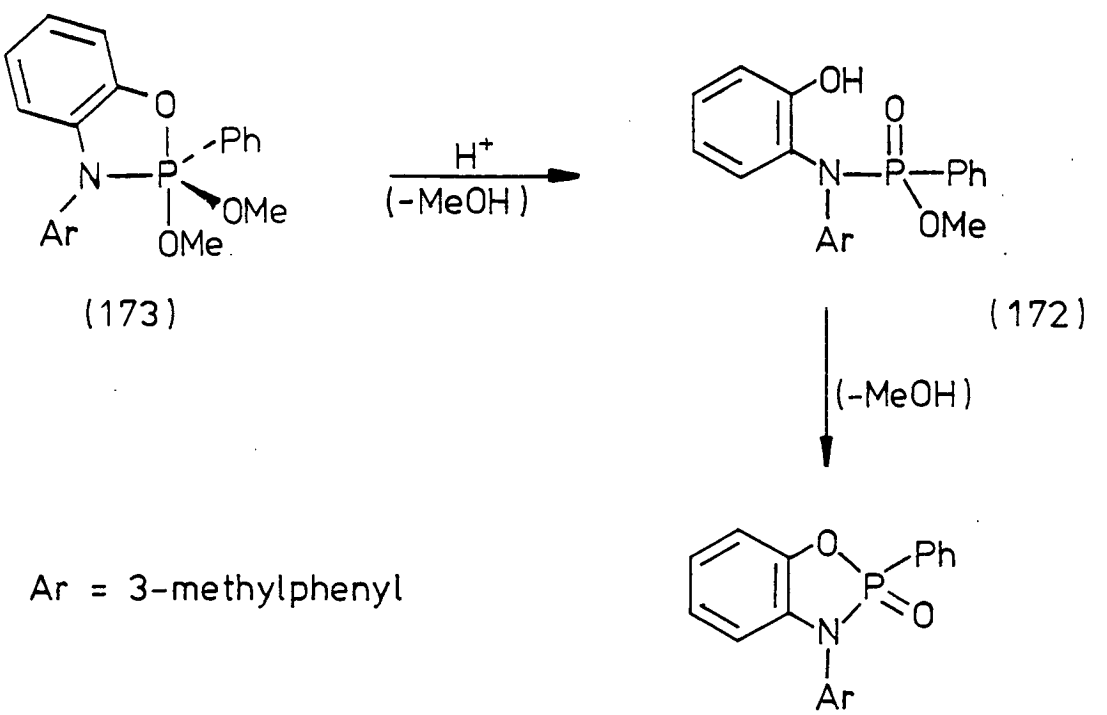
The ratio of major to minor isomer shown in Table 6 appears remarkably sensitive to the size of the ortho-N-aryl substituent. Thus, where an ortho-methyl substituent is present, this ratio is greater than 5:1, presumably because the minor isomer is disfavoured by serious steric interaction between ortho-methyl substituent and P-phenyl ligand in the syn-configuration.

In contrast, the greater flexibility of the "bent" ortho-methoxy group in (165) allows the bulky methyl part of the group to be orientated to minimise steric interaction with the P-phenyl ligand, with the result that syn- and anti-configurations are of similar energies (ratio 1:1).

In the extreme case of the large ortho-t-butyl substituent, steric interactions are so great that no minor isomer is observed at low temperatures, in accord with the conclusions made in Chapter 1.2 that the ortho-t-butyl substituted benzoxazaphosphole (167) exists entirely in the anti-configuration.

The successful isolation of pentacoordinate phosphoranes from the deoxygenation of ortho-methyl and -tertiary butyl substituted aryl 2-nitrophenyl ethers gave rise to similar expectations from deoxygenation of the corresponding meta-substituted ethers. Reaction of 3-methylphenyl 2-nitrophenyl ether with dimethyl phenylphosphonite, however, gave only the cyclic phosphonamidate (171) in 44% yield, as identified by its n.m.r. spectra (^{31}P δ+29.4) and accurate mass measure-

ment. Monitoring of a duplicate reaction by ^{31}P n.m.r. spectroscopy, however, showed the initial formation of a pentacoordinate species (^{31}P δ-46.1). This phosphorane could not be isolated on subsequent work-up of the reaction mixture, but an intermediate distillation sample was identified as a mixture of the cyclic phosphonamidate (171) and an acyclic P-OMe-containing compound tentatively identified as the phenolic product (172) from its n.m.r. spectra (POMe doublet, ^{1}H δ3.84; ^{31}P δ+18.9) and mass spectrum (M^+, m/e 353). It is postulated that the first formed benzoxazaphosphole (173)



(173) (172)

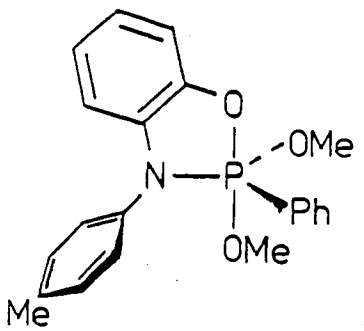
Ar = 3-methylphenyl

(171)

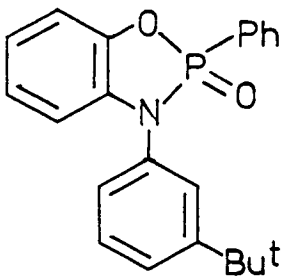
Scheme 70

undergoes mild hydrolysis in the presence of traces of moisture to give an intermediate acyclic phenol (172) which can subsequently cyclise with loss of methanol to give the cyclic phosphonamidate (171) (Scheme 70). Similar hydrolysis

reactions are known for trimethyl phosphite derived benzoxazaphospholes[114], and the isolated product is consistent with the hydrolysis mechanisms referred to in the Introduction (Chapter 4) for the closely related phosphorane (170).



(170)



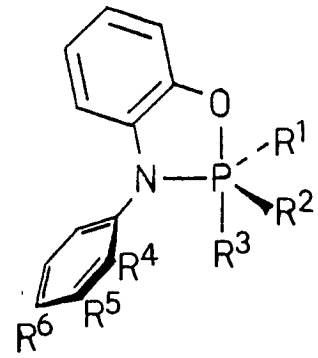
(174)

Deoxygenation of 2-nitrophenyl 3-tert-butylphenyl ether by dimethyl phenylphosphonite gave a viscous oil believed to be a mixture containing the cyclic phosphonamidate (174) (^{31}P δ+29.4) and the corresponding pentacoordinate benzoxazaphosphole (^{31}P δ-44.9) in the ratio 4:1. Although this oil could not be purified further to aid characterisation, initial phosphorane formation and subsequent decomposition probably follows an analagous mechanism to that suggested for the meta-methyl substituted compound in Scheme 70.

The cause of instability in these meta-substituted benzoxazaphospholes is not immediately evident. Repeat preparations suggest an inherent instability, possibly arising from steric interference between the meta-substituent and apical methoxy group, as a more likely reason than accidental ingress of moisture.

Prohibitive steric or electronic factors must also be considered as possible reasons for the failure of 1- and 2-naphthyl 2-nitrophenyl ethers to give any isolable products

TABLE 7



Compound	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	$^{31}P\delta$ ($CDCl_3$)	M.p. (^oC)	Analysis (%)[a] C	H	N	$^1H\delta$ H-4 ($CDCl_3$)
175	Ph	$-OCH_2CH_2O-$		Me	H	H	67	-32.3, -33.1	144-145	68.8	5.5	3.7	5.92
										69.0	5.5	3.8	
176	Ph	$-OCH_2CH_2O-$		H	Me	H	91	-31.8	183-185	68.7	5.5	3.7	6.04
										69.0	5.5	3.8	
177	Ph	$-OCH_2CH_2O-$		Bu^t	H	H	88	-31.0	174-175	70.6	6.5	3.4	5.82
										70.75	6.4	3.4	
178	Ph	$-OCH_2CH_2O-$		H	Bu^t	H	68	-32.2	164-165	70.7	6.5	3.3	6.03
										70.75	6.4	3.4	
169	2,6-dimethoxy -phenyl	OMe	OMe	H	H	Me	50	-41.7	132-134	64.7	6.1	3.25	6.10
										64.6	6.1	3.3	
179	Me	OEt	OEt	Bu^t	H	H	96	-35.6	(Oil)	375.196 765[b]			5.83
										375.196 320			
180	Me	OEt	OEt	Me	H	Me	95	-36.1	(Oil)	347.163 543[b]			5.86
										347.165 021			

[a] Upper row, 'Found' values; lower row, 'Required' values

[b] Exact mass

from deoxygenation reactions with both dimethyl phenylphosphonite and diethyl methylphosphonite. Nevertheless, some evidence of initial phosphorane formation was apparent from observation of the characteristic ^{31}P n.m.r. signals from reaction of 1-naphthyl 2-nitrophenyl ether with diethyl methylphosphonite (^{31}P δ-35.4), and from reaction of 2-naphthyl 2-nitrophenyl ether with dimethyl phenylphosphonite (^{31}P δ-47.9).

1.4 Reaction of other tervalent phosphonite esters with aryl 2-nitrophenyl ethers

A range of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles obtained from deoxygenation of aryl 2-nitrophenyl ethers with various other tervalent phosphorus di-esters (phosphonites) is shown in Table 7.

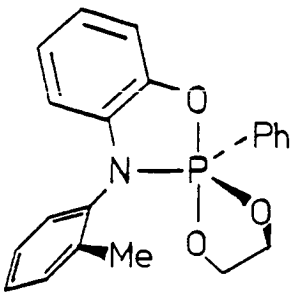
The spirobicyclic phosphoranes (175-178) derived from 2-phenyl-1,3,2-dioxaphospholan were isolated from particularly clean reactions in yields of 67-91%. These compounds were much less prone to hydrolysis than the corresponding phosphoranes derived from dimethyl phenylphosphonite. This illustrates the considerable stability afforded to spirophosphoranes by the presence of two five-membered rings which can span apical-equatorial positions, holding the TBP structure relatively rigid and strain-free. The effective "fusing" of two labile methoxy ligands into a bidentate ethylenedioxy ligand not only eliminates facile leaving groups (and hence risk of hydrolysis), but also decreases steric crowding around the phosphorus atom by holding the methylene groups

in a fixed plane away from the centre of the TBP. An illustration of this increase in stability and decrease in steric crowding is the isolation of phosphoranes (176) and (178); by comparison, meta-substituted phosphoranes could not be isolated using dimethyl phenylphosphonite.

The large difference in shielding of the 4-proton of the benzoxazaphosphole system between the ortho- and meta-substituted spirophosphoranes (Table 7) indicates that N-aryl rotation is less restricted in the meta-substituted compounds. Thus the degree of shielding in meta-substituted compounds is intermediate between the larger shielding observed for ortho-substituted examples, and the minimum shielding observed in unsubstituted or para-substituted benzoxazaphospholes.

The ^{1}H and ^{31}P n.m.r. spectra of the N-(2-methylphenyl) substituted spirophosphorane revealed that the compound exists at ambient temperatures as a mixture of unequally populated diastereoisomers (175a) and (175b) in the ratio of ca 3:1 respectively. This reduced isomer ratio (c.f. 5.5:1 for the corresponding monocyclic phosphorane) reflects the reduced steric crowding in the spirobicyclic structure. The assignment of major and minor isomers is based on greater shielding of the minor methyl group in the ^{1}H n.m.r. spectrum (δ1.95) compared with that of major methyl group at δ2.22.

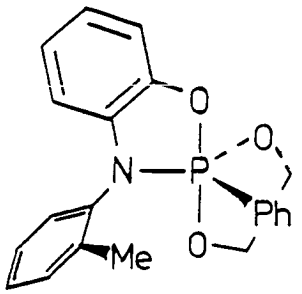
The corresponding meta-methyl substituted spirophosphorane [(176); Table 7] exhibited only a single ^{31}P n.m.r. signal (δ-31.8). A single methyl resonance was observed in its ^{1}H n.m.r. spectrum in $CDCl_3$ solution, but major and minor methyl signals were apparent in CH_2Cl_2 solution. The presence of syn- and anti-diastereoisomers therefore cannot be discounted,



(175a)

anti

^{31}P δ -32.3



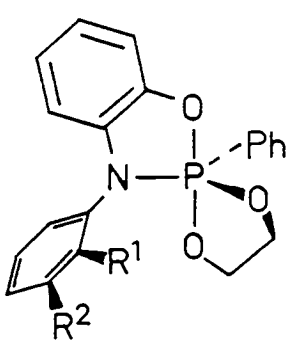
(175b)

syn

^{31}P δ -33.1

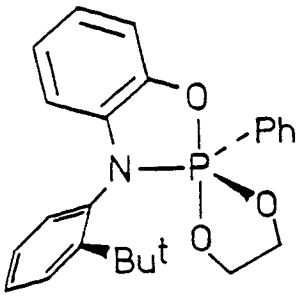
but the presence of only a single n.m.r. signal in high temperature solvents precluded investigation of the dynamic stereochemistry of (176).

Both ortho- and meta-tertiary butyl substituted spirophosphoranes, on the other hand, exhibited single ^{31}P n.m.r. signals and single t-butyl signals in the ^{1}H n.m.r. spectra at all temperatures. The increased bulk of the tertiary butyl group must therefore still disfavour the syn-configuration to such an extent that only the less hindered anti-isomers (177) and (178) were observed.



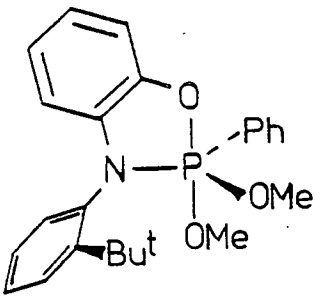
(177) : $R^1 = Bu^t$, $R^2 = H$

(178) : $R^1 = H$, $R^2 = Bu^t$



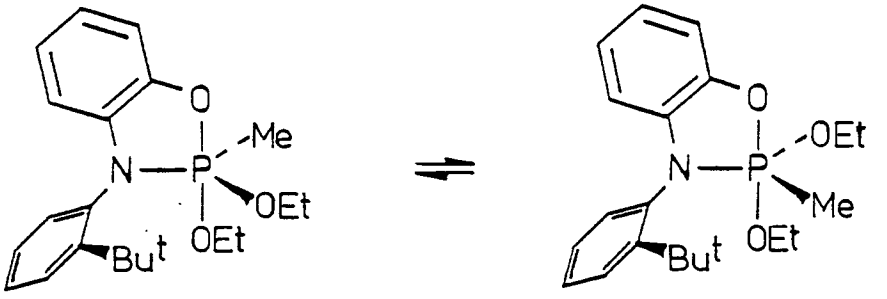
(177)

100% anti



(167)

100% anti



(179)

50% anti

50% syn

Scheme 71

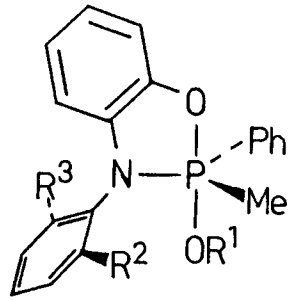
The effect of replacing the bulky P-phenyl ligand with a smaller methyl group was studied in compounds (179) and (180) (Table 7), derived from diethyl methylphosphonite. These benzoxazaphospholes were obtained as viscous oils in yields exceeding 95%. Redistillation failed to remove trace impurities sufficiently for correct elemental analysis, hence characterisation was based on accurate mass measurements.

Both the N-(2,4-dimethylphenyl) and N-(2-tert-butylphenyl) substituted benzoxazaphospholes derived from diethyl methylphosphonite displayed equally populated syn- and anti-diastereoisomers in their low temperature n.m.r. spectra. This observation contrasts with the large steric interactions which destabilised the syn-isomers in the corresponding dimethyl phenylphosphonite derivatives listed in Table 6. Scheme 71 illustrates the above stereochemical differences with reference to three ortho-t-butyl substituted benzoxazaphospholes. The spirophosphorane (177) exists 100% in the anti-configuration, as does the monocyclic compound (167) derived from dimethyl phenylphosphonite. The P-phenyl ligand in these compounds is expected to be orthogonal to the equatorial plane to maximise back-bonding to phosphorus, but such an orientation heavily disfavours a syn-configuration. The P-methyl ligand of the diethyl methylphosphonite derived phosphorane (179), on the other hand, provides no such steric hindrance to the syn-configuration. Consequently, (179) exists as a 50% mixture of syn- and anti-diastereoisomers (Scheme 71).

1.5 Reaction of tervalent phosphinite esters with aryl 2-nitrophenyl ethers

As part of a specific investigation into asymmetrically

TABLE 8



Compound	R^1	R^2	R^3	Yield (%)	$^{31}P\delta$ ($CDCl_3$)	M.p. (^oC)	Analysis (%)[a] C	H	N	$^1H\delta$ H-4 ($CDCl_3$)
181	Bu^{sec}	Bu^t	H	61	-28.6,-29.0	109-111	74.4	7.9	3.3	5.85
							74.5	7.9	3.2	
182	Bu^{sec}	Me	Me	78	-31.9	123-125	73.9	7.5	3.3	5.84
							73.7	7.4	3.4	
183[b]	Bu^{sec}	OMe	H	73	ca -28 (4-diastereo-isomers)	-		-		6.05
								-		
184	Me	OMe	OMe	88	-24.5	136-143	66.4	6.1	3.6	6.00
							66.5	6.1	3.5	
185	Me	OMe	H	81	-25.2,-26.1	126-131	68.4	6.0	3.9	6.03
							68.7	6.0	3.8	

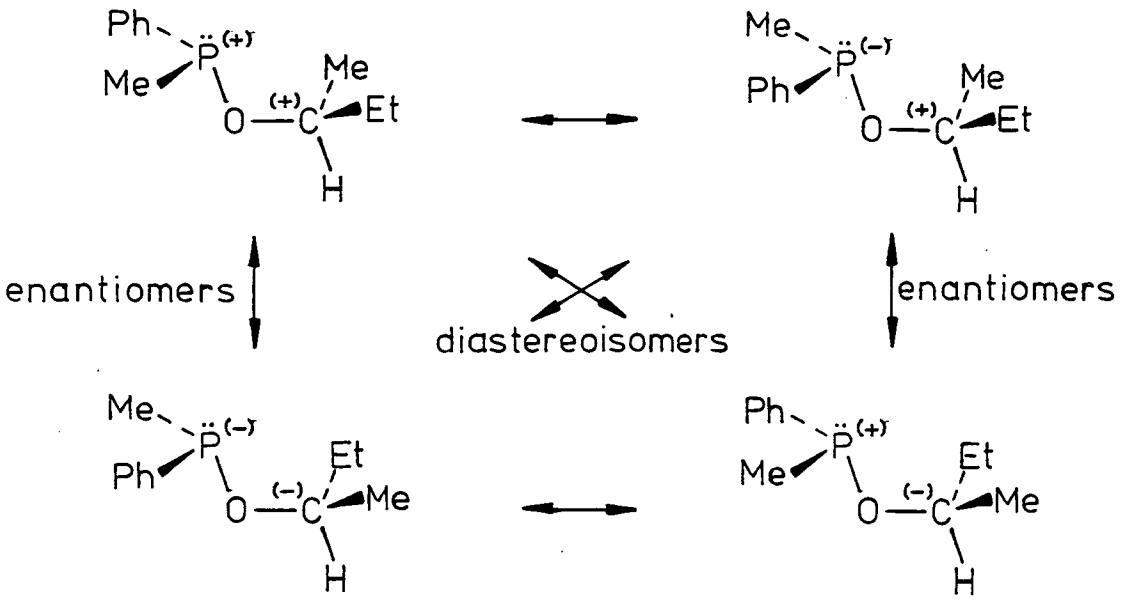
a. Upper row, 'Found' values, lower row, 'Required values.

b. Compound could not be recrystallised, hence was not obtained analytically pure.

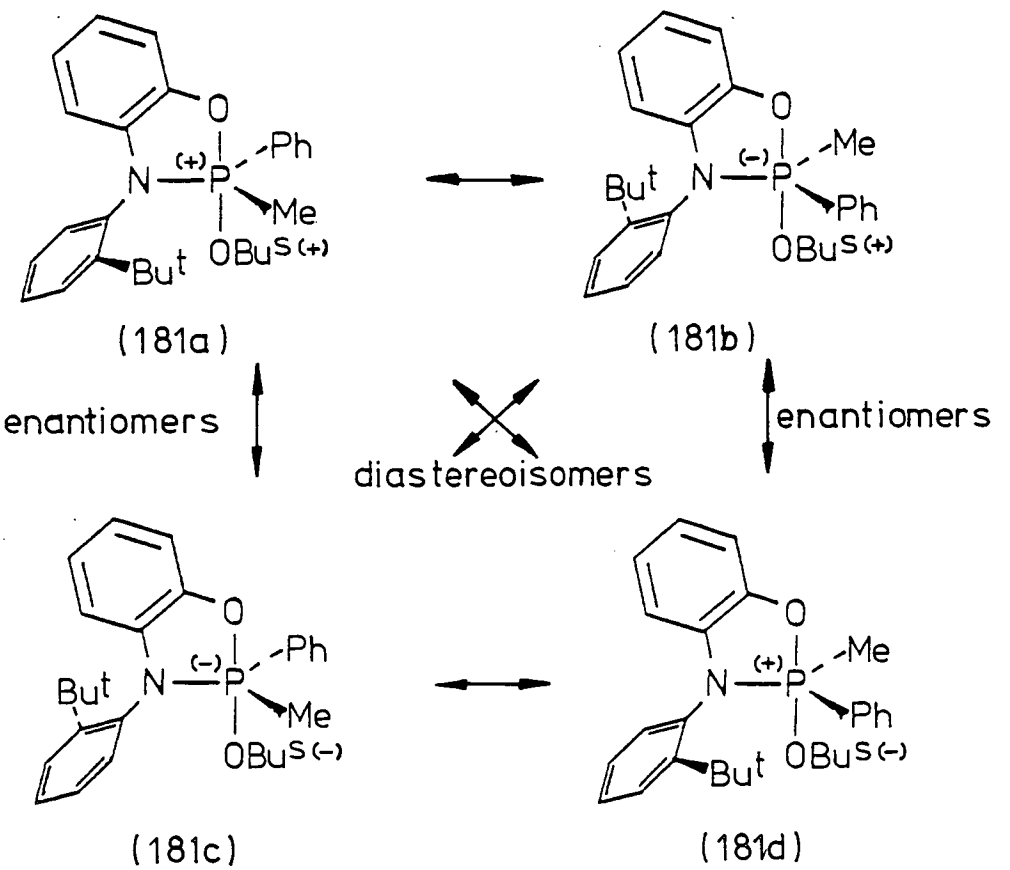
substituted benzoxazaphospholes which might permit the isolation of a chiral, non-interconverting monocyclic penta-coordinate phosphorus compound, a series of new compounds was prepared from two different tervalent phosphinite monoesters, viz. sec-butyl methylphenylphosphinite and methyl methyl-phenylphosphinite. The most stable diastereoisomeric structure for these benzoxazaphospholes are merely presented below, but have been assigned on the evidence of variable temperature n.m.r. studies and P.I. pathways detailed in Chapter 2. These phosphinite derived benzoxazaphospholes are listed in Table 8 which also includes appropriate characterisation data.

The characteristic shielding of the aromatic proton at position 4 in the benzoxazaphosphole ring is less in the case of o-methoxy substituents (δ>6.0) than for the more sterically rigid methyl and t-butyl ortho-substituents (ca δ5.85), in accord with similar observations for phosphinite derivatives.

The compound of major interest in Table 8 is the o-t-butyl substituted phosphorane (181). It follows from the absence of a minor diastereoisomer in the corresponding dimethyl phenylphosphonite derivative that no minor isomer should form in the equally crowded but more "frozen" TBP structure of (181). The introduction of a chiral carbon centre in a sec-butoxy ligand, however, might be expected to give rise not to "steric" but to "optical" diastereoisomers on interaction with a chiral pentacoordinate phosphorus atom, which cannot now be racemised by a P.I. process. The feasability of such a synthesis was assessed firstly using racemic sec-butanol, which reacted with methylphenylchlorophosphine to give sec-butyl methylphenylphosphinite as a racemic mixture of



Scheme 72



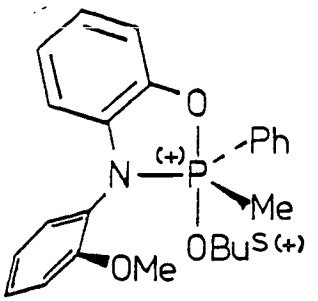
Scheme 73

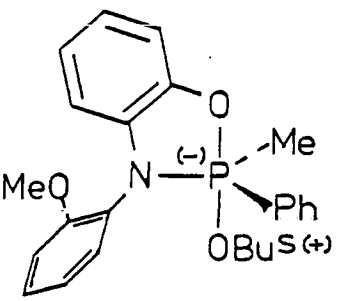
diastereoisomers ($^{31}P\delta$ +108.4 and δ+109.8), represented in Scheme 72 with the prefixes (+) and (-) arbitrarily indicating different directions of optical rotation at chiral centres. No coalescence of diastereoisomeric signals was seen for this tervalent phosphorus reagent in the ^{1}H n.m.r. spectrum up to 170°C, in accord with literature values for the energy barrier to inversion at phosphorus being >100kJ mol^{-1} [160].

Racemic sec-butyl methylphenylphosphinite was then used to deoxygenate 2-nitrophenyl 2-tert-butylphenyl ether, giving 2,3-dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole in 61% yield, as a racemic mixture of optical diastereoisomers (^{31}P δ-28.6 and δ-29.0). Using the same arbitrary designations for the direction of optical rotation, two optical diastereoisomeric phosphoranes can arise from phosphinite having dextrorotatory (+) geometry at sec-butyl carbon, viz with (+) geometry (181a) and laevorotatory (-) geometry (181b) at phosphorus (Scheme 73). The corresponding enantiomers of these structures, (181c) and (181d), will be formed from phosphinite having laevorotatory (-) geometry at sec-butyl carbon. Each ^{31}P n.m.r. signal therefore represents a pair of enantiomers which are magnetically equivalent.

The ^{1}H n.m.r. spectrum of (181) also shows two equally populated diastereoisomeric sets of signals for each of the P-OBu^{sec} and P-Me ligands. The absence of any signal coalescences at high temperatures suggests a "frozen" structure with oxygen atoms apical, as shown in Scheme 73.

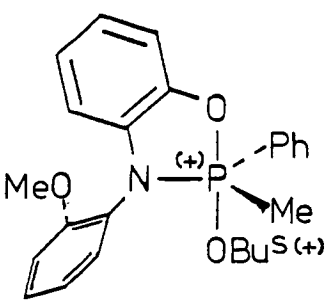
As a result of this racemic phosphinite giving stable

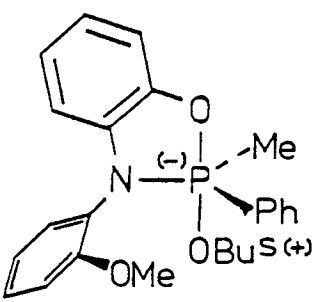




major isomers (anti)

(183)



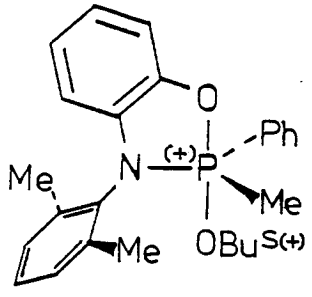


minor isomers (syn)

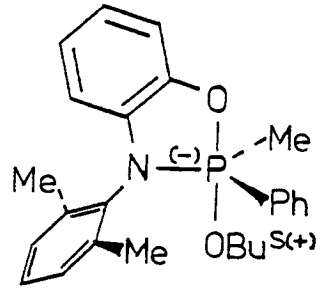
Scheme 74

optical diastereoisomers containing a chiral phosphorus centre an equivalent deoxygenation was carried out using optically active (+)-sec-butyl methylphenylphosphinite. This reaction and subsequent attempts to separate the two optically active diastereoisomers (181a) and (181b) are discussed in Chapter 3.

The remaining quantity of racemic sec-butyl methylphenylphosphinite was used to prepare two other benzoxazaphospholes composed of diastereoisomeric mixtures. Thus, deoxygenation of 2,6-dimethylphenyl 2-nitrophenyl ether gave compound (182) (Table 8), which variable temperature n.m.r. studies suggest comprises a non-interconverting mixture of optical diastereoisomers (182a) and (182b) (and their corresponding enantiomers).



(182a)

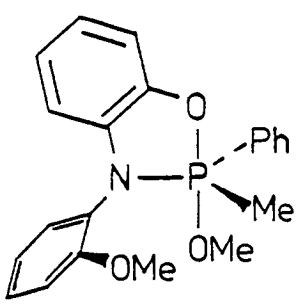


(182b)

Although it could not be isolated in a sufficiently pure state to allow complete characterisation, the benzoxazaphosphole (183) (Table 8), obtained from deoxygenation of 2-methoxyphenyl 2-nitrophenyl ether by sec-butyl methylphenylphosphinite, showed the presence of four diastereoisomers in its ^{31}P n.m.r. spectrum at +28°C. These isomers correspond to major and minor "steric" diastereoisomers in the ratio of ca 1.5:1 for each "optical" diastereoisomer arising from chiral phosphorus and carbon centres (Scheme 74).

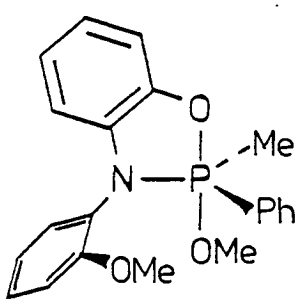
Each of these four diastereoisomers also has an enantiomeric form with the corresponding (-)-geometry at the chiral sec-butoxy ligand, but enantiomers are indistinguishable by n.m.r. spectroscopy.

By replacing the chiral sec-butoxy ligand with a simple P-OMe ligand, "optical" diastereoisomerism is lost, leaving only the possibility of "steric" diastereoisomerism. Thus, reaction of 2-methoxyphenyl 2-nitrophenyl ether with methyl methylphenylphosphinite gave a benzoxazaphosphole identified by n.m.r. spectroscopy as a slowly exchanging mixture of major (185a) and minor (185b) steric diastereoisomers in the ratio of ca. 1.4:1.



(185a)

anti



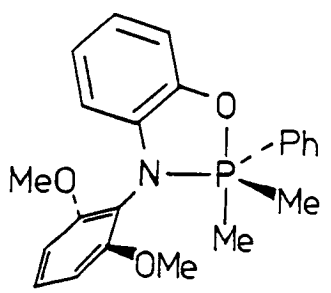
(185b)

syn

Evidence of the more "frozen" TBP structure associated with phosphinite derivatives is provided by the small coupling constant (J_{POMe} <11Hz) observed in the ^1H n.m.r. spectra of (185) and its N-(2,6-dimethoxyphenyl) analogue ((184), Table 8), which is characteristic of apical P-OMe ligands.

1.6 Reaction of phosphines with aryl 2-nitrophenyl ethers

The logical continuation of the above series of tervalent phosphorus reagents was to react dimethylphenylphosphine with aryl 2-nitrophenyl ethers, and thus to examine the effect of introducing less apicophilic exocyclic ligands on the formation and stability of pentacoordinate benzoxazaphospholes. Deoxygenation of 2,6-dimethoxyphenyl 2-nitrophenyl ether by dimethylphenylphosphine occurred rapidly in boiling cumene to give benzoxazaphosphole (186).



(186)

Its mass spectrum was unusual in displaying no fragment corresponding to loss of the phosphine oxide moiety. The most abundant fragment at m/e 245 corresponds to the anilino-phenol arising from homolysis of dimethylphenylphosphine and protonation of the resultant diradical species.

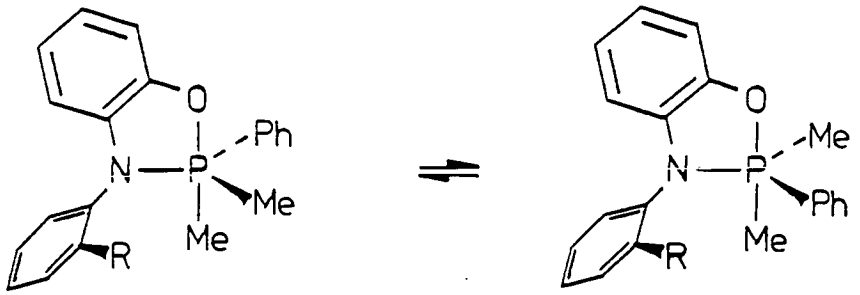
A ^{31}P n.m.r. chemical shift of δ-42.0 was obtained, and the ^{1}H n.m.r. spectrum at 28°C showed a broad 6-proton doublet at δ1.50, corresponding to magnetically equivalent P-Me ligands. A 6-proton singlet for the o-methoxy substituents also supports the view that rapid P.I. is occurring at 28°C to average both the P-methyl and ortho-substituent environments. The most

stable TBP therefore has the structure shown in (186), with the bulky and least apicophilic phenyl ligand occupying an equatorial position, and one methyl ligand equatorial and the other methyl ligand apical.

Another interesting feature of the ^1H n.m.r. spectrum of (186) was the increased shielding of the H-4 proton (δ5.85) compared with a chemical shift of δ6.05 for the similarly substituted benzoxazaphosphole derived from dimethyl phenylphosphonite (Compound (164), Table 5). This may be ascribed to the sterically less flexible P-Me ligand (compared with P-OMe) allowing less freedom for the N-aryl ring to oscillate about its mean orthogonal position.

The isolated benzoxazaphosphole stored under nitrogen in a dry-box appeared less stable than most benzoxazaphospholes; the white crystals assumed a dark green coloration after several days, characteristic of the presence of an analinophenol hydrolysis product. N.m.r. analysis of the stored compound confirmed its gradual decomposition to give a mixture of 2-(2,6-dimethoxyanilino)phenol and dimethylphenylphosphine oxide.

Two further deoxygenation reactions using dimethylphenylphosphine gave a final distillation fraction consisting of crude phosphorane, but these could not be purified sufficiently to allow complete characterisation. Nevertheless, n.m.r. spectra of the crude products suggest they exhibit a similar dynamic stereochemistry to that of the corresponding asymmetrically substituted dimethyl phenylphosphonite derivatives, with "frozen" structures comprising major and minor steric diastereoisomers (Scheme 75). Unfortunately, attempts to confirm this



anti (major) syn (minor)

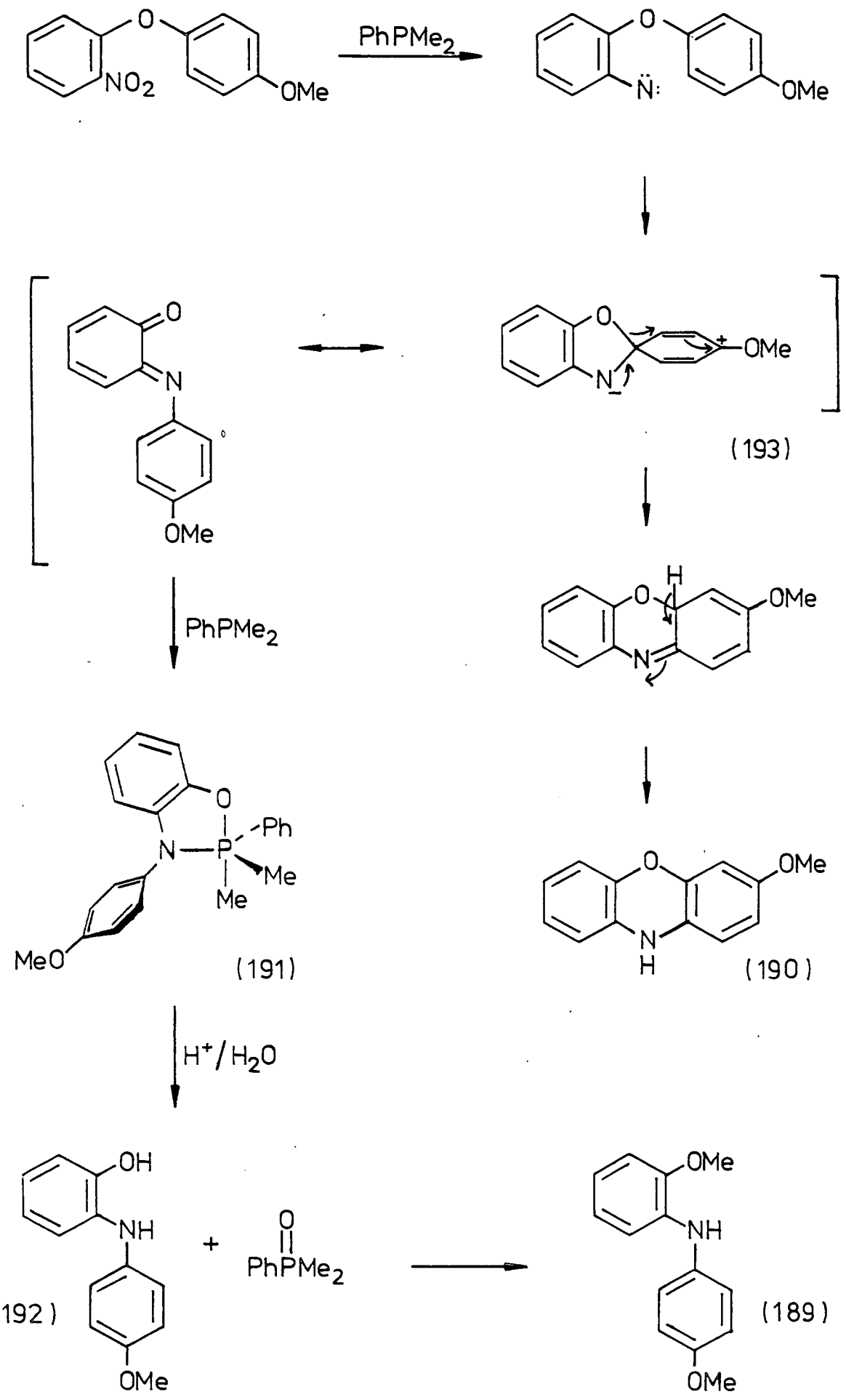
(187): R = OMe; $^{31}P\delta$ -42.5

(188): R = Me ; $^{31}P\delta$ -44.7

Scheme 75

stereochemistry through measurement of the diastereoisomer ratio in low temperature n.m.r. spectra were frustrated by rapid decomposition of solutions of the crude benzoxazaphosphole.

Reaction of dimethylphenylphosphine with 4-methoxyphenyl 2-nitrophenyl ether was monitored by ^{31}P n.m.r. spectroscopy, which showed the presence of a pentacoordinate species at δ-48.0 after 48 hours in boiling toluene. Work-up of the dark reaction mixture, however, gave only a yellow oil consisting largely of phosphine oxide, but with no pentacoordinate species. Low pressure chromatography enabled the separation and identification of 2,4'-dimethoxydiphenylamine (189) and 3-methoxyphenoxazine (190) in trace quantities from this yellow oil. Formation of these non-phosphorus containing minor products can still be rationalised within the overall mechanism proposed by Cadogan et al.[108] for benzoxazaphosphole formation. In Scheme 76 it is postulated that the lack of σ-substituents may increase the susceptibility of the pentacoordinate


PhPMe2
NO2
OMe
N:
(193)
PhPMe2
H
Ph
Me
Me
MeO
(191)
(190)
H+/H2O
OH
NH
PhPMe2
(192)
(189)

Scheme 76

benzoxazaphosphole (191) to hydrolysis during work-up, leading to a mixture of phosphine oxide and anilinophenol (192), as observed for other dimethylphenylphosphine derivatives. Methylation of the anilinophenol by dimethylphenylphosphine oxide under the reaction conditions then leads to formation of 2,4'-dimethoxydiphenylamine (189). There are several precedents for such alkylations of anilinophenols[109].

If the spirodiene intermediate (193) is reluctant to react with further tervalent phosphorus reagent, a 1,2-oxygen shift may be preferred (Scheme 76). Subsequent rearomatisation of the heterocyclic intermediate then gives rise to 3-methoxyphenoxazine (190). Analogous phenoxazines and related oxazepines have previously been isolated in low yields by Cadogan *et al.*[108], but only from deoxygenation of "*ortho*-blocked" ethers.

Trace quantities of phenoxazines are probably also formed in most deoxygenation reactions of aryl 2-nitrophenyl ethers, but the method used to isolate the main benzoxazaphosphole product (distillation followed by trituration and recrystallisation) almost inevitably precludes their isolation. (Grace and Tait[108] isolated trace phenoxazines by chromatography, but only at the expense of largely hydrolysing benzoxazaphospholes on the column, a procedure considered undesirable for the purpose of this work). Nevertheless, if benzoxazaphosphole formation can be sufficiently disfavoured by incorporating potentially bulky electropositive ligands, the spirodiene intermediate can be directed towards giving a phenoxazine exclusively. This was in fact observed in the

deoxygenation of 4-methoxyphenyl 2-nitrophenyl ether by tri-n-butylphosphine, where ^{31}P n.m.r. monitoring showed no pentacoordinate species, but dry column chromatography identitified 3-methoxyphenoxazine (24%) and tri-n-butylphosphine oxide as the major reaction products.

1.7 Scope of reaction

Earlier deoxygenation studies in this laboratory[108] using symmetrically substituted aryl 2-nitrophenyl ethers have indicated that the isolation of stable benzoxazaphospholes is more readily achieved using phosphonites than phosphites. The latter give rise to products which are more susceptible to hydrolysis, having three good alkoxy leaving groups of which two must occupy equatorial positions. Steric crowding also appears to influence susceptibility to hydrolysis, as phosphite derived benzoxazaphospholes with no ortho substituents were particularly difficult to isolate free from hydrolytic decomposition products. Both unsubstituted and ortho-blocked ethers, by comparison, gave relatively stable benzoxazaphospholes from dimethyl phenylphosphonite, due to the increased crowding associated with the bulky equatorial phenyl ligand.

Although this present work has not included phosphite deoxygenation reactions, the above trend has been evident in the general absence of hydrolytic impurities and good yields of asymmetrically substituted benzoxazaphospholes obtained from dimethyl phenylphosphonite and diethyl methylphosphonite. The sensitivity of dimethyl phenylphosphonite derivatives in particular to steric influences arising from the size of

various single σ-substituents is illustrated by the diastereoisomer ratios (Table 6) observed in low temperature n.m.r. spectra.

Exceptions to the general case of isolation of pentacoordinate benzoxazaphospholes from phosphonites were reactions involving meta-substituted aryl 2-nitrophenyl ethers. The isolation of meta-substituted spirophosphoranes from 2-phenyl-1,3,2-dioxazaphospholan, and evidence obtained from monitoring reactions by ^{31}P n.m.r. spectroscopy suggest that benzoxazaphospholes are at least formed initially. The presence of a meta-substituent however, may impart a steric or stereoelectronic instability to the pentacoordinate structure, leading to the isolation of cyclic phosphonamidates on work-up.

Phosphinites tended to give stable benzoxazaphospholes (Table 8) because of the "frozen" structure afforded by having both phosphorus-oxygen bonds apical and two electropositive ligands occupying equatorial positions. Only in the extreme case where a bulky ortho-t-butyl substituent can cause steric interference with the equatorial ligands was their evidence of hydrolysis of the benzoxazaphosphole (181) to an acyclic phosphinate (see Experimental section 4.2).

The utility of the deoxygenation reaction as a preparative route for benzoxazaphospholes approaches its limits with the use of phosphines. Dimethylphenylphosphine derivatives are extremely susceptible to hydrolytic decomposition, and increasingly so as the number of ortho-substituents decreases. Finally the reduced nucleophilicity of tri-n-butylphosphine compared with dimethylphenylphosphine may be sufficient to discourage even transient pentacoordinate phosphorane formation in favour of phenoxazine products, although steric factors cannot be discounted from influencing the course of this reaction.

2. Variable Temperature N.M.R. Studies on 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles

Preamble

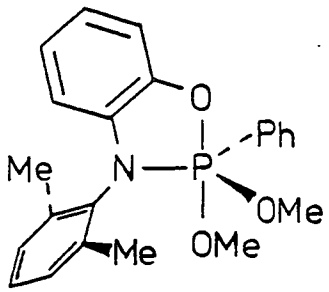
Previous variable temperature n.m.r. studies by Cadogan et al.[110] have measured coalescence temperatures (T_c) and hence the free energy of activation (ΔG^*) for permutational isomerisation in phosphoranes bearing a symmetrically substituted N-aryl group. These studies, summarised in the Introduction (Chapter 3), have shown that steric barriers between the heteroaromatic ring system and the essentially orthogonal N-aryl ring markedly affect the ease of ligand reorganisation.

This present work extends these variable temperature n.m.r. studies to several new symmetrically substituted phosphoranes, and also to a large number of asymmetrically substituted phosphoranes which give rise to the possibility of diastereoisomerism.

The general procedure employed in the variable temperature n.m.r. experiments is described in the Experimental section, together with the tabulated data (Tables 2 and 3) summarising measurements obtained from the spectra. Pseudorotation pathways in this chapter will be depicted using the Turnstile notation, which is more appropriate for describing cyclic TBP structures.

2.1 Benzoxazaphospholes bearing a symmetrically substituted N-aryl group

Numerical data obtained from variable temperature ^1H



(194)

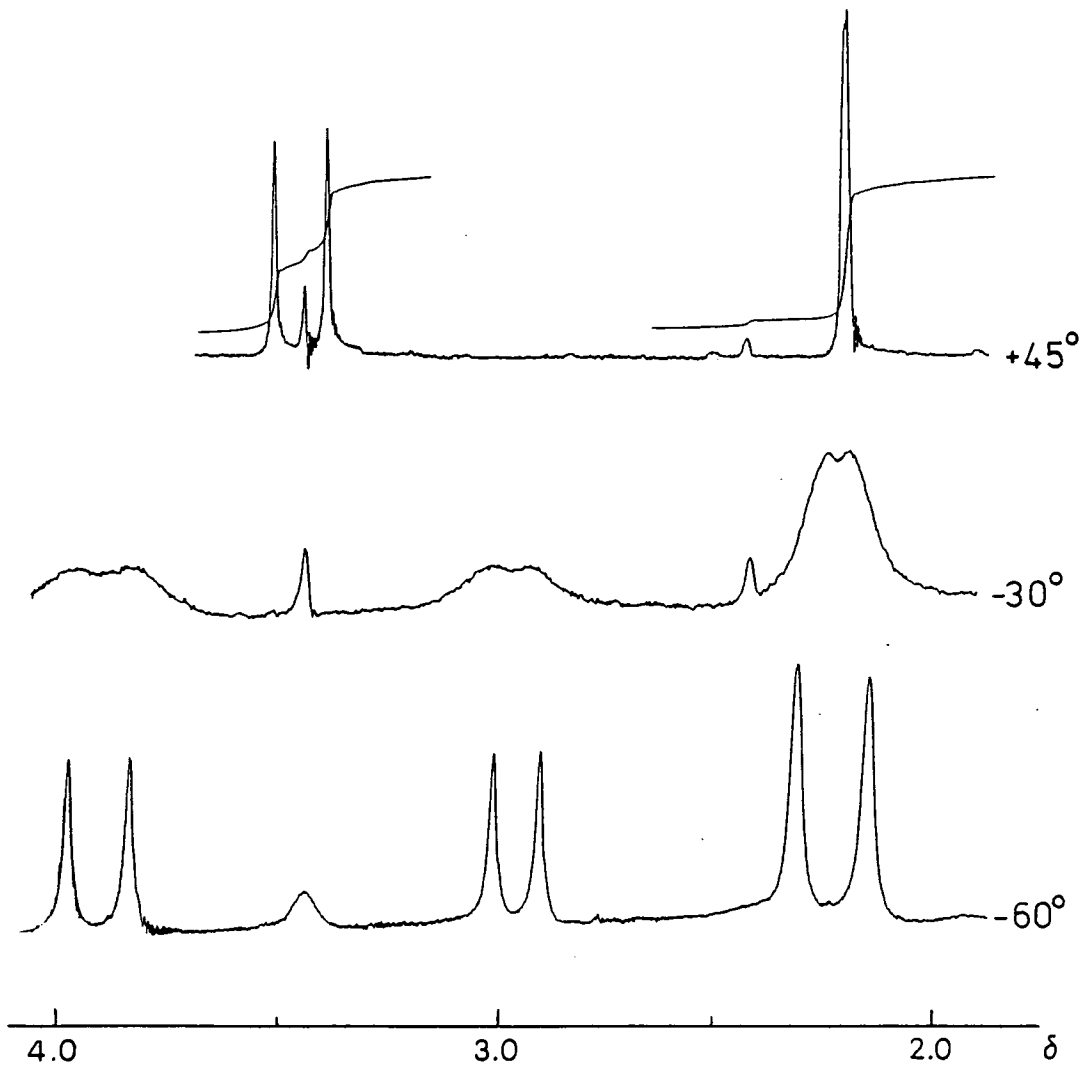
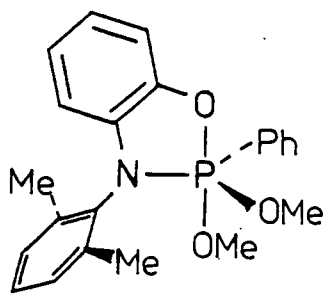


FIGURE 3: Variable temperature ^{1}H n.m.r. spectra of 3-(2,6-dimethylphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole (194).

n.m.r. studies of these compounds is summarised in Table 2 of the Experimental section.

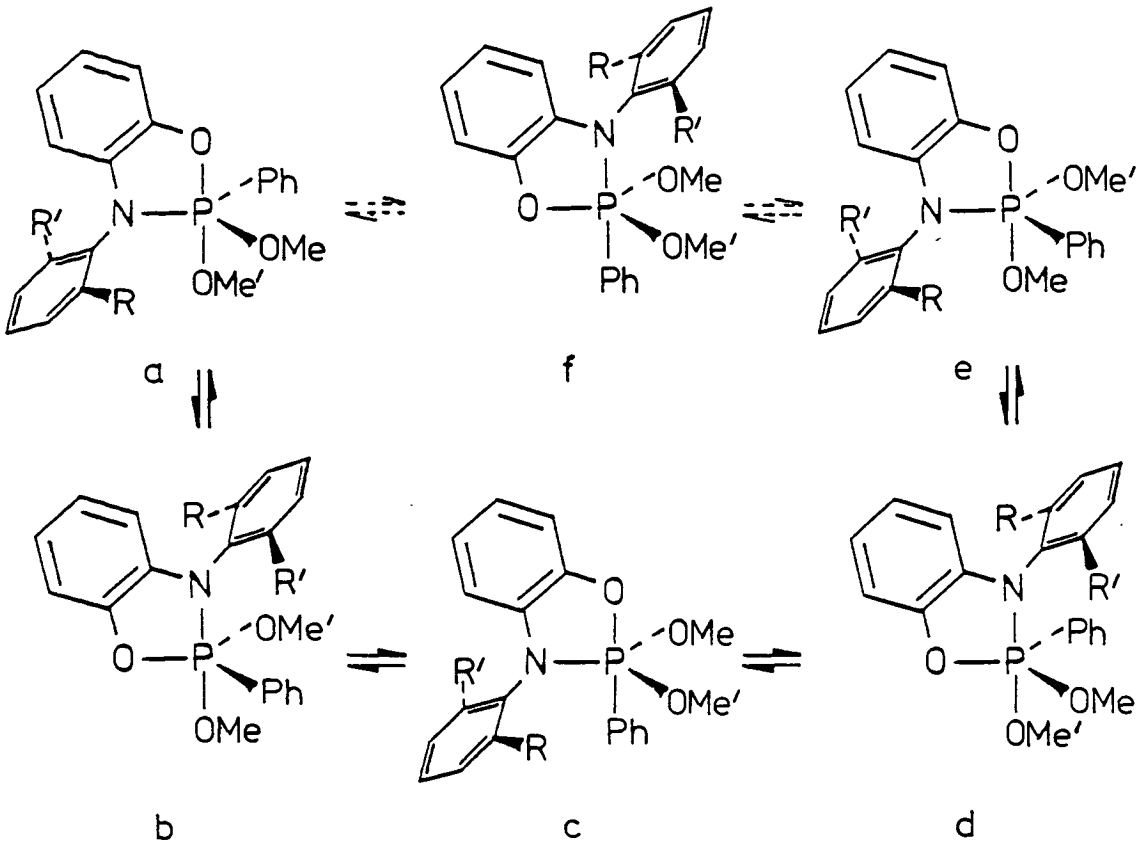
(i) 3-(2,6-Dimethylphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole



(194)

The temperature dependent ^1H n.m.r. spectra of the title compound (194) had not been investigated when it was first characterised by Tait[109], and hence preparation of a fresh sample provided a convenient starting point for dynamic n.m.r. studies.

The sharp doublet at +45°C (J_{POMe} 12.0Hz) due to the magnetically equivalent methoxy ligands broadened progressively as the temperature was lowered (Figure 3). By -60°C it had been replaced by two sharp three-proton doublets, the high-field doublet (J_{POMe} 10.7Hz) being assigned to the apical methoxy ligand and the low-field doublet (J_{POMe} 14Hz) to the equatorial methoxy ligand on the basis of the expected lower coupling constant for the longer apical bond. A temperature of -15±5°C was recorded for coalescence of these apical and equatorial doublets which had previously been separated by 96Hz ($\Delta\nu$). Thus, insertion of these values into the simplified Gutowsky-Holm[153] and Eyring equations[154] for equally populated



(194) : R = R′ = Me

(164) : R = R′ = OMe

Scheme 77

two-site exchange processes gave a free energy of activation of 51.4±1.1 kJ mol^{-1} for exchange of apical and equatorial methoxy ligands.

The sharp singlet corresponding to the σ-methyl substituents at +45°C also broadened with cooling, indicating retardation of the rapid P.I. process which equilibrates σ-methyl environments. By -60°C, two sharp three-proton singlets had arisen, consistent with each σ-methyl substituent now experiencing a different environment (syn and anti to the equatorial phenyl ligand). With a coalescence temperature of -32±3°C and $\Delta\nu$ of 17Hz, a free energy of activation of 51.3±0.7 kJ mol^{-1} was obtained for equivalence of σ-methyl groups.

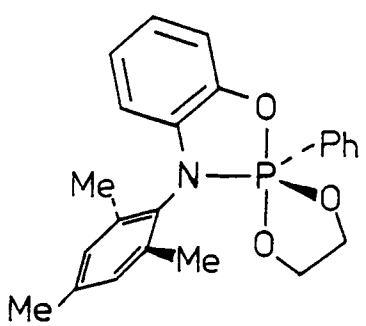
Both of the above coalescences can be accounted for by the same pseudorotation cycle, shown in Scheme 77. The most stable TBP is seen "frozen" in the low temperature spectra and is equivalent to structures (194a) or (194e), which are magnetically equivalent. This assignment satisfies the observation of separate P-OMe doublets at low temperatures, and is in full agreement with the factors affecting TBP stability discussed in the Introduction.

As the temperature increases, P.I. occurs faster than the n.m.r. timescale, causing coalescence of the separate methoxy resonances and the appearance of an averaged, rapidly interconverting environment at higher temperatures. In Scheme 77, the "frozen" TBPs (194a) and (194e) can be considered as separate enantiomers which must overcome an energy barrier of ca.51 kJ mol^{-1} (ΔG^{*}) in order to interconvert, or racemise, via the higher energy intermediate TBP structure (194b/c/d).

A shorter pathway to the equivalence of methoxy groups

via intermediate TBP (194f) is unlikely to occur because such a structure has both phenyl and amino functions apical, and is therefore a particularly high energy structure.

The rapid exchange of methoxy ligands represented in Scheme 77 also has the effect of averaging the environments of the o-methyl groups in (194), hence it is not surprising that the same free energy of activation is found for coalescence of o-methyl signals. An alternative explanation for ortho-substituent equivalence, involving simple N-aryl rotation, is ruled out by the very high energy barrier ($\Delta G^{*} > 96$ kJ mol^{-1}) found for coalescence of o-methyl signals in the spirophosphorane (195)[110].



(195)

Pseudorotation pathways analogous to that shown in Scheme 77 can adequately explain the dynamic n.m.r. spectra of the remaining benzoxazaphospholes bearing symmetrical N-aryl substituents, which are described below.

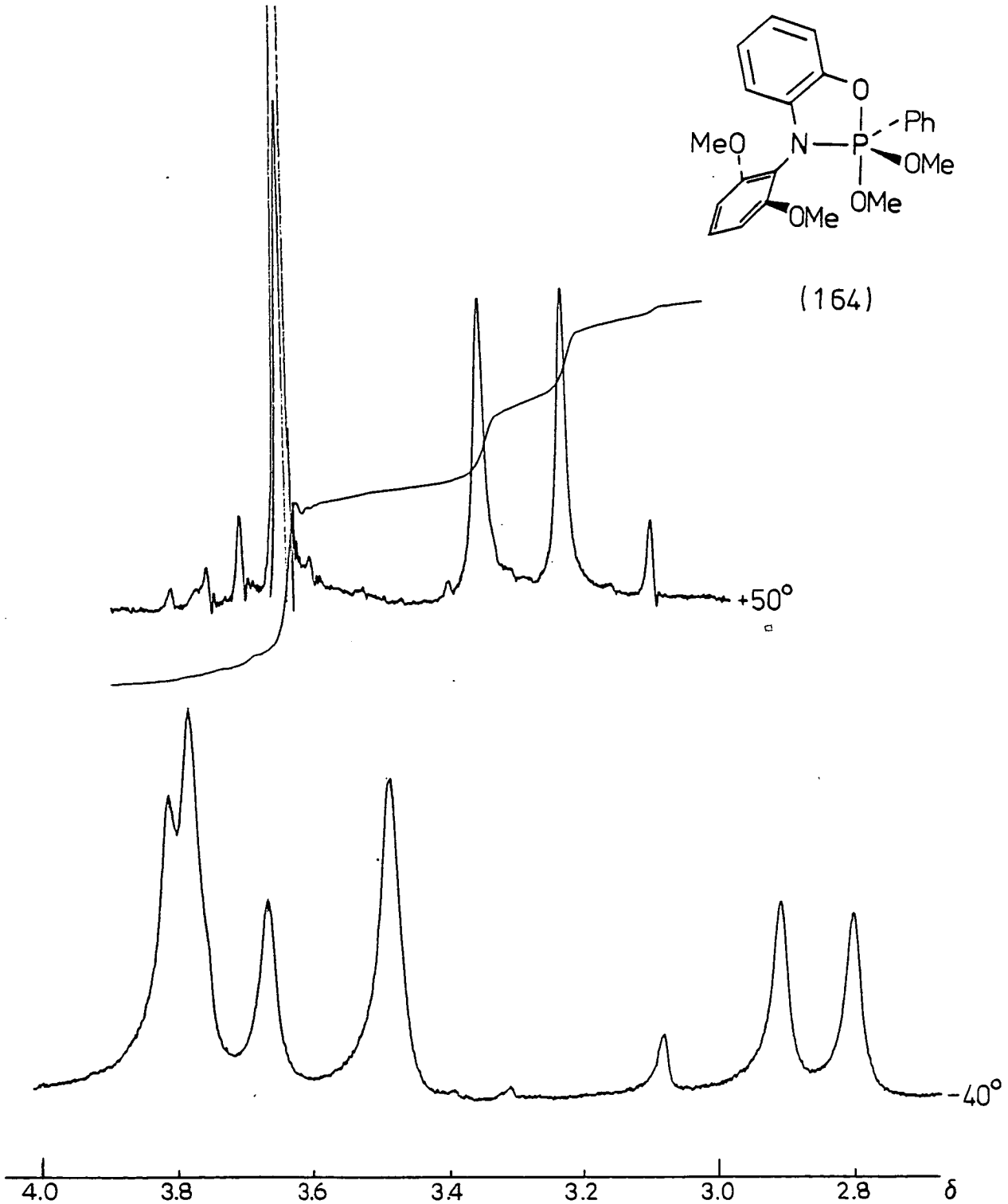


FIGURE 4: Variable temperature ^{1}H n.m.r. spectra of 3-(2,6-dimethoxyphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole.

(ii) 3-(2,6-Dimethoxyphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole

The ^{1}H n.m.r. spectrum of the title compound (164) at ambient temperature (28°C) shows a broad doublet at δ3.35, corresponding to magnetically equivalent P-OMe ligands exchanging above coalescence. This doublet sharpened to reveal a coupling constant of 12.2Hz at ca.+50°C (Figure 4). On cooling below ambient temperature loss of phosphorus coupling and peak broadening occurred until at ca.-15°C the coalescence point was approached. Below T_c, the broad mound split into two broad humps which by -60°C had sharpened to reveal two distinct doublets - a low-field doublet (J_{POMe} 14.0Hz) due to the equatorial P-OMe ligand, and a higher field doublet corresponding to the apical P-OMe ligand (J_{POMe} 10.7Hz). ΔG^* for exchange of P-OMe ligands was calculated to be 51.0±1.1 kJ mol^{-1} (T_c = -17±5°C; $\Delta\nu$=96Hz).

The magnetically equivalent σ-methoxy substituents at +28°C (δ 3.64) also split into two singlets as the temperature was reduced to -60°C. Although coalescence of these signals was masked to some extent by the P-OMe coalescence and the presence of impurity peaks in the spectra, ΔG^* of 50.1±0.8 kJ mol^{-1} was obtained from T_c of -36±3°C and $\Delta\nu$ of 20Hz.

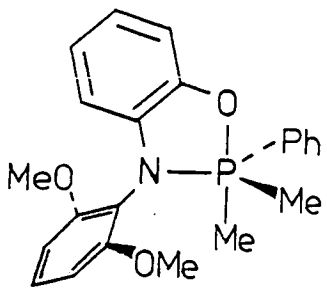
The P.I. process which rationalises the above coalescences is exactly analogous to that described for the N-(2,6-dimethylphenyl) analogue. Thus in Scheme 77, enantiomeric "frozen" TBPs (164a) and (164e) are rapidly interconverted via high energy TBP structure b, c, and d, leading to averaging of the environments of both the P-OMe ligands and σ-methoxy substituents by one and the same P.I. process.

(iii) 3-(2,6-Dimethoxyphenyl)-2,3-dihydro-2,2-dimethyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole

This first example of a 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)ole (186) with no exocyclic oxygen-containing ligands has temperature dependent n.m.r. features very similar to those of the dimethyl phenylphosphonite derivatives discussed above.

Thus, a fairly sharp six-proton doublet was observed at ca.+40°C (J_{PMe} 9Hz) due to rapid exchange of methyl ligands. As the temperature was reduced, this signal broadened and by -20°C had been replaced by two broad resonances. By -70°C, these resonances had sharpened to a low field three-proton doublet (J_{PMe} 12.5Hz), assigned to the equatorial methyl ligand on the basis of its larger coupling constant, and a higher field three-proton broad signal with barely resolved coupling, assigned to the apical methyl ligand. This absence of phosphorus coupling may possibly reflect a hindering of free rotation in the apical methyl ligand as a result of steric interaction with the pendant N-aryl group. The measured coalescence temperature of -18±3°C and frequency separation of 171Hz below coalescence gave a free energy of activation of 49.5±0.6kJ mol^{-1} for equivalence of apical and equatorial methyl ligands. The six-proton singlet corresponding to the o-methoxy substituents of the N-aryl ring at +28°C also separated below ca.-70°C, but only by ca.2Hz, to give ΔG^* of 47.7±1.7 kJ mol^{-1} (T_c -65±5°C).

The above variable temperature n.m.r. evidence indicates that the most stable form of this phosphine derived benz-

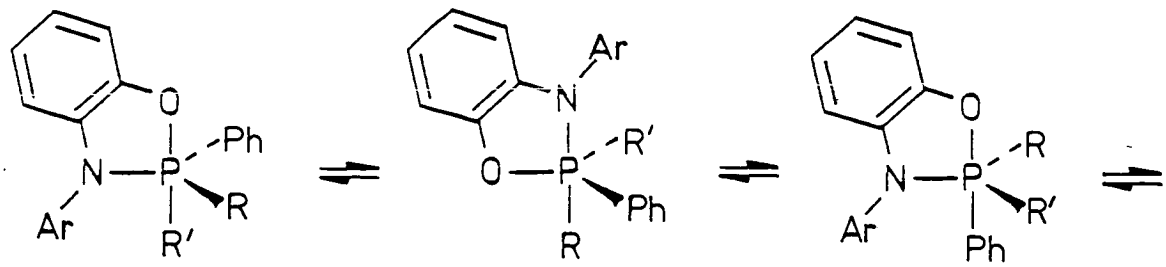


(186)

oxazaphosphole possesses structure (186), with P.I. occurring by a pathway exactly analogous to Scheme 77.

At first sight, it might appear that replacing the methoxy ligands of (164) with the less apicophilic methyl ligands of (186) should increase the energy barrier to P.I., but this is not the case in practice. Certainly, the initial probability of pentacoordinate phosphorane formation and subsequent stability is decreased by introducing less apicophilic ligands, as found in the deoxygenation reactions using dimethylphenylphosphine and tri-n-butylphosphine. Barriers to P.I., however, are controlled by energy differences between individual interconverting TBP isomers, which can be analysed in terms of changes in relative ligand apicophilicities, ring strain, and steric strain[44], as described in the Introduction (chapter 1.3.2). For example, the changes which occur for each compound (164) and (186) can be compared in Scheme 78, which shows the first half of a P.I. cycle.

The overall difference in energy between TBP 'b' and the "ground state" 'a' is the same for both compounds, as only the



a b c

(164) : R = R′ = OMe ;Ar = 2,6-dimethoxyphenyl

(186) : R = R′ = Me ;Ar = "

Scheme 78

endocyclic ring termini have exchanged positions. Comparison of structures 'c' and 'a' for compound (164) shows that an apicophilic methoxy ligand has been placed in an equatorial position, and an apicophobic phenyl ligand has been placed in an apical position, giving a resultant doubly destabilising energy increase. A similar comparison between structures 'a' and 'c' for compound (186) shows that methyl and phenyl ligands have exchanged positions, but these ligands are much closer in relative apicophilicity, and therefore gives a much lower energy difference between TBPs 'a' and 'c'. Since the relative energy levels of TBPs 'b' and 'c' will determine the free energy barrier to pseudorotation, the close proximity in measured ΔG^{*} values for compounds (164) and (186) strongly suggests that TBP 'b' is the highest energy structure in the pseudorotation cycles represented in Schemes 77 and 78.

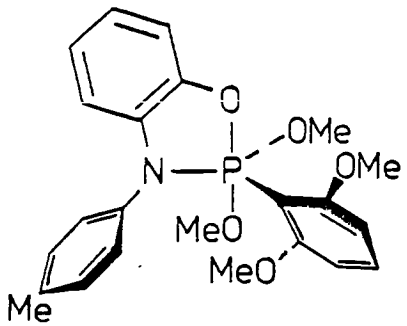
(iv) 2-(2,6-Dimethoxyphenyl)-2,3-dihydro-2,2-dimethoxy-3-(4-methylphenyl)-1,3,2-benzoxazaphosph(v)ole

The title compound (169) was primarily synthesised for use in hydrolysis studies, but it was also of interest to examine the effect of ortho-methoxy substituents attached to the P-phenyl ligand on the energy barrier to P.I.

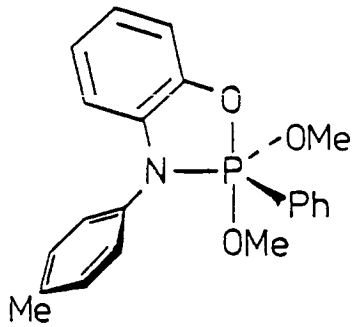
At +45°C, the ^{1}H n.m.r. spectrum exhibited a sharp doublet (J_{POMe} 13.1Hz) due to the rapidly exchanging P-OMe ligands at δ3.25. This doublet gradually broadened as the temperature was lowered and by -60°C had been replaced by two three-proton doublets, corresponding to the "frozen" high-field apical P-OMe ligand (J_{POMe} 12.7Hz) and the low-field equatorial P-OMe ligand (J_{POMe} 14.4Hz). Coalescence occurred at -27±5°C ($\Delta\nu$ = 114±2Hz), giving a free energy of activation of 48.5±1.1 kJ mol^{-1} for exchange of apical and equatorial P-OMe ligands.

The ortho-methoxy substituents on the P-phenyl ligand also gave rise to a coalescence. Thus, the six-proton singlet (δ3.58) at +45°C broadened and separated on cooling to give two three-proton singlets by -60°C. A coalescence temperature of -40±2°C and frequency separation of 41Hz were measured, giving ΔG^* of 47.8±0.5 kJ mol^{-1} for equilibration of ortho-methoxy substituents.

The above data indicates that the lowest energy TBP has structure (169), with P.I. following a similar pathway to that shown earlier in Scheme 77. A predicted orthogonal orientation of the P-aryl ring with respect to the equatorial plane would therefore place the ortho-methoxy substituents in different environments above and below this plane in the "frozen" structure (169).



(169)



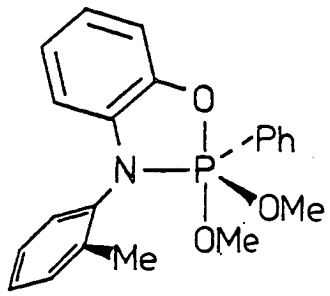
(170)

The barrier to P.I. in (169) is ca.4 kJ mol^{-1} higher than in the corresponding P-phenyl phosphorane (170)[110], and is consistent with the corresponding increase in ΔG^{*} when the N-aryl group possesses ortho-substituents[110]. In both cases, this higher energy barrier probably reflects an increase in steric crowding in the high energy TBPs during P.I., where N-aryl and P-aryl groups can become 90^{o} neighbours, compared with 120^{o} neighbours in the "ground state" TBP structures.

2.2 Benzoxazaphospholes bearing an asymmetrically substituted N-aryl group

Numerical data obtained for asymmetrically substituted benzoxazaphospholes which exhibit temperature dependent n.m.r. spectra is summarised in Table 3 of the Experimental section. A detailed analysis is given below of the spectral changes observed for these compounds, and also for various other benzoxazaphospholes not listed in Table 3.

Unlike their symmetrically substituted analogues which showed a single phosphorus resonance at all temperatures



(166)

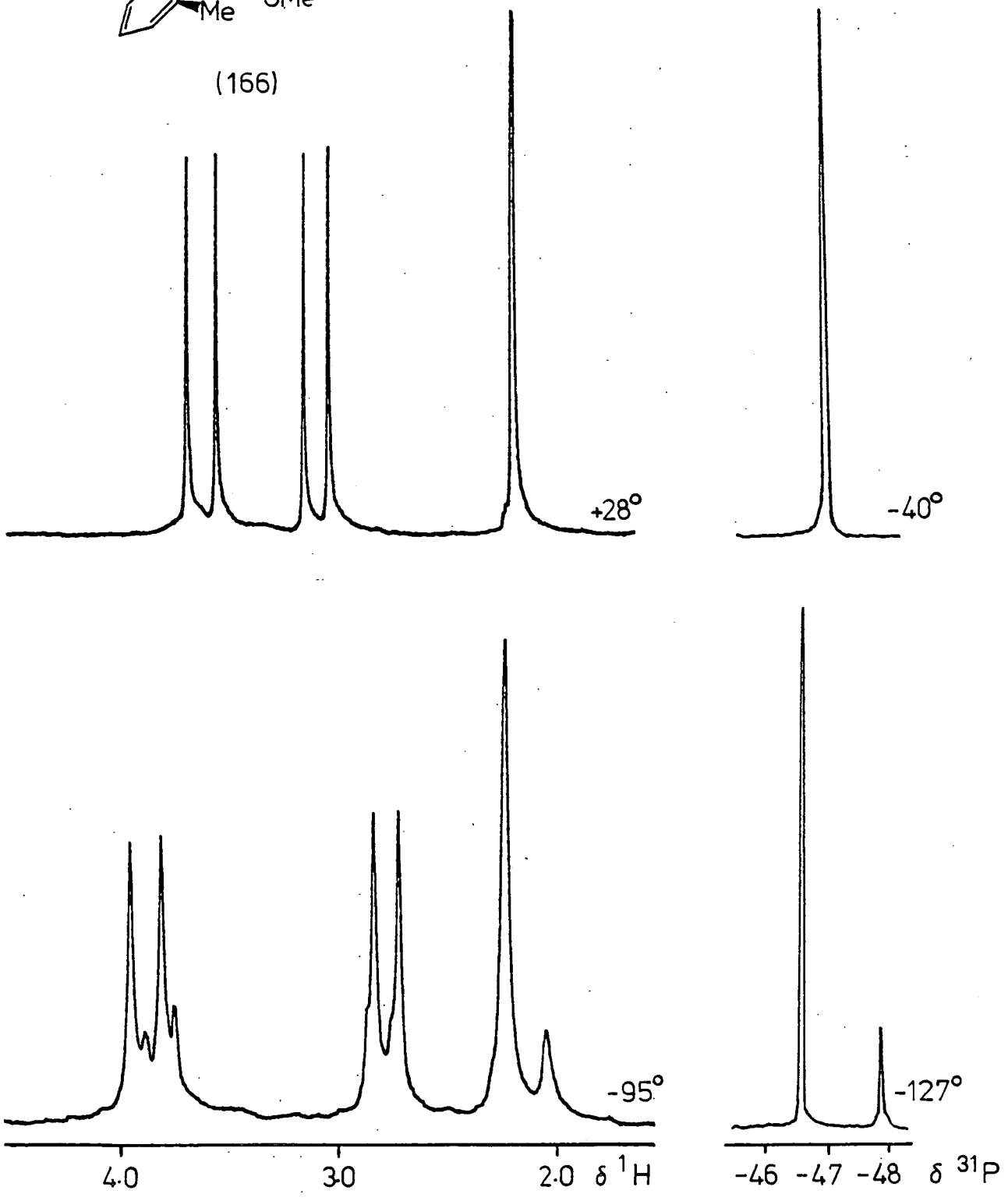


FIGURE 5: Variable temperature ^{1}H and ^{31}P n.m.r. spectra of 2,3-dihydro-2,2-dimethoxy-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole (166).

studied, many of these asymmetrically substituted benzoxazaphospholes also exhibited temperature dependent ^{31}P n.m.r. spectra. Because of the large number of asymmetrically substituted compounds studied, a further sub-division has been made to group benzoxazaphospholes according to the type of tervalent phosphorus reagent used in their preparation.

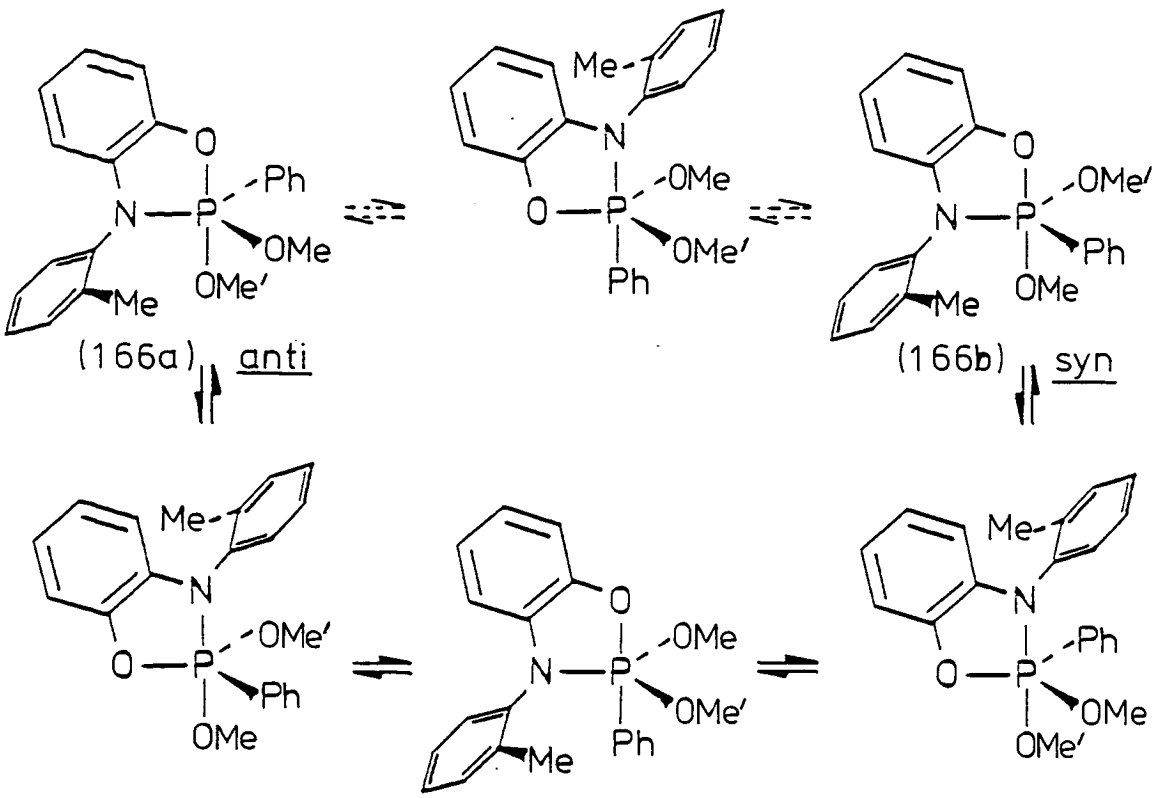
2.2.1 Asymmetrically substituted benzoxazaphospholes derived from dimethyl phenylphosphonite

(i) 2,3-Dihydro-2,2-dimethoxy-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole

The proton decoupled ^{31}P n.m.r. spectrum of this ortho-methyl substituted benzoxazaphosphole (166) at -127°C consisted of two unequal singlets at δ-46.75 and δ-47.88 in the ratio of 5.5:1 (Figure 5). These signals correspond to the "major" and "minor" diastereoisomers mentioned in Chapter 1.3 (Table 6) and constitute the lowest energy "frozen" TBP structures (166a) and (166b) respectively in the P.I. process shown in Scheme 79.

As the temperature was raised, these signals coalesced and by -40°C a sharp singlet was obtained at δ-46.90, in a roughly weighted average position (Figure 5). The phosphorus centre now effectively experiences an averaged environment due to rapid ligand reorganisation between diastereoisomers (166a) and (166b) via the higher energy TBP structures shown in Scheme 79.

A coalescence temperature of -60°C and $\Delta\nu$ of 46Hz therefore



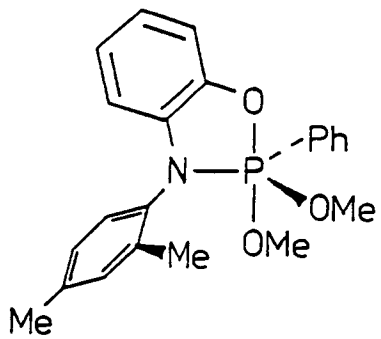
Scheme 79

gave a free energy of activation for conversion of "major" to "minor" isomer ($\Delta G_A^{\ddagger}$) of 45.9±2.4 kJ mol^{-1}, using the method of Shanan-Atidi and Bar-Eli[155] for coalescence of unequally populated exchanging signals.

The ^1H n.m.r. spectrum of the same compound at -95°C similarly exhibited major and minor signals in the ratio 5.4:1 for each of the equatorial methoxy ligand, apical methoxy ligand, and σ-methyl substituent (Figure 5). On heating, major and minor signals coalesced and a sharp averaged spectrum was observed at +28°C. From the positions and coupling constants of the two methoxy doublets in the averaged ^1H n.m.r. spectrum at 28°C (Figure 5), it is apparent that coalescence has occurred between the major equatorial P-OMe doublet and minor apical P-OMe doublet, and between the major apical P-OMe doublet and minor equatorial P-OMe doublet, giving two averaged P-OMe doublets in approximately weighted average positions.

This interpretation of the spectral changes can easily be verified by following the fate of the ligand marked P-OMe' throughout the P.I. process which interconverts major and minor diastereoisomers in Scheme 79. The above analysis also confirms that N-aryl rotation does not occur, since such a rotation would cause major and minor equatorial P-OMe doublets to coalesce with each other, and similarly for major and minor apical P-OMe doublets. A coalescence temperature of -44±10°C and $\Delta\nu$ of 105±2Hz were measured, giving $\Delta G_A^{\ddagger}$ of 47.7±3.7 kJ mol^{-1} for the P-OMe coalescences described above.

Similarly, the much simpler coalescence of major and minor σ-methyl signals gave $\Delta G_A^{\ddagger}$ of 48.0±2.6 kJ mol^{-1} (T_c = -58±5°C;



(168)

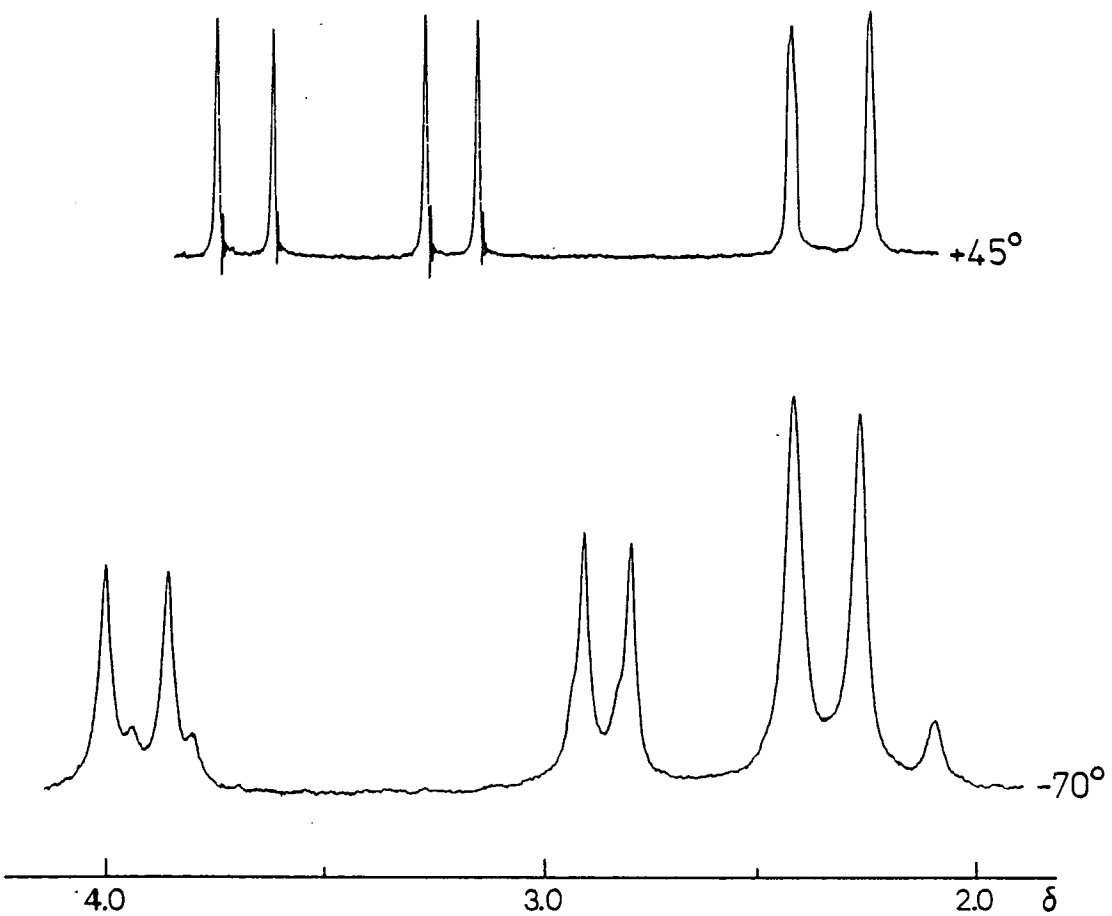


FIGURE 6: Variable temperature ^{1}H n.m.r. spectra of 3-(2,4-dimethylphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole (168).

$\Delta\nu$ = 17.5±0.5Hz). The fact that all three calculations of $\Delta G_A^{\ddagger}$ for coalescence of major and minor signals (from ^{31}P n.m.r., P-OMe and σ-Me signals) gave the same value, within experimental error, serves to verify the above interpretation of the spectral charges in terms of a single P.I. process.

From a comparison of Schemes 77 and 79, it is apparent that P.I. processes and free energy barriers are closely related for both symmetrically and asymmetrically substituted benzoxazaphospholes. The only difference is that the introduction of asymmetry into the N-aryl group leads to interconversion of a pair of diastereoisomers during P.I., whereas magnetically equivalent enantiomers are interconverted during P.I. of symmetrically substituted compounds.

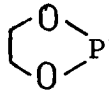
Full equivalence of P-OMe ligands, however, is not achieved by the P.I. process outlined in Scheme 79. The partially averaged P-OMe doublets in the spectrum at +28°C remained unchanged up to a temperature of +160°C, which equates to a minimum free energy of activation ($\Delta G_2^{\ddagger}$) of 93 kJ mol^{-1} (T_c >160°C;$\Delta\nu$ = 25Hz) for full averaging of P-OMe environments. Since either N-aryl rotation or diequatorial ring placement would be required to achieve fully averaged P-OMe environments, this observation provides further evidence that N-aryl rotation is a very high energy process in 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles.

(ii) 3-(2,4-Dimethylphenyl)-2,3-dihydro-2,2-dimethoxy-2-phenyl-1,3,2-benzoxazaphosph(v)ole

Not surprisingly, the title compound (168) exhibited very similar temperature dependent spectral features to the previous

TABLE 3*

Variable temperature n.m.r. studies on 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles bearing single σ-substituents.

N-Phenyl Substituent	$R^1R^2R^3P$	^bT_c (°C)	Δν (Hz)	$\Delta G_A^{\ddagger}$ (kJmol^{-1})	$\Delta G_B^{\ddagger}$ (kJmol^{-1})	$^h\Delta G_2^{\ddagger}$ (kJmol^{-1})	$^a\Delta G$ (kJmol^{-1})
2-Me	$(MeO)_2PPh$	^{d}-44±10	105±2	47.7±3.7	45.3±2.7	^{c} >93	2.4
		^{e}-58±5	17.5±0.5	48.0±2.6	45.7±1.7		
		^{f}-60±5	46	45.9±2.4	43.5±1.5		
2,4-Me_2	$(MeO)_2PPh$	^{d}-40±15	105±2	48.5±5.0	46.2±3.8	^{c} >95.6	2.4
		^{e}-55±4	17±1	48.7±2.5	46.4±1.5		
		^{f}-57.5±7.5	41	46.6±3.2	44.2±2.2		
2-OMe	$(MeO)_2PPh$	^{d}-30±5	98±5	^{a} 48.2±1.2		^{c} 97.4±2.7	0
		^{e}-45±10	22±1	48.0±2.3			
		^{f}-50±5	31	46.2±1.1			
2-t-Bu	$(EtO)_2PMe$	^{d} -1±2	69±5	55.0±0.6			0
		^{g}-20±2	18±1	53.9±0.6			
		^{f} +5±2	70±2	56.3±0.6			
2,4-Me_2	$(EtO)_2PMe$	^{d}-52±2	83±5	44.0±0.6			0
		^{f}-59±2	40	43.8±0.5			
2-Me		^{e}+196±4	17.5±0.5	^{c}104.5±1.3	102.8±1.3		1.7
2-OMe	PhMePOMe	^{d}+113±4	5.5±0.5	^{c} 88.8±1.7	87.7±1.6		1.1
		^{g}+125±4	10±0.5	89.7±1.5	88.5±1.5		
		^{e}+125±4	9.5±0.5	89.8±1.6	88.7±1.5		
		^{f}+146±6	33±1	90.3±1.9	89.2±1.8		

* Refer to page 141 for footnotes

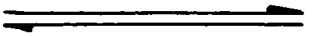
N-(2-methylphenyl) derivative (166). Thus at low temperatures, unequally populated diastereoisomeric signals were observed in the ratio of ca.5.5:1 (Figure 6) and three consistent values of $\Delta G_A^{\ddagger}$ were again obtained viz. from coalescence of major and minor signals in the ^{31}P n.m.r. spectra (46.6±3.2 kJ mol^{-1}), and from coalescence of major and minor P-OMe (48.5±5.0 kJ mol^{-1}) and o-methyl substituent signals (48.7±2.5 kJ mol^{-1}) in the ^{1}H n.m.r. spectra.

The partially equilibrated P-OMe doublets in the ^{1}H n.m.r. spectrum at +28°C did not coalesce at high temperature, giving $\Delta G_2^{\ddagger}$ of >95.6 kJ mol^{-1} (T_c >180°C; $\Delta\nu$ = 40Hz) for complete averaging of P-OMe environments.

Table 3 is reprinted on the facing page from the Experimental section, and displays the values of T_c and $\Delta\nu$ used to calculate $\Delta G_A^{\ddagger}$ for compound (168) above. Another column in Table 3 lists values of $\Delta G_B^{\ddagger}$, the free energy of activation for the reverse equilibrium i.e. for conversion of minor to major diastereoisomers. The difference between $\Delta G_A^{\ddagger}$ and $\Delta G_B^{\ddagger}$ (listed under ΔG in the final column of Table 3) is ca. 2.4 kJ mol^{-1} for both singly o-methyl substituted benzoxazaphospholes (166) and (168). This ΔG value represents the thermodynamic energy difference between major and minor diastereoisomers. Insertion of the equilibrium diastereoisomer ratio (ca.5.5:1) into the thermodynamic equation for free energy ($\Delta G = (-)RT \ln K$) gives the same value of 2.4 kJ mol^{-1}.

A simple model which illustrates these different free energy relationships appears in Figure 7, in the form of an

A
major
isomer



B
minor
isomer

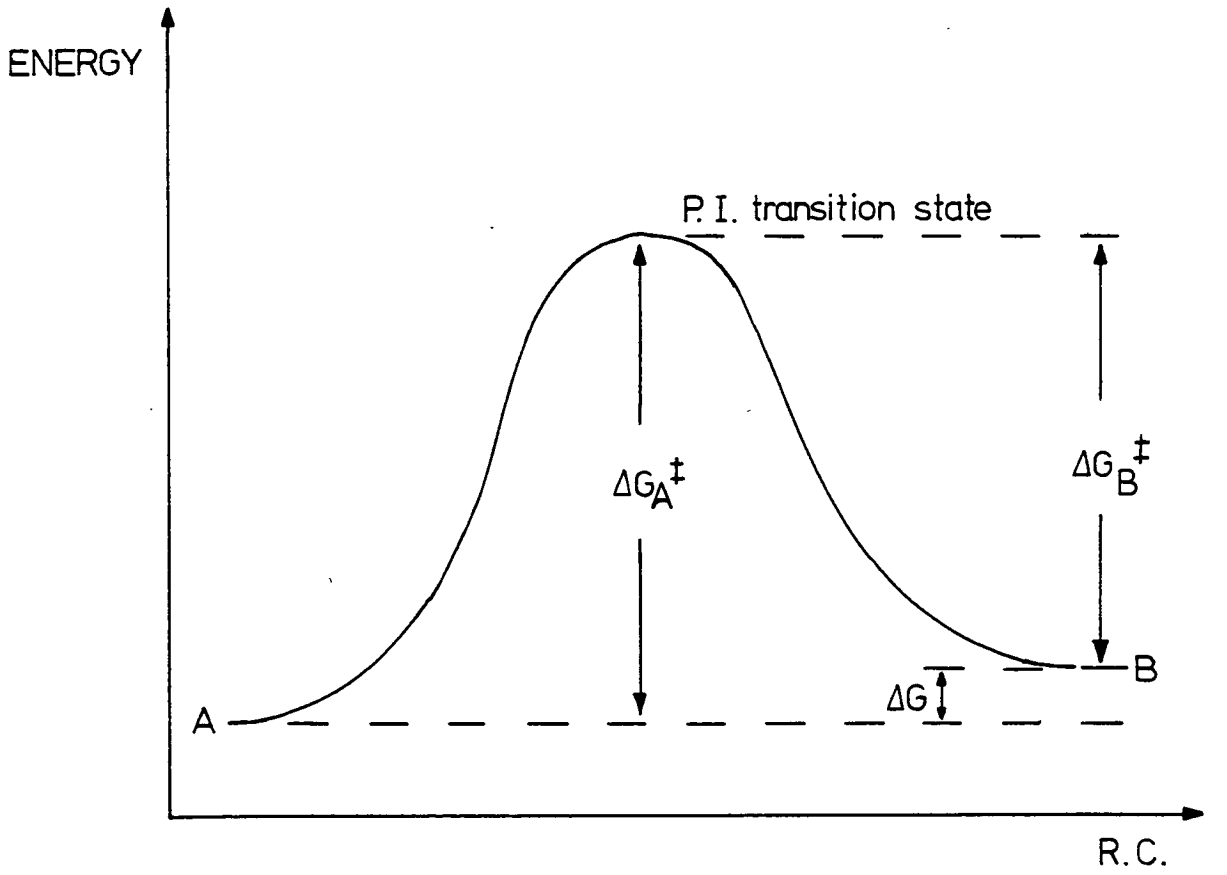


FIGURE 7

idealised energy profile diagram. Figure 7 shows major diastereoisomer A lying at a lower thermodynamic energy level than isomer B, and therefore a higher activation energy is required to reach the common transition state for the "forward" reaction (A → B), than for the reverse reaction (B → A). For unequally populated isomers, therefore,

$$\Delta G_A^{\ddagger} = \Delta G_B^{\ddagger} + \Delta G$$

For equally populated exchanging signals (or enantiomers), however, $\Delta G = 0$; Hence $\Delta G_A^{\ddagger} = \Delta G_B^{\ddagger} \equiv \Delta G^{*}$.

(iii) 2,3-Dihydro-2,2-dimethoxy-3-(2-methoxyphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole

The low temperature ^{31}P n.m.r. spectrum of the title compound (165) at ca -100°C again showed the presence of two diastereoisomers (δ-44.5 and δ-45.0), corresponding to the lowest energy TBP structures (165a) and (165b) shown in Scheme 80. In this case, however, the "major" and "minor" signals were of approximately equal intensity, indicating that the tetrahedral oxygen of the σ-methoxy substituent is able to orientate the methyl group so that negligible steric interference occurs with the syn-phenyl ligand in the "minor" isomer (165b).

These phosphorus resonances coalesced to a singlet at -50°C giving a free energy of activation of 46.2±1.1 kJ mol^{-1} ($\Delta G_A^{\ddagger} = \Delta G_B^{\ddagger} \equiv \Delta G^{*}$). Almost equally populated separate diastereoisomeric signals were also observed for the "frozen" apical P-OMe, equatorial P-OMe and σ-methoxy groups in the low temperature ^{1}H n.m.r. spectrum (Figure 8). Correct assignment

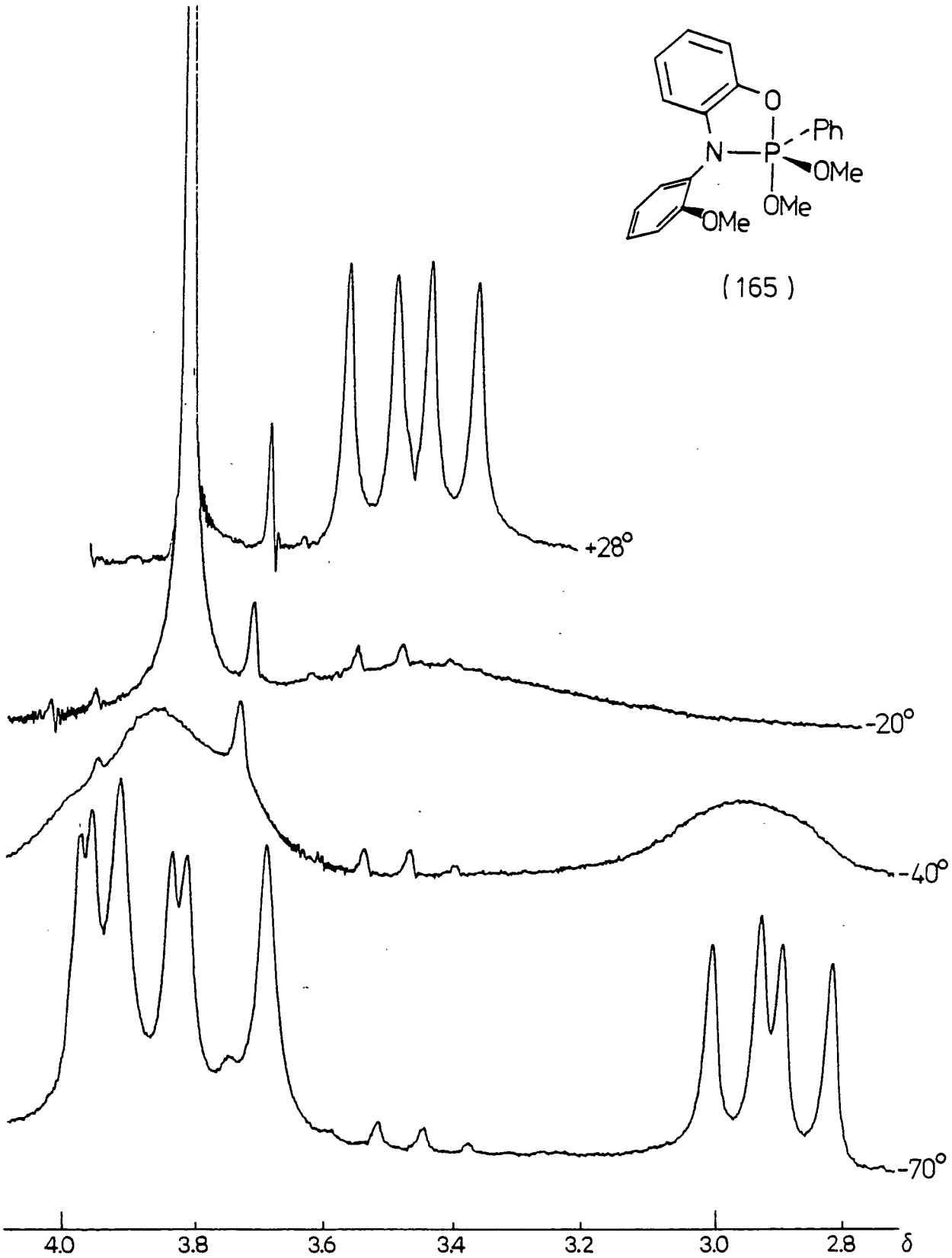
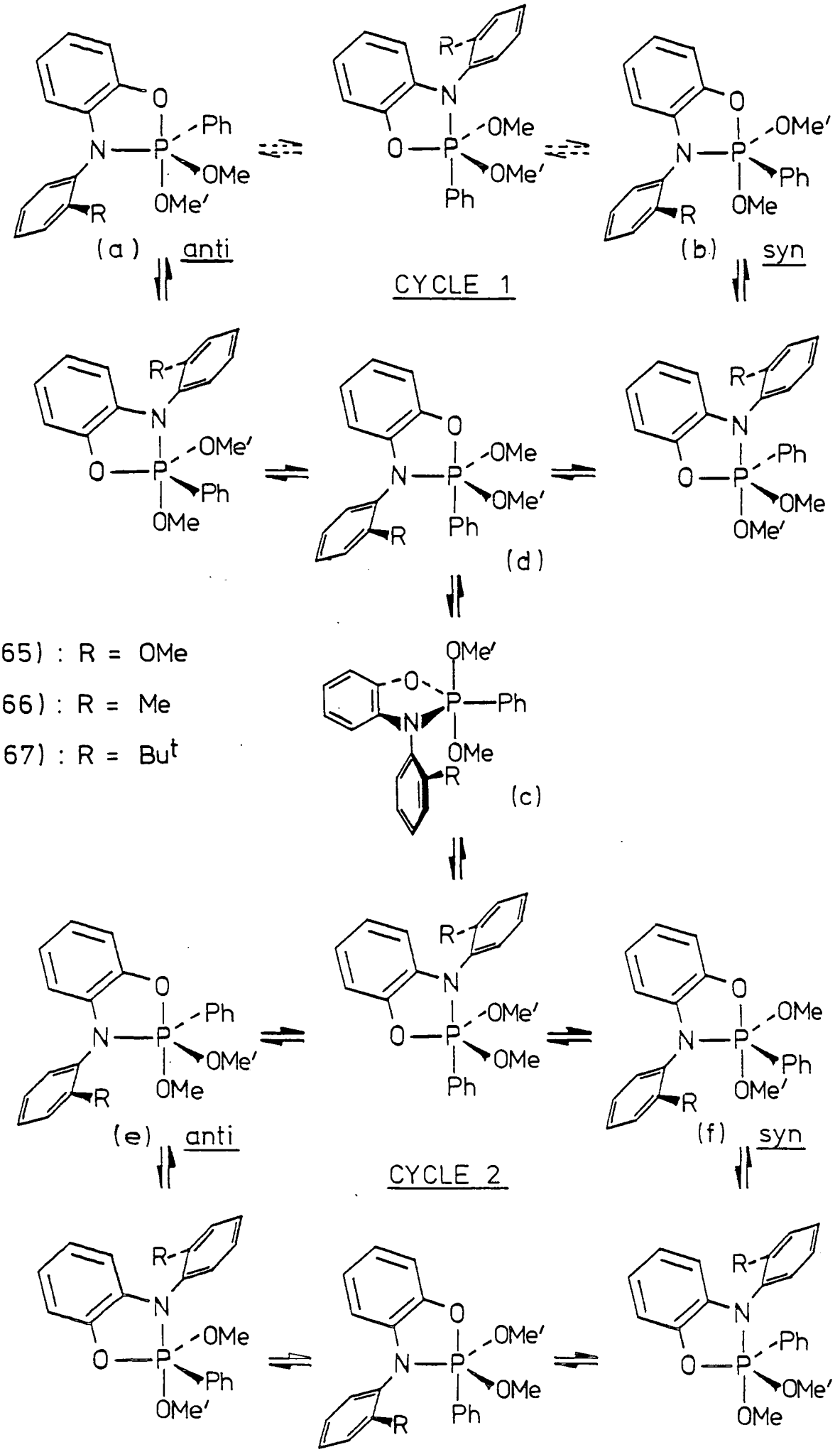


FIGURE 8: Variable temperature ^{1}H n.m.r. spectra of 2,3-dihydro-2,2-dimethoxy-3-(2-methoxyphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole (165).

of the complex overlapping signals was aided by phosphorus decoupling, and as the temperature was raised an averaged singlet was obtained on coalescence of the σ-methoxy signals (T_c = -45±10°C; ΔG^* = 48.0±2.3 kJ mol^{-1}). Coalescence of the apical "major" P-OMe doublet (J_{POMe} 11Hz) with the equatorial "minor" P-OMe doublet (J_{POMe} 14Hz) and *vice versa* resulted in partial equilibration of P-OMe environments. Because of the approximately equal population of diastereoisomers (165a) and (165b), the weighted average positions of these POMe signals after coalescence appeared as two closely overlapping doublets in dichloromethane and diphenyl ether at +28°C; in deuteriochloroform solution, these doublets overlapped exactly giving one doublet (J_{POMe} 12.5Hz). This partial equilibration of P-OMe environments gave a value for ΔG^* of 48.2±1.2 kJ mol^{-1} (T_c = -30±5°C). All three coalescences described above can be rationalised by the P.I. process (Cycle 1) shown in the top half of Scheme 80. This cycle is exactly analogous to Scheme 79 described previously for the case of σ-methyl substituted benzoxazaphospholes. Thus, a relatively low energy barrier (ΔG^* *ca*.50 kJ mol^{-1}) exists for interconversion of the "frozen" *anti* (165a) and *syn* (165b) diastereoisomers via higher energy intermediate TBPs in which either amino or phenyl functions are placed apical, but the five-membered ring always spans an apical-equatorial position.

Complete averaging of the P-OMe environments in (165) was observed above *ca* +160°C in diphenyl ether when the two overlapping doublets coalesced to one doublet (J_{POMe} 12.5Hz), giving a free energy of activation ($\Delta G_2^{\ddagger}$) of 97.4±2.7 kJ mol^{-1} (T_c = +157±10°C; $\Delta\nu$ = 6Hz).



(165) : R = OMe

(166) : R = Me

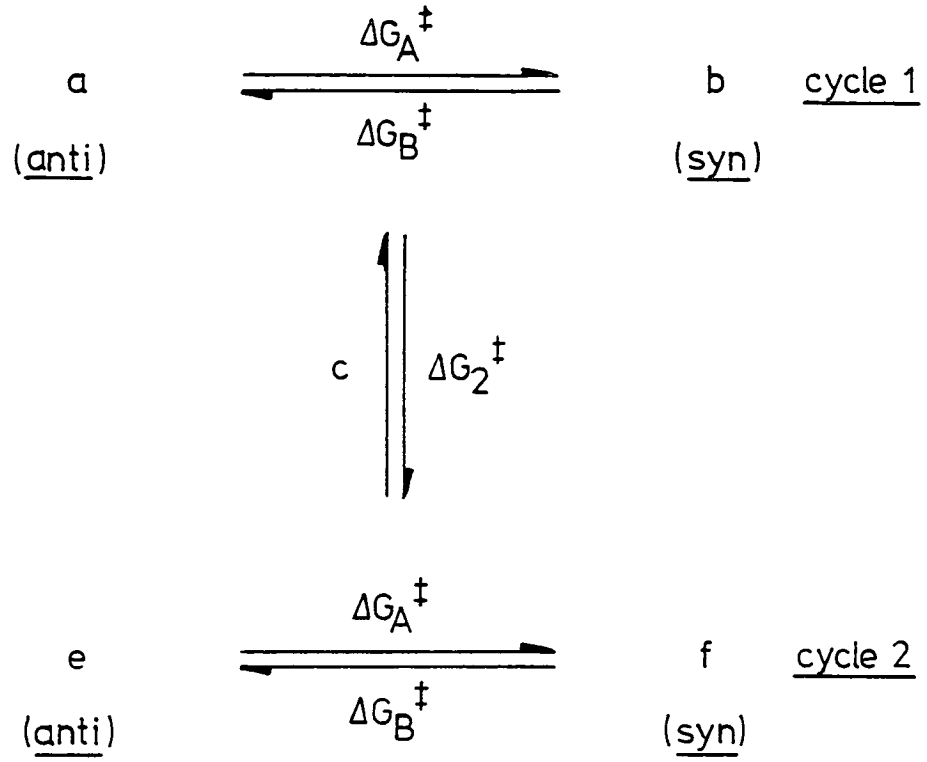
(167) : R = Bu^t

Scheme 80

This high free energy value is similar to those obtained for P.I. processes involving diequatorial placement of a five-membered heteroatomic ring[110,44], and suggests that complete equilibration of the P-OMe groups of (165) occurs via the diequatorial ring intermediate (165c) rather than by a combination of pseudorotation via intermediate TBP (165d) (Scheme 80) and simple N-aryl rotation.

An important consequence of overcoming this high energy barrier to diequatorial ring placement is that optical geometry at phosphorus is inverted. This has the effect of linking two separate lower energy pseudorotation pathways (Cycles 1 and 2) which differ only in the fact that the sequence of exocyclic ligands (Ph, MeO, MeO') appears clockwise in one cycle, and anticlockwise in the other cycle. Complete averaging of P-OMe environments is therefore achieved by rapid pseudorotation which links magnetically equivalent anti-configurations, (165a) and (165e) (or magnetically equivalent syn-configurations (165b) and (165f)) via a high energy diequatorial ring structure (165c) which bridges the otherwise separate low energy pathways (Cycles 1 and 2). It is noteworthy that none of the TBP structures shown in Scheme 80 are enantiomeric, because of the constant orientation of the asymmetric N-aryl substituent in its orthogonal plane. Therefore, no P.I. process alone is capable of racemising any TBP shown in Scheme 80, without also invoking N-aryl rotation.

The earlier observations on unequally populated diastereo-isomers in compounds (166) and (168) bearing single α-methyl



Scheme 81

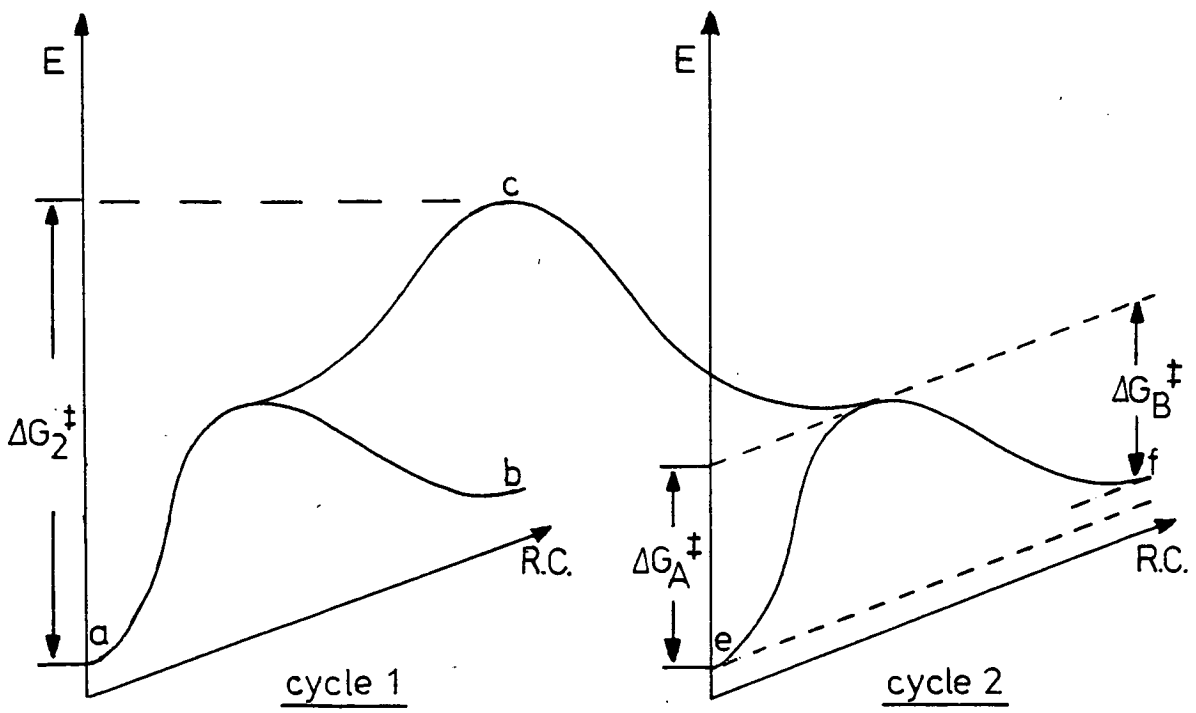


FIGURE 9

substituents (Scheme 79) can now be reconsidered in the more general context of Scheme 80. Thus, at ambient temperatures (166) and (168) are experiencing a rapid, partial equilibration of major (anti) and minor (syn) diastereoisomers by a low energy P.I. process ($\Delta G_A^{\ddagger}$ ca.50 kJ mol^{-1}). This partial equilibration of major and minor diastereoisomers can occur independently and simultaneously by either of Cycles 1 and 2, but these separate cycles cannot be distinguished by n.m.r. spectroscopy since they differ only in their optical geometry at phosphorus. Full equilibration of P-OMe environments is slower than the n.m.r. timescale, even at the maximum probe temperature. Thus a higher activation energy ($\Delta G_2^{\ddagger}$ >93 kJ mol^{-1}) is necessary to place the heteroaromatic ring di-equatorially and link the two separate lower energy pseudo-rotation cycles.

In Scheme 81 and Figure 9, an attempt is made to illustrate the concept that two possible low energy profiles (Cycles 1 and 2) can exist separately, and yet differ only in their optical geometries at phosphorus. Only a high energy pathway via the diequatorial ring intermediate ($\Delta G_2^{\ddagger}$) can link these otherwise independent low energy P.I. pathways by inverting the geometry at phosphorus. This concept therefore provides a general shorthand method of describing complex P.I. processes.

(iv) 2,3-Dihydro-2,2-dimethoxy-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

As noted earlier in Table 6, the title compound (167) differs from other singly ortho-substituted benzoxazaphospholes obtained from dimethyl phenylphosphonite in showing no minor

diastereoisomer signals in its low temperature ^{1}H or ^{31}P n.m.r. spectra. This indicates a large steric interaction between adjacent t-butyl and P-phenyl groups which destabilises the syn-configuration. The thermodynamic energy difference between anti (major) and syn (minor) diastereoisomers can be viewed in perspective with the activation energies for P.I. by arbitrarily considering a diastereoisomer ratio of 99:1. This ratio approaches the limit observable by n.m.r. spectroscopy and corresponds to a free energy difference of ca.11 kJ mol^{-1} (from $\Delta G = (-)RT \ln K$).

Two separate P-OMe doublets were observed in the ^{1}H n.m.r. spectrum of (167) at -85°C viz. a low-field doublet (J_{POMe} 13.5Hz) assigned to the equatorial methoxy ligand, and a high field doublet (J_{POMe} 10.7Hz) assigned to the apical methoxy ligand. This "frozen" structure corresponds to the anti-configuration (167a) shown in Scheme 80 (ignoring for the meantime the magnetically equivalent anti-structure (167e) in Cycle 2). The absence of any spectral changes on heating to +28°C may be interpreted as indicating that partial equilibration has already occurred at low temperatures, but that the "minor" signal is so small (<1%) that the observed separate P-OMe resonances already represent the weighted average positions of rapidly equilibrating "major" (say 99%) and minor (say 1%) diastereoisomers.

No significant spectral changes occurred on heating to +160°C, which is again consistent with the general P.I. pathway shown in Scheme 80. Thus a free energy of activation ($\Delta G_2^{\ddagger}$) of >90 kJ mol^{-1} would be required for full equilibration of P-OMe environments ((167a)$\rightleftharpoons$(167e)) via the high energy di-equatorial ring intermediate (167c).

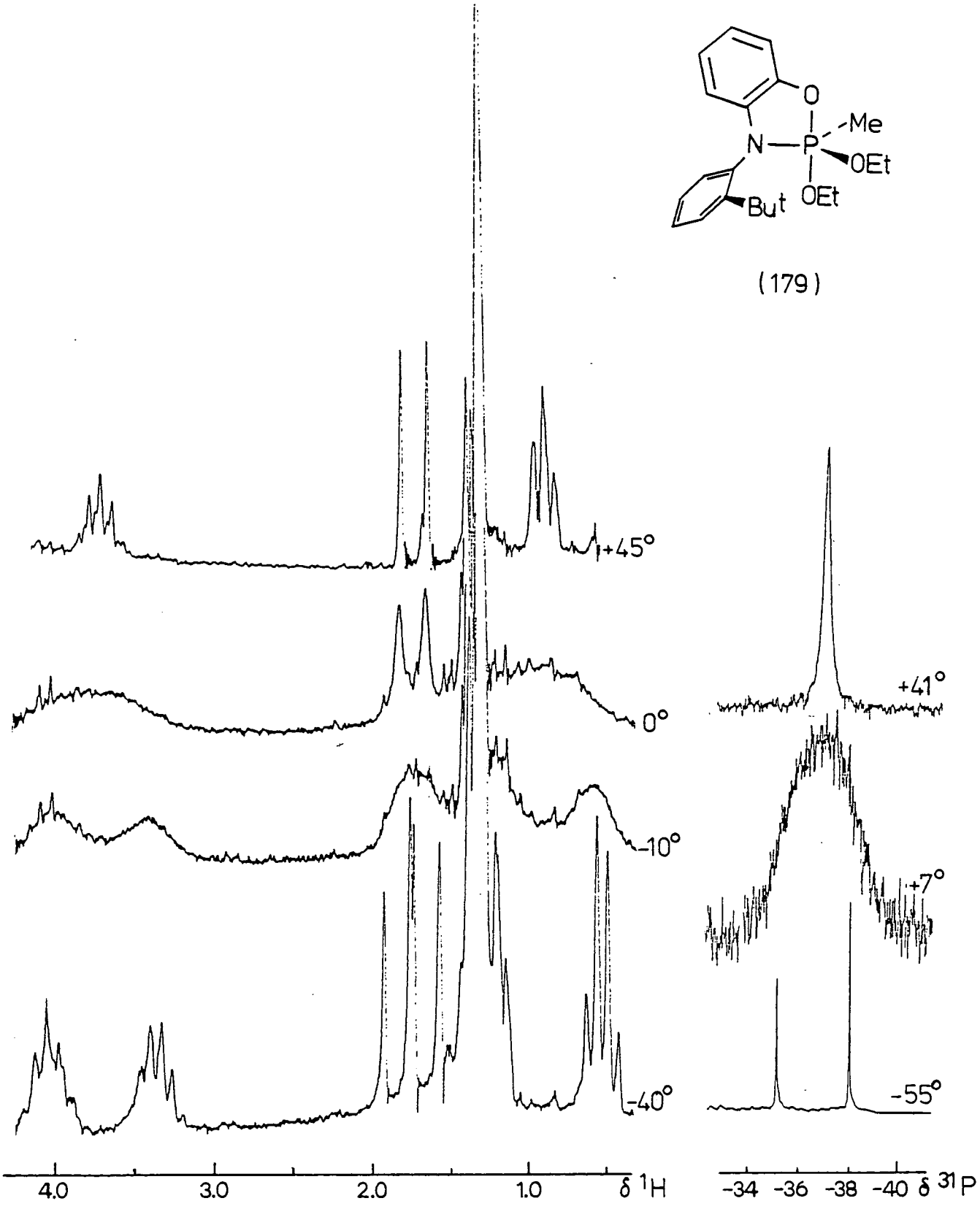


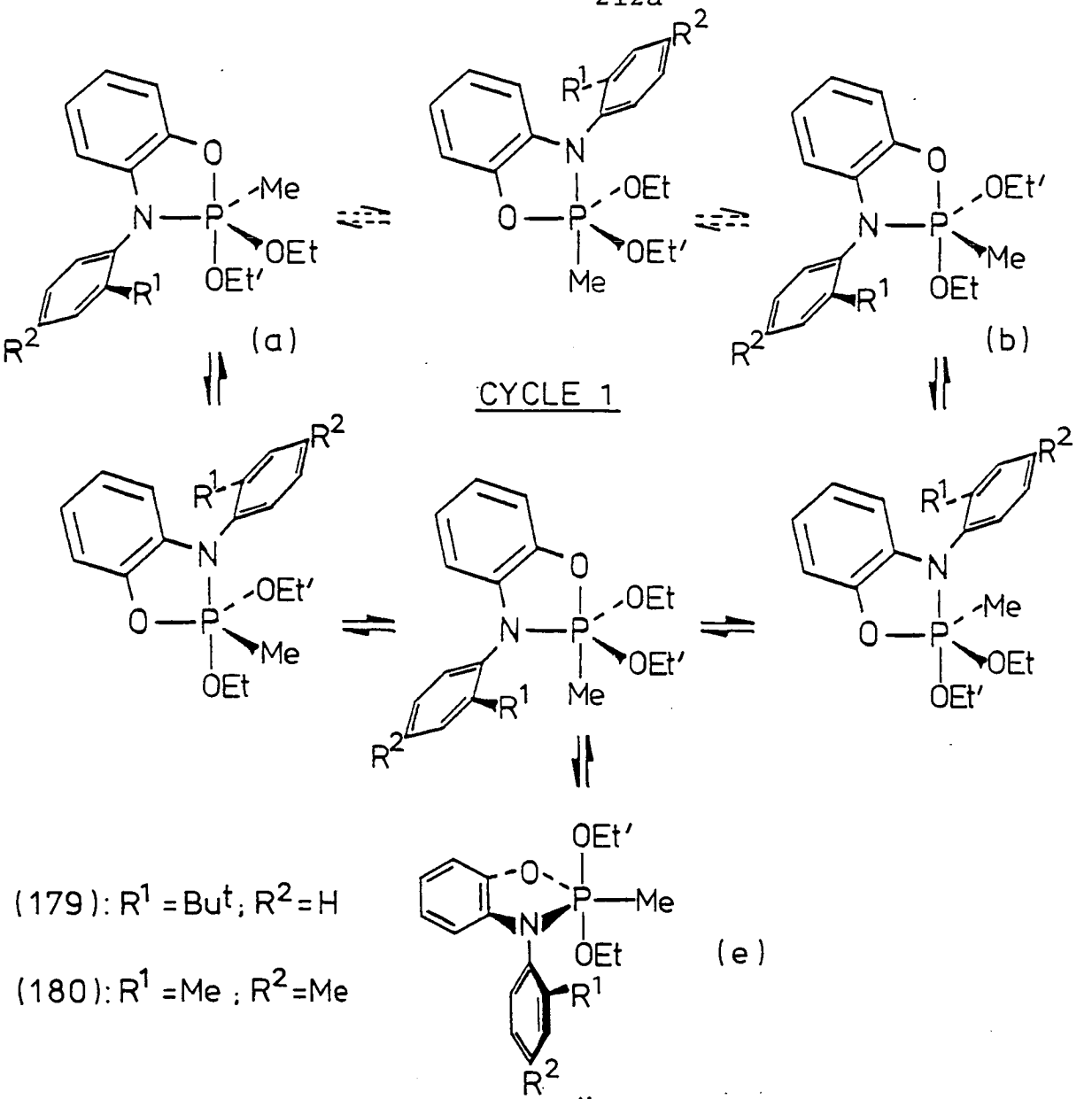
FIGURE 10: Variable temperature ^{1}H and ^{31}P n.m.r. spectra of 2,2-diethoxy-2,3-dihydro-2-methyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole (179).

2.2.2 Asymmetrically substituted benzoxazaphospholes derived from other tervalent phosphonite esters

(i) 2,2-Diethoxy-2,3-dihydro-2-methyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

Four separate coalescences were observed in the variable temperature n.m.r. spectra of the title compound (179), obtained as a slightly impure viscous oil. Firstly, the ^{31}P n.m.r. spectrum showed a broad singlet at +45°C (δ-36.5) which was gradually replaced by two almost equally populated singlets (δ-35.2 and δ-38.1) as the temperature was lowered (Figure 10). Coalescence was measured at +5±2°C, giving a value of 56.3±0.6 kJ mol^{-1} for ΔG^* ($\Delta\nu$ = 70±2Hz).

Three similar ΔG^* values were obtained for coalescence of P-OEt and P-Me signals in the ^1H n.m.r. spectrum. Thus the methyl groups of the P-OEt ligands were observed as a broad triplet (δ0.9) at ca.+45°C (Figure 10). These were replaced by two broad signals by -10°C which eventually sharpened to two multiplets by -40°C. The lower field multiplet at δ1.2 was partly obscured by the large t-butyl signal, but resembled two closely overlapping triplets. The higher field signal (δ0.5) appeared as a distorted quartet which was not coupled to phosphorus, and hence was ascribed to two sets of overlapping triplets of almost equal intensity. Coalescence of these two multiplets occurred at ca.-1°C, giving ΔG^* of 55.0±0.6 kJ mol^{-1}. Similarly, the methylene protons of the P-OEt ligands were seen as separate multiplets at -40°C, but coalesced at ca.-3°C to give a phosphorus coupled



(179): $R^1 = Bu^t$; $R^2 = H$

(180): $R^1 = Me$; $R^2 = Me$

Scheme 82

multiplet centred on δ3.76 as the temperature was raised to +45°C (ΔG^* = 54.6±0.6 kJ mol^{-1}).

Finally, the P-Me group resonated as a sharp doublet (J_{PH} 17Hz) at +45°C, but gradually broadened as the temperature was lowered to be replaced by two overlapping doublets (J_{PH} ca.17Hz) by -40°C. A measured coalescence temperature of -20±2°C gave a ΔG^* value of 53.9±0.6 kJ mol^{-1} for equilibration of P-Me signals.

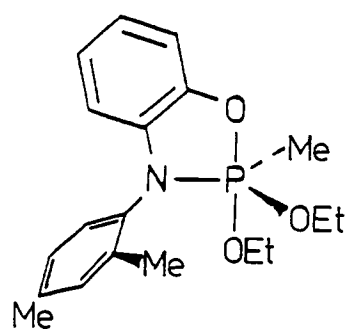
All four coalescences described above and shown in Figure 10 can be explained by one and the same P.I. process (Scheme 82) in which the low temperature spectra represent the "frozen" diastereoisomeric structures (179a) and (179b). These can exchange by a relatively low energy P.I. process (ΔG^* ca.55 kJ mol^{-1}) represented by Cycle 1, which is exactly analogous to Cycle 1 from Scheme 80 in having higher energy intermediate TBP structures with apical methyl or amino functions. By the same analogy, the above coalescences can equally well be represented by "frozen" diastereoisomers (179d) and (179e) which interconvert by Cycle 2. Cycles 1 and 2 differ only in the artificial labels used to distinguish ethoxy ligands and thus denote a change in optical geometry at phosphorus.

Above +45°C, the broad triplet at δ 0.9 in the ^1H n.m.r. spectrum of (179) sharpened to reveal 4 closely overlapping triplets at ca.+60°C. Phosphorus decoupling at a frequency which completely decoupled the P-Me signal (40,480 685Hz) still left two sets of overlapping triplets, suggesting that complete averaging of P-OEt environments had not taken place. Complete P-OEt equilibration would necessitate a linking of low energy Cycle 1 and 2 via the high energy diequatorial ring

intermediate (179c). Unfortunately, accidentally equivalent signals were found in high temperature solvents which prevented investigation of the energy barrier to complete ligand equivalence in (179).

It is worth repeating here the contrast in steric interactions between the bulky ortho-t-butyl group and equatorial P-C linked ligands. Compound (179) exhibited equally populated syn- and anti-diastereoisomers at low temperatures, indicating negligible P-methyl interference with the t-butyl group. The corresponding dimethyl phenylphosphonite derivative (167) however showed no syn-isomer in its low temperature n.m.r. spectra due to the larger bulk of an equatorial P-phenyl ligand.

(ii) 3-(2,4-Dimethylphenyl)-2,2-diethoxy-2,3-dihydro-2-methyl-1,3,2-benzoxazaphosph(v)ole

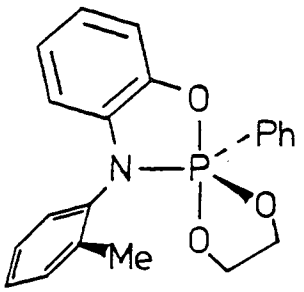


(180)

The variable temperature n.m.r. spectra of the benzoxazaphosphole (180) were found to be broadly similar to those of (179) described above, and the observed coalescences rationalised by the same P.I. process shown in Scheme 82.

The main difference between these two derivatives was an approximately 20% lower energy barrier to P.I. in the case of the 2,4-dimethyl-substituted compound (180). Thus, two diastereoisomeric signals of equal intensity were observed in the ^{31}P n.m.r. spectrum of (180) at ca.-80°C. These coalesced at -59±2°C ($\Delta\nu$ = 40Hz) giving a free energy of activation of 43.8±0.5 kJ mol^{-1} for interconversion of "frozen" diastereoisomers (180a) and (180b) (Scheme 82). Similarly, "frozen" apical and equatorial P-OEt signals were observed in the ^{1}H n.m.r. spectrum at ca.-70°C. Coalescence of the closely overlapping triplets arising from the methyl groups of the P-OEt ligands in diastereoisomers (180a) and (180b) was particularly clear, giving a ΔG^{*} value of 44.0±0.6 kJ mol^{-1} (T_c = -52±2°C; $\Delta\nu$ = 83±5Hz). As in the case of compound (179), it was not possible to determine any higher energy barriers indicative of diequatorial ring placement, because of accidental equivalence of P-OEt environments. Thus, low energy coalescence of approximately equally populated syn- and anti-diastereoisomers occurred to give two partially averaged POEt environments which unfortunately possessed the same chemical shift.

The higher value of ΔG^{*} (55 kJ mol^{-1}) for the t-butyl derivative (179) compared with the 2,4-dimethyl derivative (180) presumably reflects an increase in steric crowding on interconversion to some of the higher energy TBP intermediates during P.I.



(175)

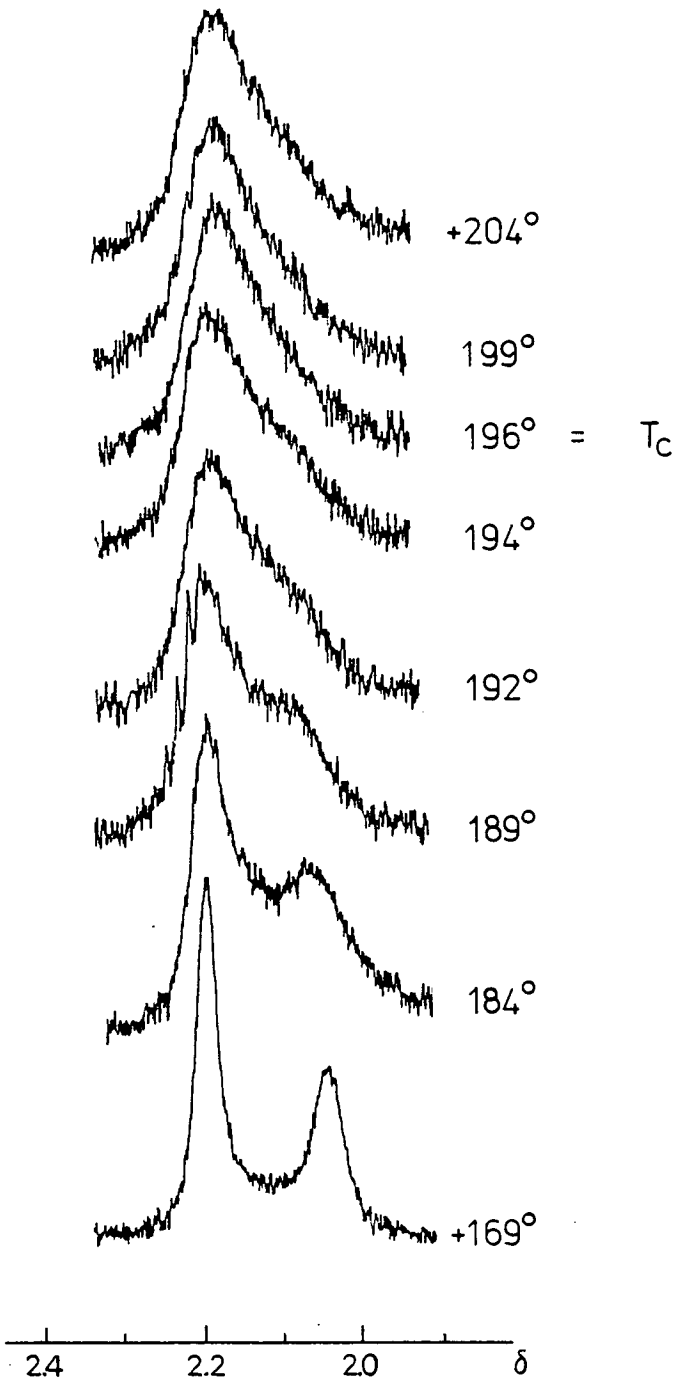


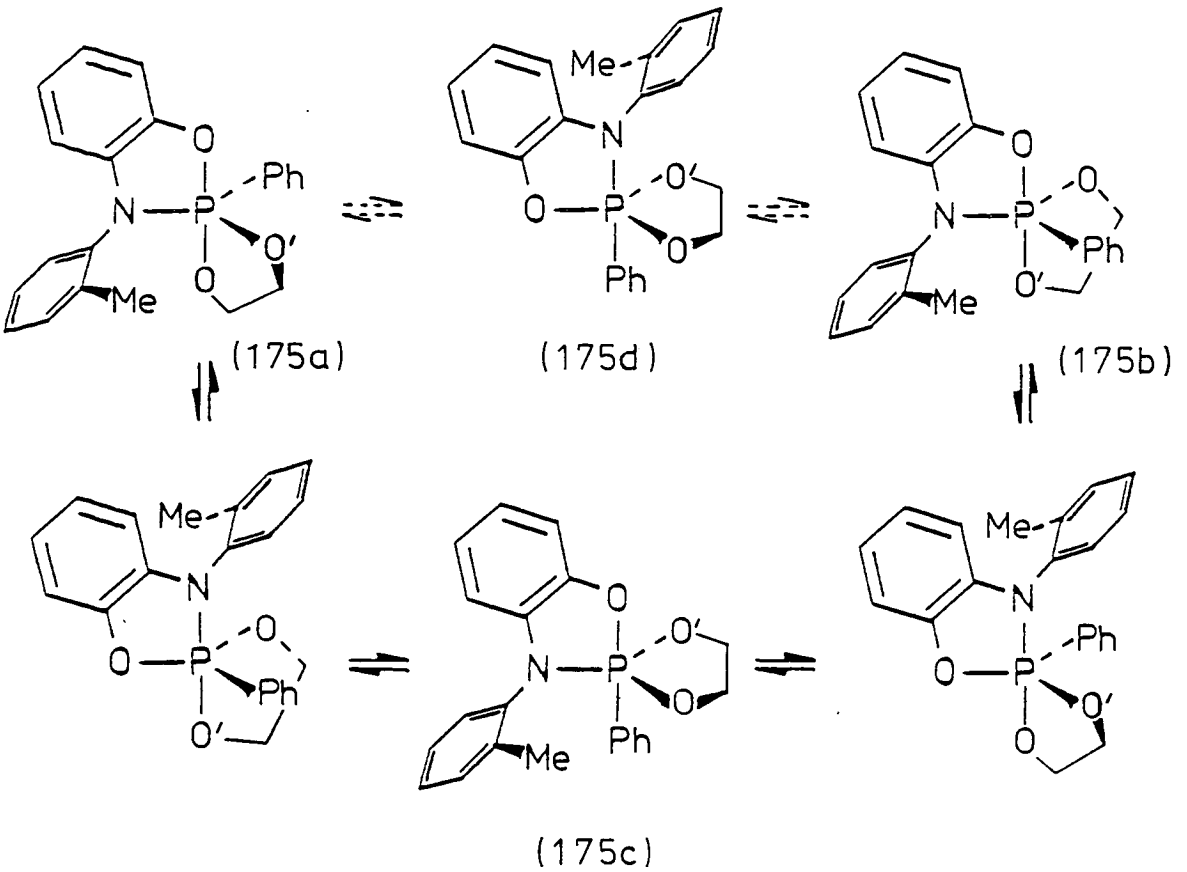
FIGURE 11: Variable temperature ^1H n.m.r. spectra of 2,3-dihydro-3-(2-methylphenyl)-2-phenylspiro{1,3,2-benzoxazaphosphole-2,2'-[1,3,2]dioxaphospholan}

(iii) 2,3-Dihydro-3-(2-methylphenyl)-2-phenylspiro{1,3,2-benzoxazaphosphole-2,2'-[1,3,2]dioxaphospholan}

The symmetrically substituted spirobicyclic compound (175) exhibited two unequally populated signals in its ^{31}P n.m.r. spectrum at ambient temperature, corresponding to the "frozen" anti (175a) and syn (175b) diastereoisomeric configurations in the ratio of approximately 3:1 (Scheme 83). These signals did not coalesce, but had begun to broaden as the temperature was raised to a maximum of +190°C, giving a free energy of activation of >97.5 kJ mol^{-1} for interconversion of diastereoisomers.

The ^{1}H n.m.r. spectrum of (175) also displayed separate "major" and "minor" o-methyl signals in the ratio 3:1 over the temperature range of -70°C to +160°C, confirming that interconversion of diastereoisomeric structures was slow on the n.m.r. timescale. However, gradual peak broadening was observed above 160°C, and coalescence occurred at +196±4°C (Figure 11). This represents a free energy barrier ($\Delta G_A^{\ddagger}$) of 104.5±1.3 kJ mol^{-1} for conversion of the "major" isomer (175a) into the "minor" isomer (175b), with the reverse interconversion ($\Delta G_B^{\ddagger}$) requiring an energy of 102.8±1.3 kJ mol^{-1} (ΔG = 1.7 kJ mol^{-1}, equivalent to the thermodynamic free energy difference between two isomers present in the ratio 3:1).

Although simple N-aryl rotation cannot be discounted as a possible explanation for this equivalence of o-methyl environments, it is more likely that the diequatorial five-membered ring intermediate (175c) shown in Scheme 83 constitutes the highest energy point of the P.I. process. Similar



Scheme 83

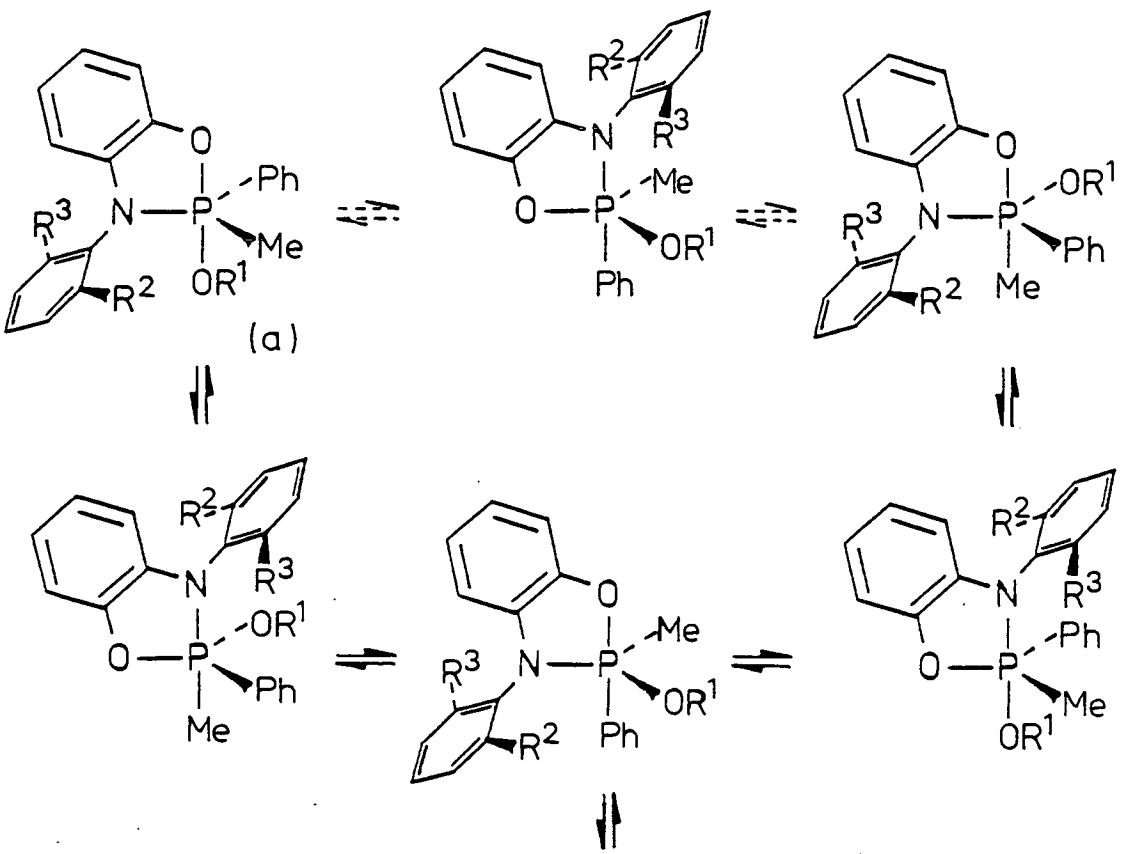
precedents exist both in symmetrically substituted spirobicyclic compounds of the same class[110], and more importantly, in other spirobicyclic phosphorane systems[44,82,83] where alternative modes of equilibration cannot arise.

In Scheme 83, the P.I. process which equilibrates structures (175a) and (175b) will proceed along the lowest energy pathway possible. Therefore, although structure (175d) is included as one of six possible TBPs which can arise during a complete P.I. cycle, the preferred pathway will proceed via (175c), as (175d) is a particularly high energy structure with both phenyl and amino functions in apical positions, and a diequatorial ring.

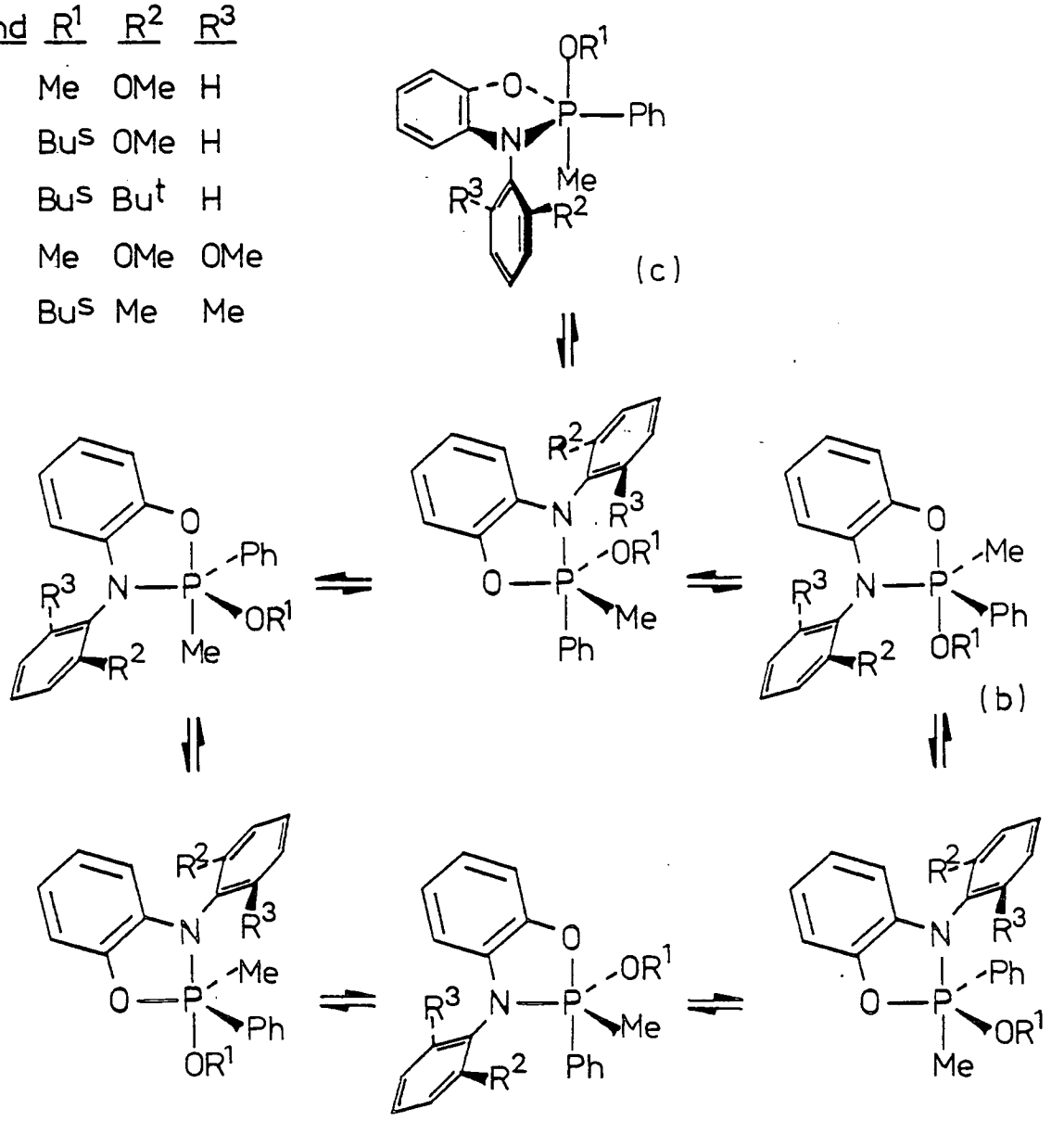
2.2.3 Asymmetrically substituted benzoxazaphospholes derived from tervalent phosphinite esters

The benzoxazaphospholes discussed in this section are derived from two tervalent phosphinite esters *viz*. methyl methylphenylphosphinite and sec-butyl methylphenylphosphinite. Their variable temperature n.m.r. spectra were generally found to be less complex than those of the phosphonite derived benzoxazaphospholes discussed above, because of the reduced fluxionality inherent in a TBP with only two apicophilic ligands (ring oxygen and alkoxy ligand). Thus, there exists only one clearly defined lowest energy TBP in any given cycle of six possible isomeric TBP structures which can arise during P.I. by the Turnstile mechanism.

For example, by substituting a methyl ligand for the equatorial methoxy ligand shown in the earlier full phosphonite



Compound	R^1	R^2	R^3
(185)	Me	OMe	H
(183)	Bu^s	OMe	H
(181)	Bu^s	Bu^t	H
(184)	Me	OMe	OMe
(182)	Bu^s	Me	Me

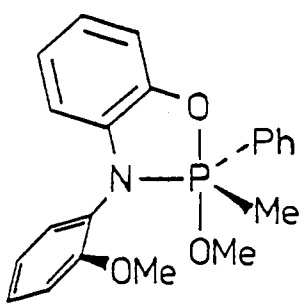


Scheme 84

pseudorotation cycle (see Scheme 80), a general pseudorotation cycle applicable to any methylphenylphosphinite derivative is obtained (Scheme 84). This model of the pathways available for P.I. is used below to rationalise spectral changes occurring in a range of phosphinite derived benzoxazaphospholes listed in Scheme 84.

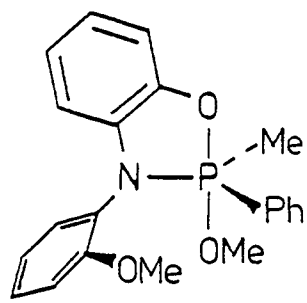
(i) 2,3-Dihydro-2-methoxy-3-(2-methoxyphenyl)-2-methyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole

Major and minor diastereoisomeric signals were observed in the n.m.r. spectra of the title compound (185) at +28°C. These were identified as the two lowest energy TBP structures (185a) and (185b) on the basis of the small coupling constants (J_{PH} 11Hz) corresponding to the apical P-OMe ligand in each isomer.



(185a)

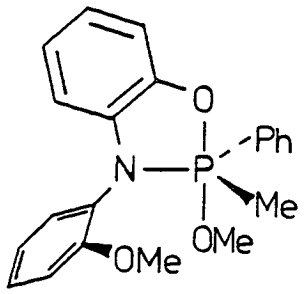
anti



(185b)

syn

The observed isomer ratio of 1.4:1 implies a greater degree of steric crowding in this compound than in the corresponding dimethyl phenylphosphonite derivative (165), which



(185)

FIGURE 12: Variable temperature ^{1}H and ^{31}P n.m.r. spectra of 2,3-dihydro-2-methoxy-3-(2-methoxyphenyl)-2-methyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole (185).

gave an isomer ratio of 1:1. The minor isomer is assigned the syn-configuration in accord with the greater degree of shielding conferred on the g-methoxy signal by the adjacent phenyl ligand.

Coalescence of the unequally populated ^{31}P n.m.r. signals at δ-26.9 and δ-27.7 in diphenyl ether did not occur until a temperature of +146±6°C, giving a $\Delta G_A^{\ddagger}$ value of 90.3±1.9 kJ mol^{-1} for conversion of the anti-diastereoisomer into the syn-configuration (Figure 12).

Similar high energy barriers were found from the three distinct coalescences observed in the ^1H n.m.r. spectra at high temperature (Figure 12). Thus, the major and minor singlets at ca.δ3.7 coalesced at 125±4°C ($\Delta\nu$ = 9.5Hz; $\Delta G_A^{\ddagger}$ = 89.8±1.6 kJ mol^{-1}), while at higher fields, major and minor P-OMe doublets (J_{PH} 11Hz) coalesced at 113±4°C ($\Delta\nu$ = 5.5Hz; $\Delta G_A^{\ddagger}$ = 88.8±1.7 kJ mol^{-1}). Finally, the separate major and minor P-Me doublets (J_{PH} 15.5Hz) also coalesced at 125±4°C, giving a value for $\Delta G_A^{\ddagger}$ of 89.7±1.5 kJ mol^{-1} ($\Delta\nu$ = 10Hz). The corresponding activation energy for the reverse equilibrium (i.e. $\Delta G_B^{\ddagger}$ for minor to major isomer interconversions) is ca.1.1 kJ mol^{-1} lower in energy, being the thermodynamic free energy difference (ΔG) between ground state structures.

The above $\Delta G^{\ddagger}$ values are self-consistent, and support the general P.I. process of Scheme 84. The energy barrier between major and minor diastereoisomers is almost twice as large for (185) as for the phosphonite analogue (165). This follows from the fact that the general P.I. process for phosphonite derivatives linked diastereoisomers (165a) and (165b) via a low energy pathway (Cycle 1, Scheme 80). The "frozen"

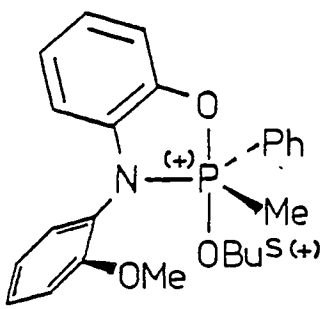
diastereoisomers (185a) and (185b), on the other hand, can only be interconverted via the diequatorial five-membered ring intermediate (185c) shown in Scheme 84. It is not surprising, therefore, that such a high energy intermediate should present an energy barrier of almost 90 kJ mol^{-1}.

Simple N-aryl rotation could also explain the spectral changes shown in Figure 12, but as in the case of spirobicyclic benzoxazaphospholes, the high energy barriers observed mean that N-aryl rotation can only be considered as an alternative high energy pathway to equilibration, requiring at least as much energy as diequatorial ring placement.

(ii) 2,3-Dihydro-3-(2-methoxyphenyl)-2-methyl-2-phenyl-2-sec-butoxy-1,3,2-benzoxazaphosph(v)ole

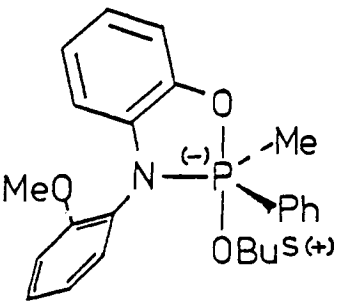
The foregoing P.I. process (Scheme 84) depicted interconversi of a major diastereoisomer (185a) and a minor diastereoisomer (185b) via a diequatorial intermediate which effectively changes the "optical" geometry at phosphorus i.e. an initial clockwise sequence of exocyclic ligands is effectively reversed to give a resultant anticlockwise sequence.

The same principle is also involved in explaining the spectral changes which occur when a chiral carbon centre is introduced in the form of a sec-butoxy ligand. This gives rise to two "optical" diastereoisomers for each major and minor "steric" diastereoisomer. Thus the ^{31}P n.m.r. spectrum of (183) at +28°C showed four signals (two major and two minor; ratio 1.5:1) corresponding to the four diastereoisomeric structures shown in Scheme 85. Major and minor signals coalesced at ca.+130°C to give a broad signal up to +200°C.

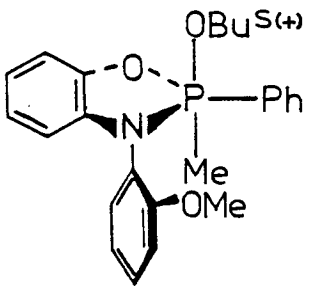


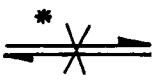
(+)183a)

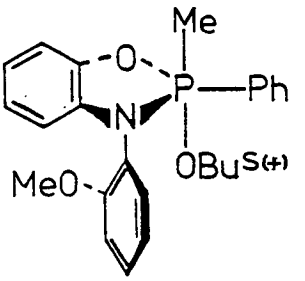
major isomers (anti)

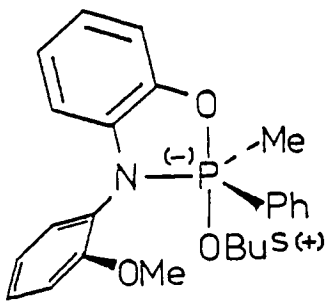


(−)183a)



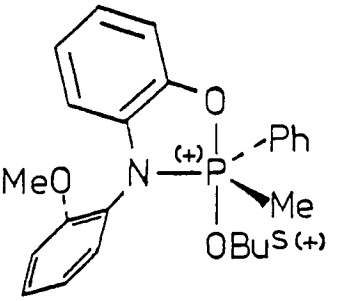






(−)183b)

minor isomers (syn)



(+)183b)

* N-aryl rotation required to link separate P.I. pathways

Scheme 85

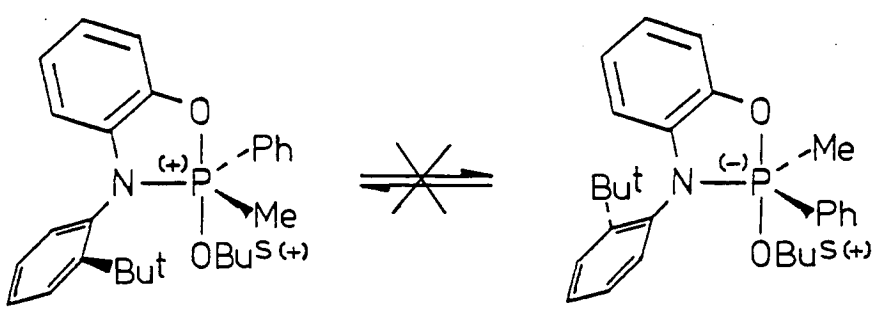
This coalescence corresponds to an activation energy of ca.87 kJ mol^{-1}, and can be most readily interpreted by using the arbitrary prefixed (+) and (-) to denote the direction of optical rotation at chiral carbon and phosphorus centres, and by considering only structures with (+)-sec-butoxy geometry. Scheme 85 then becomes exactly analogous to the previous P.I. process (Scheme 84), in that interconversion of "frozen" major and minor diastereoisomers leads to equivalence of ((+)183a) with ((-)183b), and of ((-)183a) with ((+)183b). Thus, optical geometry at carbon is conserved while P.I. racemises the chiral phosphorus centre via a high energy diequatorial ring intermediate. The above theory predicts that two separate signals should still be present in the ^{31}P n.m.r. spectrum of (183) above coalescence, since no P.I. process can possibly interconvert the two major optical diastereoisomers ((+)and (-)183a) or the two minor optical diastereoisomers ((+) and (-)183b). The experimentally observed broad singlet at ca.+200°C is not inconsistent with these ideas since the average positions of the two coalescences involving major and minor steric diastereoisomers would be expected to roughly coincide.

It is worth reiterating that each of the four diastereoisomers shown in Scheme 85 also exists in a mirror image form (enantiomer) corresponding to four structures having (-)-sec-butoxy geometry, but because enantiomeric pairs are magnetically equivalent, they remain indistinguishable by n.m.r. spectroscopy.

(iii) 2,3-Dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

The same principles used in the foregoing phosphinite derived benzoxazaphospholes apply for the g-tertiary butyl derivative (181). This compound exhibited no minor diastereoisomeric signals in its n.m.r. spectra, which remained unchanged over the temperature range of +28°C to +200°C. This concurs with the previously observed large steric hindrance between bulky phenyl and tertiary butyl groups when placed in a syn-configuration.

As before, by considering only the (+)-sec-butoxy forms, formation of the pentacoordinate compound will occur to give the lowest energy TBP structures. These will have anti-configurations of t-butyl and phenyl groups, and have either (+) or (-) geometry at phosphorus. By analogy with Scheme 85, these "major" optical diastereoisomers ((+)181a) and ((-)181a) (Scheme 86) cannot be interconverted by any P.I.



(+)181a) (-)181a)

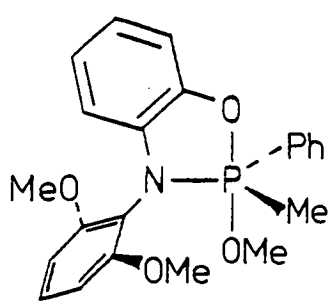
anti optical diastereoisomers

Scheme 86

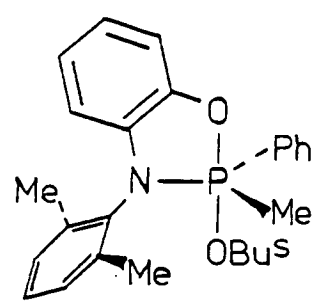
process (or even by N-aryl rotation), as even diequatorial ring placement would only succeed in converting a major steric diastereoisomer into its highly sterically hindered minor form.

This compound therefore exists as two non-interconvertible optical diastereoisomers (and their enantiomers). Consequently the corresponding benzoxazaphosphole prepared from optically active (+)-sec-butyl methylphenylphosphinite should consist of a mixture of optically active diastereoisomers ((+)181a) and ((-)181a) alone, and as such is an ideal compound with which to attempt to isolate the first monocyclic pentacoordinate phosphorane with an optically active phosphorus centre (see Chapter 3).

Finally, two further phosphinite derived benzoxazaphospholes deserve comment in this section, although strictly speaking, they are symmetrically substituted compounds in which both ortho-positions are"blocked".



(184)



(182)

Compound (184) differs from compound (185) discussed earlier in having an additional o-methoxy substituent, yet

no coalescence was observed for the separate σ-methoxy signals in its high temperature ^1H n.m.r. spectra. This equates to an energy barrier of >108 kJ mol^{-1} (T_c > 205°C; $\Delta\nu$ = 6Hz) for the P.I. process shown in Scheme 84 which averages the σ-methoxy environments of (184a) and (184b) via a high energy diequatorial ring intermediate (184c). This energy barrier is at least 18 kJ mol^{-1} higher than in compound (185), and is possibly due to greater steric interaction in (184) between the apical P-Me ligand and the adjacent "lower" σ-methoxy substituent in the critical highest energy diequatorial ring structure ((184c), Scheme 84).

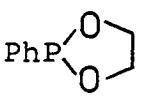
This explanation gains further support for the similar high energy barrier to equilibration of σ-methyl substituents found in compound (182) (ΔG^* >104 kJ mol^{-1}). At lower temperatures, (182) exhibited some peculiar peak broadening effects, which may reflect a partial restricting of movement in the sec-butoxy ligand caused by steric interference with the adjacent 2,6-dimethyl-substituted N-aryl ring.

2.3 Conclusions from variable temperature n.m.r. studies

The average free energy barriers to P.I. discussed in the preceding sections are summarised in Table 9. The results of earlier variable temperature n.m.r. studies on symmetrically substituted 3-aryl-2,3-dihydro-1,3,2-benzoxazaphospholes[110] have also been included in Table 9 to provide a broader basis for analysing the effect of benzoxazaphosphole structure on the energy barrier to P.I. These earlier results have been modified to incorporate a common transmission coefficient of unity in all calculations of ΔG^*, in place of the originally

TABLE 9

Summary of average ΔG^* values obtained for 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles

Compound	N-Phenyl Substituent	Tervalent Phosphorus Reagent	ΔG^* ($kJmol^{-1}$)
196[a]	None	$MeP(OEt)_2$	42.9
180	$2,4\text{-}Me_2$	"	43.9
197[a]	$2,4,6\text{-}Me_3$	"	49.9
179	$2\text{-}Bu^t$	"	55.1
198[a]	None	$PhP(OMe)_2$	42.2
199[a]	4-OMe	"	42.4
165	2-OMe	"	47.5; 97.4
164	$2,6\text{-}OMe_2$	"	50.6
170[a]	4-Me	$PhP(OMe)_2$	44.0
166	2-Me	"	46.0
168	$2,4\text{-}Me_2$	"	46.8
194	$2,6\text{-}Me_2$	"	51.4
200[a]	$2,4,6\text{-}Me_3$	"	52.4
175	2-Me		103.6
201[b]	$2,6\text{-}Me_2$	"	100.1
195[a]	$2,4,6\text{-}Me_3$	"	98.6
185	2-OMe	PhMePOMe	89.1
186	$2,6\text{-}OMe_2$	$PhPMe_2$	48.6
169[c]	4-Me	$ArP(OMe)_2$	48.2

a. Modified results, previously reported in Ref.110.

b. Unpublished observations by Dr.N.J. Tweddle, University of Edinburgh.

c. Ar = 2,6-dimethoxyphenyl

reported coefficient value of 0.5[110].

Asymmetrically substituted benzoxazaphospholes derived from diethyl methylphosphonite showed no thermodynamic preference for the anti-stereochemistry, demonstrating an absence of steric interference between the equatorial P-methyl ligand and the pendant N-aryl group, even in the presence of a bulky ortho-t-butyl substituent. This observation contrasts with the marked preference for anti-stereochemistry exhibited by asymmetrically substituted dimethyl phenylphosphinite derivatives, where the bulky P-phenyl ligand can significantly interfere with any syn-orientated ortho-alkyl substituent (see Table 6).

Within both of these classes of phosphonite derivatives, a similar trend was observed towards higher ΔG^* values with increasing N-aryl ring substitution especially at the ortho-positions. Both methyl and methoxy substituents, for example, increase the energy barrier by ca. 3-5 kJ mol^{-1} when one ortho-position is substituted, and by ca.7-9 kJ mol^{-1} when both ortho-positions are substituted. The single bulky ortho-t-butyl substituent of the diethyl methylphosphonite derivative (179) however, increased ΔG^* by ca.12 kJ mol^{-1} compared with the corresponding unsubstituted compound (196). The reason for these relatively large differences in ΔG^* is attributed to an increase in steric crowding during P.I. Thus, the highest energy intermediate TBP structure in a P.I. cycle is probably more susceptible to destabilisation by bulky ortho-substituents in the N-aryl ring, leading to a greater difference in energy (ΔG^*) between the highest energy intermediate or transition

state and ground state TBP structures. Although steric hindrance prevented observation of any minor diastereoisomer, the trends shown in Table 9 suggest that the ortho-t-butyl substituted derivative of dimethyl phenylphosphonite (167) would require an activation energy of ca.55-60 kJ mol^{-1} to interconvert anti- and syn-configurations by a P.I. process.

The free energy barriers discussed above correspond to relatively low energy P.I. processes (ΔG^* <60 kJ mol^{-1}) which maintain the five-membered heteroatomic ring in an apical-equatorial position. A much higher free energy barrier (ΔG^* ca.100 kJ mol^{-1}) was found in spirobicyclic benzoxazaphospholes derived from 2-phenyl-1,3,2-dioxaphospholan, which necessitate intermediate diequatorial ring placement during P.I. to equilibrate ortho-environments. Similar high energy diequatorial ring intermediates are invoked in rationalising the complete averaging of environments observed at high temperatures for the monocyclic benzoxazaphospholes (165) and (185). Other asymmetrically substituted monocyclic benzoxazaphospholes probably also share this mode of achieving full ligand equivalence, but evidence is limited to P.I. remaining slow on the n.m.r. timescale even at the maximum spectrometer temperature available. Nevertheless, these higher range ΔG^* values are entirely consistent with numerous literature precedents for P.I. processes occurring via diequatorial ring intermediates[44,82].

The main schematic diagrams used to represent P.I. processes in the different classes of benzoxazaphospholes studies can be summarised as follows:

(i) Phosphonite derived benzoxazaphospholes

A low energy P.I. cycle (ΔG^{*} <60 kJ mol^{-1}) exchanges enantiomeric TBP structures when the N-aryl group is symmetrically substituted, but exchanges unequally populated steric diastereoisomers when the N-aryl group is asymmetrically substituted.

A higher energy P.I. pathway involving diequatorial placement of a five-membered ring (ΔG^{*} >90 kJ mol^{-1}) is required to achieve complete averaging of ligand environments in asymmetrically substituted compounds and spirobicyclic benzoxazaphospholes.

(ii) Phosphinite derived benzoxazaphospholes

No low energy P.I. pathway exists for interconversion of enantiomers (for symmetrical N-aryl groups) or steric diastereoisomers (for asymmetric N-aryl groups). Interconversion in these cases is only achieved by a high energy P.I. pathway involving diequatorial ring placement, which effectively inverts the optical geometry at chiral phosphorus.

The introduction of a second chiral centre of fixed geometry as part of an exocyclic ligand gives rise to optical diastereoisomers which cannot be racemised by any P.I. process. By a judicious choice of ligands and N-aryl substituents, the aforementioned features of steric and optical diastereoisomerism can be married to give a benzoxazaphosphole which provides the possibility of resolving an optically active pentacoordinate phosphorus centre.

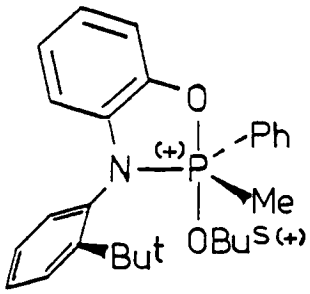
3. Attempted Synthesis and Isolation of an Optically Active Monocyclic Pentacoordinate Phosphorane

The stereochemistry of tri- and tetracoordinate phosphorus compounds has been well documented[161], and much of the work has been devoted to the use of optically active phosphines, phosphine oxides, and phosphonium salts to elucidate important reaction mechanisms. Progress in understanding the stereochemical course of reactions of pentacoordinate phosphoranes has been hampered by the ease with which most of these compounds undergo racemisation by P.I.

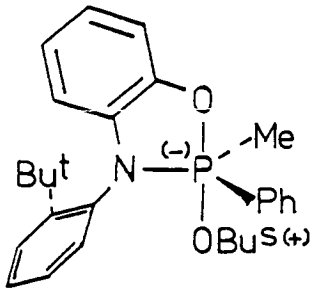
Hellwinkel has isolated a spirobicyclic phosphorane with optical activity at phosphorus[7], but to date no monocyclic phosphorane has been isolated with specific configuration at phosphorus. The preceding variable temperature n.m.r. studies, however, have indicated that the steric constraints placed on one particular benzoxazaphosphole may provide the opportunity to isolate such a chiral species.

3.1 Preparation of pentacoordinate chiral diastereoisomers from (+)-sec-butyl methylphenylphosphinite

Deoxygenation of 2-nitrophenyl 2-tert-butylphenyl ether by (+)-sec-butyl methylphenylphosphinite gave a benzoxazaphosphole in 48% yield as an equal mixture of chiral diastereoisomers ((+)181a) and ((-)181a). The same mixture was also obtained by an alternative synthesis from 2-(2-tert-butylanilino)phenol and optically active phosphinite (see Experimental, section 9).



(+)181a)



(−)181a)

It has been established in a previous chapter (see section 2.2.3) that these diastereoisomers cannot be interconverted by any regular P.I. process or by N-aryl rotation. This suggests that application of conventional diastereoisomer separation techniques to this mixture may enable the separation and isolation of the first monocyclic pentacoordinate phosphorane with defined optical activity at phosphorus.

3.2 Attempted separation and isolation of diastereoisomers

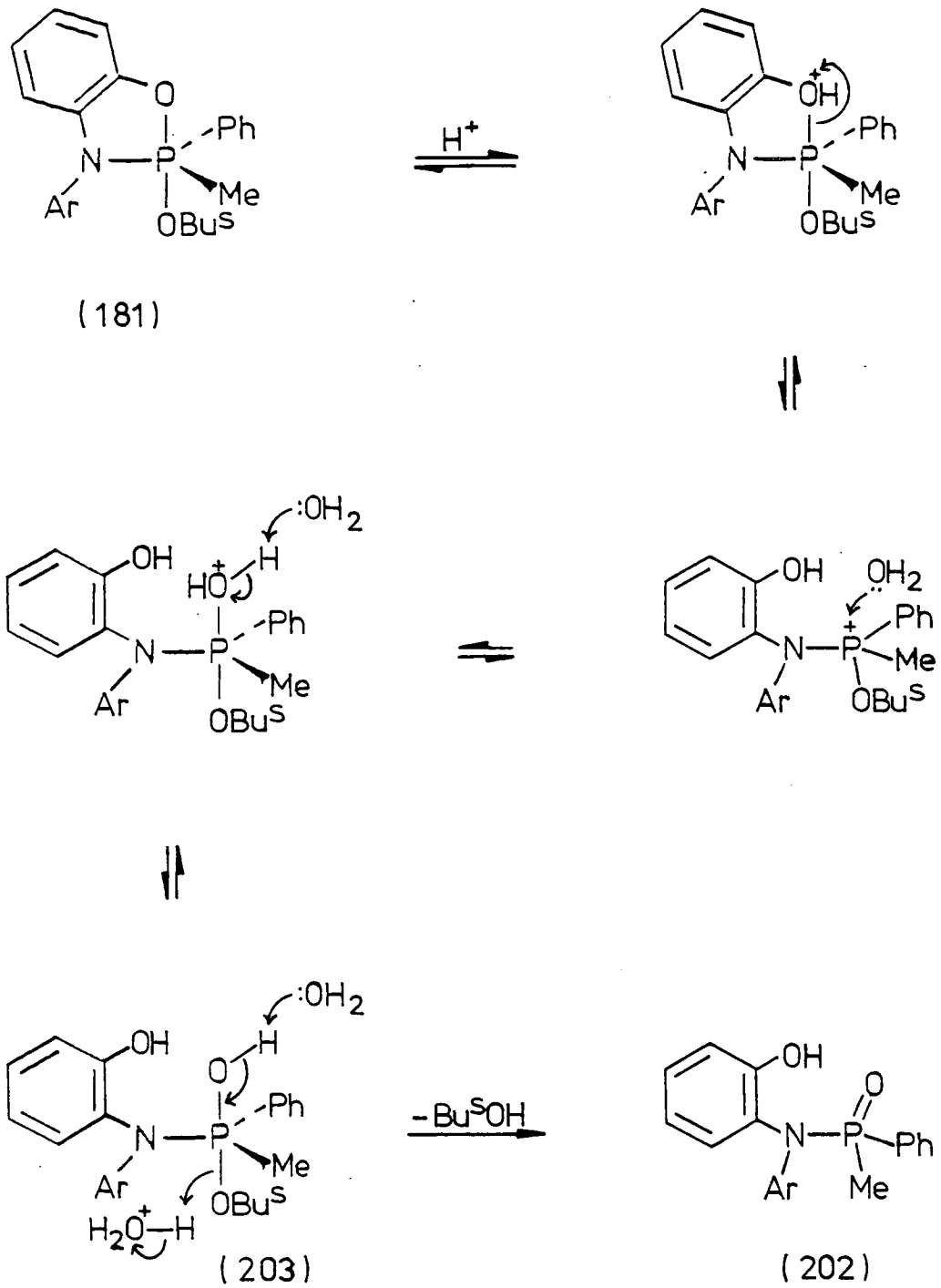
As detailed in the Experimental Section (see chapter 10), repeated recrystallisations of these optically active diastereoisomers from generous quantities of dry petrol and various solvent mixtures failed to show any enrichment in the ^{31}P n.m.r. signals of either diastereoisomer (δ-28.6 and δ-29.0). Consequently, various chromatographic techniques were investigated, using racemic pairs of diastereoisomers derived from racemic phosphinite until optimum conditions were defined. A small but finite separation of diastereoisomers was eventually achieved by h.p.l.c., and the pentacoordinate assignment confirmed by ^{31}P n.m.r. spectroscopy, but scale-up to l.p.c.

subsequently revealed that greater than 90% of the injected sample was being hydrolysed on the columns.

Despite this setback, separation of a single diastereoisomer (and its enantiomer) was finally achieved by the repeated collection and recombination of fractions from the second peak eluted from the analytical scale h.p.l.c. column (^{31}P δ-32.6) Because of the impractical nature of this method of separation, it was considered futile to attempt separation of the corresponding optically active diastereoisomers by the same technique, as insufficient product would be available to measure an optical rotation.

In conclusion, partial success can be claimed in having synthesised non-interconverting chiral diastereoisomers and, despite the problems of hydrolysis and inadequate separation, achieve the isolation of one pure diastereoisomer with its enantiomer.

Possible future solutions to the problem of separating chiral diastereoisomers may lie in the use of optically active phosphinites[162] with high optical purity at phosphorus. Incorporation of such a phosphinite into a benzoxazaphosphole containing the N-(2-tert-butylphenyl) group might reasonably be expected to form one diastereoisomer in large excess, and hence facilitate isolation of a pure chiral pentacoordinate centre by fractional crystallisation.



(181)

(203)

(202)

Ar = 2-t-butylphenyl

Scheme 87

4. Hydrolysis Reactions of 3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles

Previous hydrolysis studies by Cadogan et al.[114,115] have attempted to correlate the type of hydrolysis product obtained with the structure of the original pentacoordinate phosphorane. The resultant acid and base catalysed mechanisms proposed for hydrolysis of symmetrically substituted benzoxazaphospholes have been summarised in the Introduction (Chapter 4).

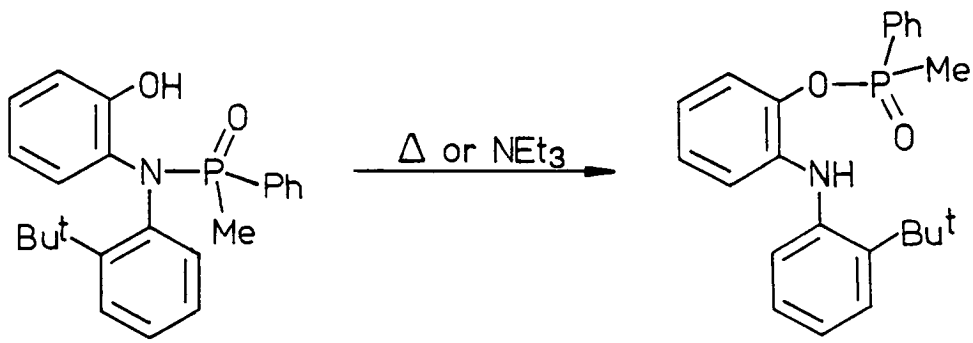
As a continuation of this study, it was of interest to examine the hydrolysis reactions of a number of new benzoxazaphospholes to test the above mechanisms more thoroughly, especially in view of the subtle steric differences observed in asymmetric or partially "ortho-blocked" compounds.

4.1 2,3-Dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

Acid catalysed hydrolysis of the title compound (181) gave rise to a single phosphorus containing product by ^{31}P n.m.r. spectroscopy, identified as the acyclic phosphinic amide (202). This observation is consistent with the general acid catalysed hydrolysis mechanism proposed by Cadogan et al.[114] and depicted for this compound in Scheme 87. Thus, endocyclic P-O bond cleavage and attack by water at the phosphonium centre leads to an intermediate hydroxyphosphorane (203), which then loses the apical alkoxy ligand as an alcohol to yield the phosphinic amide (202).

Although the phosphinic amide was only isolated in 71% yield, the presence of a single ^{31}P n.m.r. peak during monitoring of the reaction strongly suggests that none of the isomeric

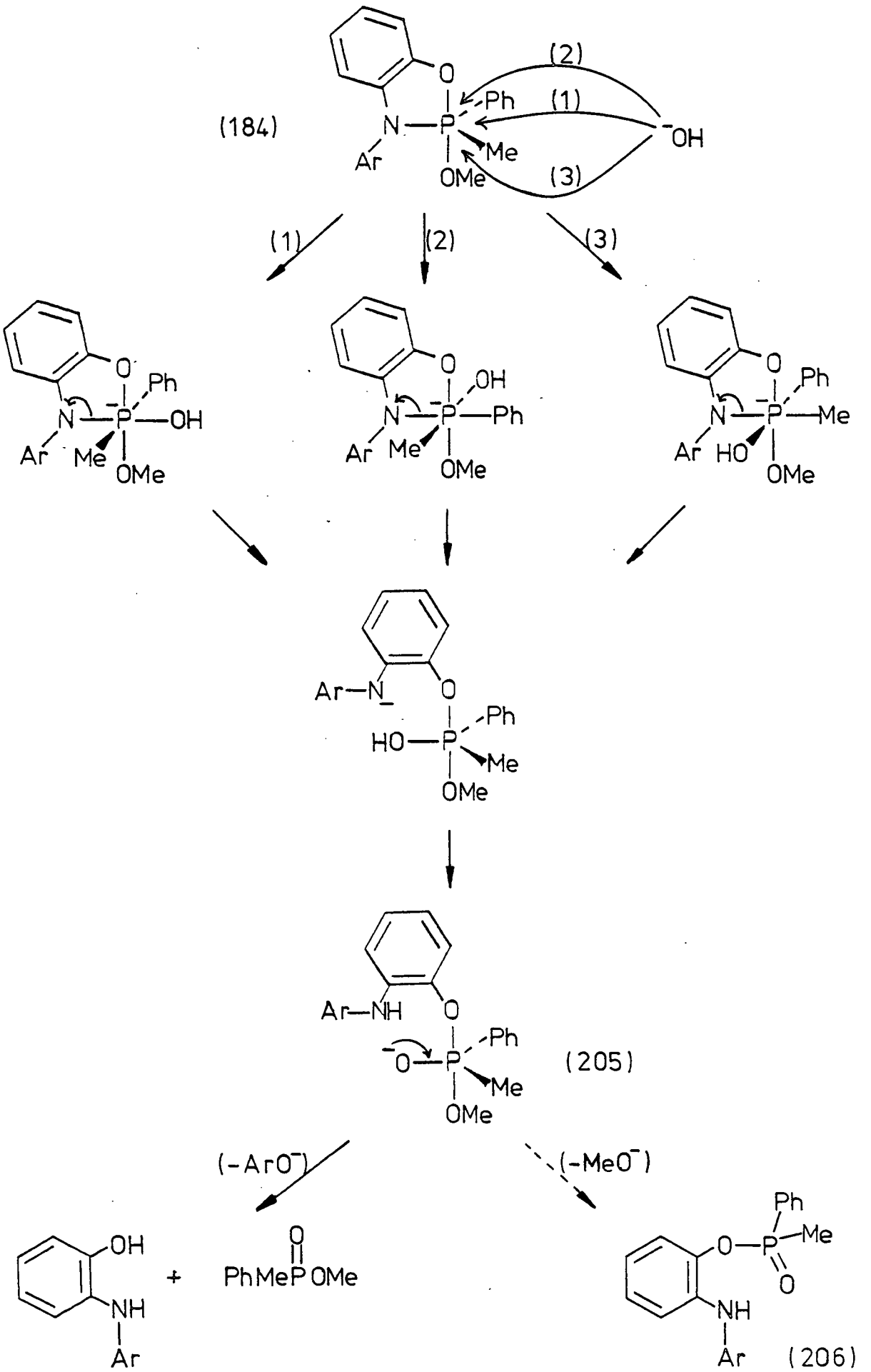
phosphinate (204) is formed during hydrolysis. This is not unexpected since hydrolysis of an intermediate TBP structure during P.I. in which the amino function occupies an apical position would have to be invoked to explain phosphinate formation, and such an intermediate TBP structure is unlikely to be present in significant proportion compared with the ground state TBP structure (181). The assignment of a phosphinic amide structure (202) to the acyclic hydrolysis product rather than the isomeric phosphinate structure (204) is based on the sharp singlet at δ11.19 in the ^{1}H n.m.r. spectrum, which is characteristic of the phenolic proton in related phosphinic amides[114], and on the thermal and base-catalysed rearrangement of the phosphinic amide to its isomeric phosphinate (Scheme 88).



(202) (204)

Scheme 88

Similar thermal and base-catalysed rearrangements have also been reported for related P,P-diphenylphosphinic amides[114]. This rearrangement explains the isolation of (204) from an attempted preparation of the benzoxazaphosphole (181) (see Experimental section 4.2(ii)); accidental ingress of moisture or acidity to the reaction system would be expected to give the phosphinic amide (202) initially, but subsequent thermal rearrangement to the phosphinate (204) would be expected



Scheme 89

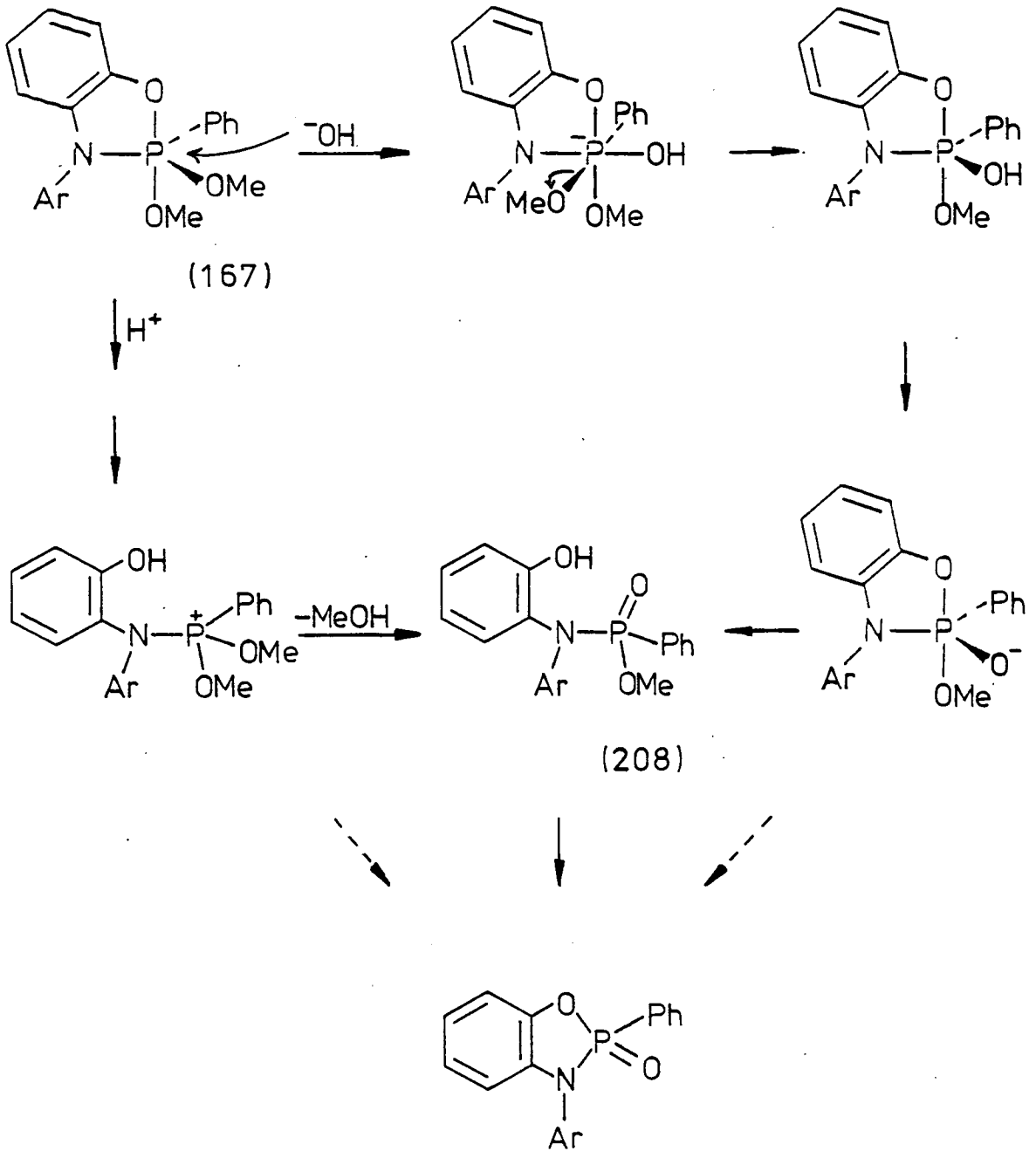
with the high temperatures of reaction and work-up.

4.2 3-(2,6-Dimethoxyphenyl)-2,3-dihydro-2-methoxy-2-methyl-2-phenyl-1,3,2-benzoxazaphosph(v)ole

Base catalysed hydrolysis of the symmetrically substituted title compound (184) derived from methyl methylphenylphosphinite occurred relatively slowly (30% unreacted after 22 hours at ambient temperature) to give a product identified as 2-(2,6-dimethoxyanilino)phenol by comparison of its n.m.r. spectrum with that of an authentic sample; the presence of a phosphorus acid salt was also suspected on the basis of solubility and ^{31}P n.m.r. data.

There are three possible positions for hydroxyl ion attack in base-catalysed hydrolysis, as outlined in the Introduction (Chapter 4.2). Attack opposite the most electronegative nitrogen atom (Route (1), Scheme 89) would be expected to be most favoured, with steric hindrance to attack certainly being less severe than in the methyl diphenyl-phosphinite derivatives[114] where adjacent bulky phenyl ligands prevented hydrolysis. The resultant hexacoordinate intermediate cannot lose the ligand adjacent to the greatest number of electronegative ligands, however, as both possible ligands (methyl and phenyl) are very poor leaving groups. Thus, leaving group ability on this occasion outweighs the "dipole expulsion effect", so that the arylamino anion is lost, leading to the most stable TBP intermediate (205) with oxygen anion equatorial.

The alternative positions of attack are shown in routes (2) and (3) (Scheme 89). Such attack opposite non-electro-



Ar = 2-t-butylphenyl

Scheme 90

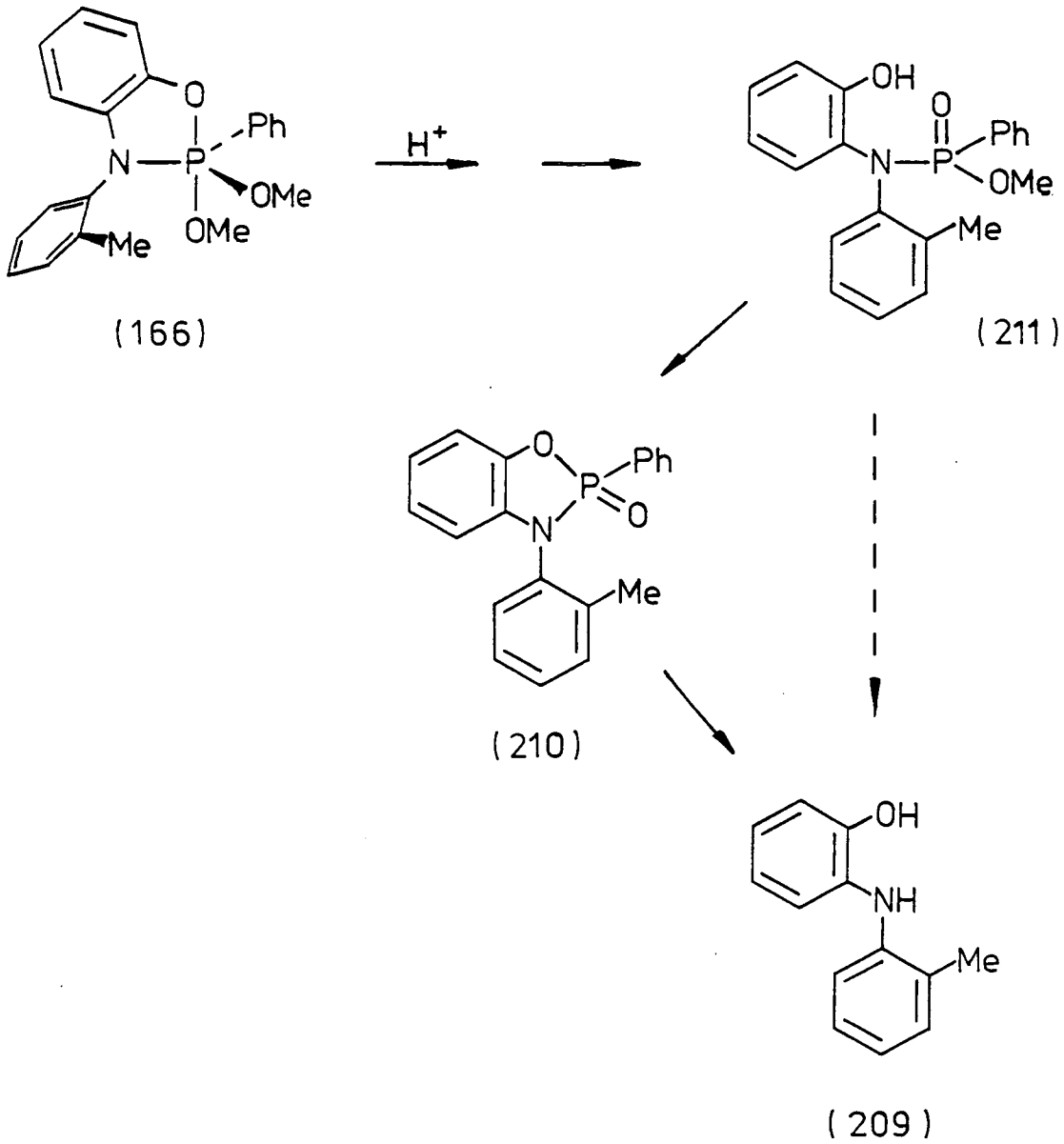
negative ligands is less favourable, but nevertheless would still lead to the same TBP intermediate anion (205), since the arylamino group is adjacent to the greatest number of electronegative ligands in both hexacoordinate intermediates.

Collapse of (205) by loss of the best apical leaving group (ArO) would give 2-(2,6-dimethoxyanilino)phenol plus methyl methylphenylphosphinate as the final hydrolysis products; alternatively loss of the other apical leaving group (OMe) would give rise to the acyclic phosphinate (206). Identification of the anilinophenol alone from the hydrolysis of (184) does not wholly support the mechanism proposed in Scheme 89, as no methyl methylphenylphosphinate was observed. A tentative explanation may be that the acyclic phosphinate (206) is indeed the major hydrolysis product, but that it further hydrolyses to the anilinophenol and a phosphinous acid (suspected from n.m.r. and solubility data).

4.3 2,3-Dihydro-2,2-dimethoxy-2-phenyl-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

Both acid and base-catalysed hydrolysis of the title compound (167) gave rise to the same cyclic phosphonamidate (207), in accord with the analogous observations by Tweddle[115] on the hydrolysis of the corresponding N-(2,4,6-trimethylphenyl) derivative (see Introduction, Chapter 4).

The mechanism shown in Scheme 90 can account for this product either via a common acyclic hydrolysis product (208) which subsequently cyclises to relieve crowding at sp^3 hybridised nitrogen, or by direct loss of apical methoxy leaving groups from charged intermediates, to give the observed cyclic



(166)

(211)

(210)

(209)

Scheme 91

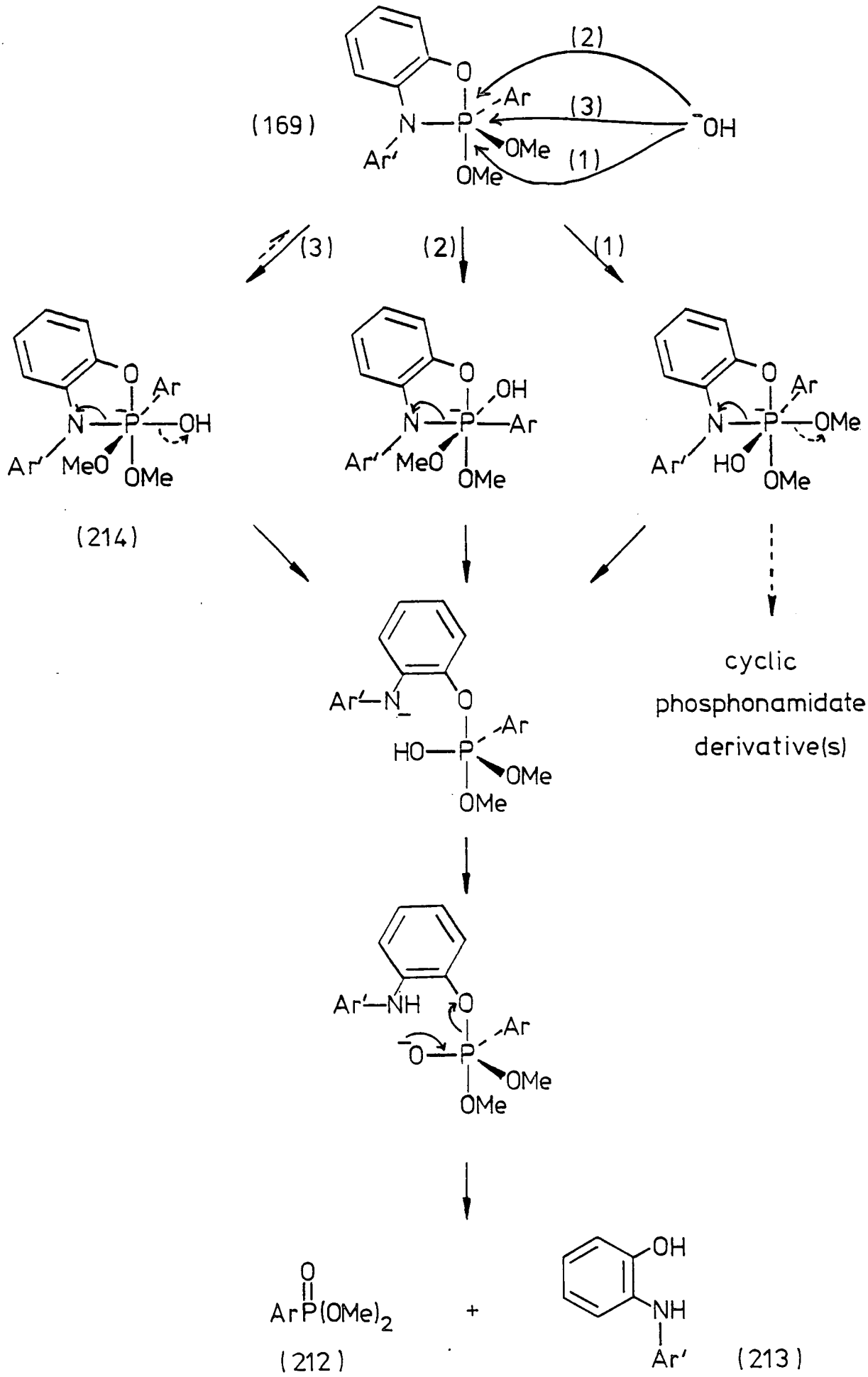
phosphonamidate (207). It is not unreasonable, based on variable temperature n.m.r. evidence, that the steric crowding caused by a single ortho-t-butyl group should be considered at least equal to that caused by two g-methyl substituents.

4.4 2,3-Dihydro-2,2-dimethoxy-3-(2-methylphenyl)-2-phenyl-1,3,2-benzoxazaphosph(v)ole

In contrast to the above ortho-t-butyl substituted compound (167), the ortho-methyl substituted title compound (166), was hydrolysed under mild acid conditions to give an approximately 2:1 mixture of 2-(2-methylanilino)phenol (209) and the cyclic phosphonamidate (210). Scheme 91 suggests a pathway consistent with the general acid-catalysed hydrolysis mechanism as far as the acyclic hydrolysis product (211). With a smaller g-substituent, however, the driving force to relieve steric crowding by forming the cyclic phosphonamidate (210) is reduced. The anilinophenol could arise from further hydrolysis of the first formed cyclic phosphonamidate, as anilinophenols are invariably obtained as the ultimate hydrolysis products of benzoxazaphospholes.[108] The cyclic product certainly appears unstable; repeated attempts to isolate (210) by mild hydrolysis of (166) in the presence of toluene-4-sulphonic acid proved unsuccessful. Alternatively, the anilinophenol could arise by direct hydrolysis of the intermediate phosphinic amide (211) rather than via the cyclic phosphonamidate. It is evident, however, that parameters governing anilinophenol formation from either intermediate hydrolysis products are not sufficiently well defined to allow a more detailed analysis of the acidic hydrolysis mechanism at this stage.

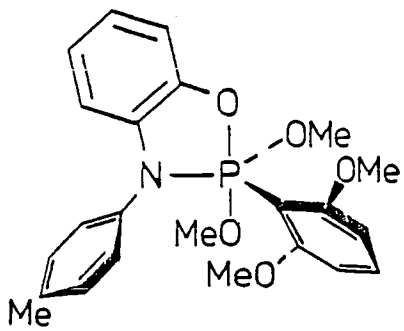
4.5 2-(2,6-Dimethoxyphenyl)-2,3-dihydro-2,2-dimethoxy-3-(4-methylphenyl)-1,3,2-benzoxazaphosph(v)ole

The title compound (169) was synthesised primarily for the purpose of testing the "dipole" interaction theory proposed by Cadogan and Tweddle[115] to explain the base-catalysed hydrolysis products from various pentacoordinate phosphoranes. This theory postulates that the initial hexacoordinate intermediate reacts by loss of the ligand adjacent to the greatest number of electronegative ligands. For instance, a group of four planar ligands, all bonded to phosphorus via an oxygen atom, effectively present a large negative dipole surface to a fifth perpendicular ligand, thus enhancing the leaving group ability of this perpendicular ligand. "Normal" ligand leaving group abilities can therefore be perturbed by the combined electronegativity or "dipole" potential of their four nearest neighbouring ligands in a hexacoordinate intermediate. The limits of this perturbation have already been mentioned in Scheme 89, where the poor leaving group ability and low electronegativity of both methyl and phenyl ligands apparently outweighed the "dipole" effect of neighbouring ligands. A better comparison of the strength of the "dipole" theory, however, should be provided by the dimethyl 2,6-dimethoxyphenylphosphonite derivative (169). In this benzoxazaphosphole, the o-methoxy substituents effectively create a dipole on the P-phenyl ligand, and hence hydrolysis of (169) can be compared directly with the corresponding unsubstituted P-phenyl compound (170). Basic hydrolysis of (170), previously described in the Introduction,

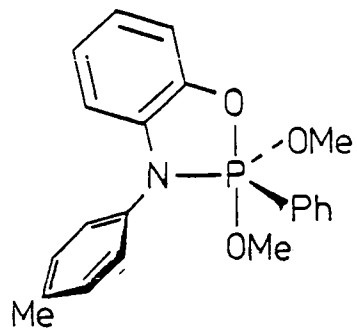


Ar = 2,6-dimethoxyphenyl ; Ar' = 4-methylphenyl

Scheme 92



(169)



(170)

gave a mixture of cyclic phosphonamidate (20%), dimethyl phenylphosphonate (20%), and an acyclic hydrolysis product (60%). Such a product distribution suggests a mechanism (Scheme 67, Introduction) in which hydroxyl ion attack occurs predominantly via route (3), but with at least 20% hydrolysing via route (2).

Compound (169), on the other hand, hydrolyses roughly 40 times slower under the same conditions, indicative of an increase in steric crowding which hinders hydroxyl ion access to the phosphorus centre. The hydrolysis products also differed, being a mixture of dimethyl 2,6-dimethoxyphenyl-phosphonate ((212); 47%), 2-(4-methylanilino)phenol ((213); 40%) and an unidentified minor product (13%) which is possibly a phosphorus acid. These products are postulated in Scheme 92 as arising by a mechanism equivalent to route (2). Because of the "dipole" effect, the hexacoordinate intermediate (214) formed by hydroxyl ion attack opposite nitrogen (route (3), Scheme 92) now experiences a strong dipole contribution from the P-aryl ligand. Thus, instead of the best leaving group (methoxy) being lost, as happened in the hydrolysis of (170), the leaving group ability of the amino function is enhanced

by the "dipole" effect. Loss of the amino group gives a pentacoordinate anion intermediate identical to that obtained by route (2), and subsequently reaction as shown in Scheme 92 leads to the observed phosphonate and anilinophenol products.

Neutral hydrolysis of (169) in aqueous dioxan also gave dimethyl 2,6-dimethoxyphenylphosphonate and 2-(4-methylanilino)-phenol as the major products. This is not unexpected, since neutral hydrolyses are known to occur by a mechanism analogous to that base-catalysed hydrolysis[115].

Acid catalysed hydrolysis of (169) gave rise to a multi-component mixture in which both the phosphonate and anilino-phenol were again detected by n.m.r. spectroscopy, but not as particularly major products. Any intermediate products from acid-catalysed hydrolysis of (169) appear to be very unstable, possibly as a result of steric crowding about phosphorus. Reactions under different acid conditions consistently gave only multi-component mixtures by ^{31}P n.m.r. monitoring, with numerous resonances in the phosphorus acid region of the spectrum (δ+13 to δ+18). Identification of the anilinophenol suggests that complete hydrolysis may be occurring to give this ultimate acid-catalysed hydrolysis product.

4.6 Conclusions from hydrolysis studies

The selected hydrolysis reactions discussed above provide further insight into the variation of reaction product type with ligand character and steric features of the original pentacoordinate benzoxazaphosphole. For the most part, the observed products can be rationalised within the framework

of the general acid and base catalysed hydrolysis mechanisms postulated by Cadogan *et al.*[114,115]. Some uncertainty remains, however, over the precise mechanism for anilinophenol formation in acid-catalysed reactions, and the factors governing the stability of intermediate tetracoordinate phosphorus compounds with respect to further hydrolytic degradation.

The base catalysed "dipole" theory is strengthened by the observed products from hydrolysis of (169) in particular. However, with at least three interdependent parameters which can also be invoked to explain a reaction pathway (steric strain, ligand apicophilicity, and leaving group ability alone), the "dipole" theory is not put under any great threat by the compounds considered here. Any defects in this theory might perhaps be more easily identified by investigating different types of pentacoordinate phosphoranes where alternative pathways are more limited.

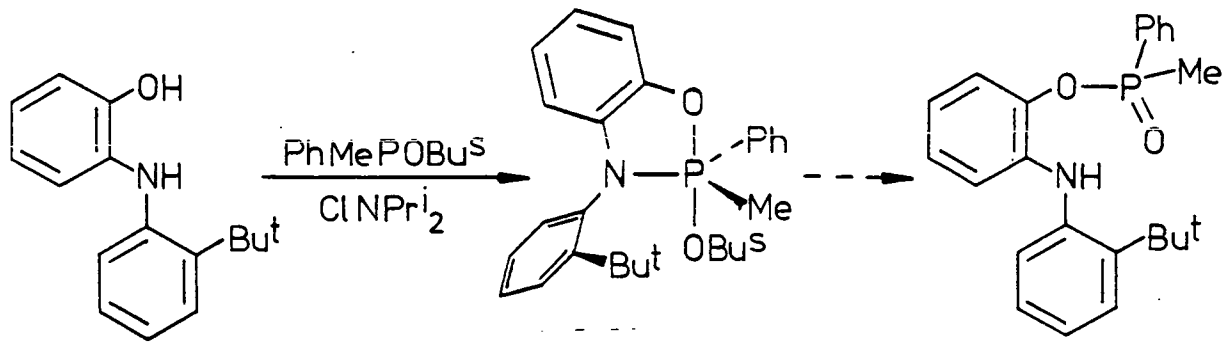
5 Miscellaneous Studies

5.1 Reaction of 2-anilinophenols with tervalent phosphorus reagents

Formation of 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles from deoxygenation reactions necessitates high vacuum distillation at temperatures up to 200°C. Under these conditions, it is possible that some of the less stable benzoxazaphospholes might be formed initially, but subsequently decompose under the high reaction or distillation temperature. In order to investigate this possibility, advantage was taken of the milder reaction conditions offered by reacting several anilinophenols with tervalent phosphorus reagents in the presence of N-chlorodi-isopropylamine and ether at -78° [82,83].

2-(2-Tert-butylanilino)phenol (215) was reacted with sec-butyl methylphenylphosphinite to give the benzoxazaphosphole (181) in similar yield to that obtained by deoxygenation,. In a replicate experiment, however, a mixture of the benzoxazaphosphole and acyclic hydrolysis products were detected when monitoring the reaction by ^{31}P n.m.r. spectroscopy. The acyclic phosphinate (204) was eventually isolated from this reaction mixture after distillation and recrystallisation of the crude product (Scheme 93).

2-(2-Methylanilino)phenol reacted similarly with dimethylphenylphosphine to give an ether solution containing the desired benzoxazaphosphole by ^{31}P n.m.r. spectroscopy (δ-50.1). Solvent removal at ambient temperature, however, gave an oil composed solely of dimethylphenylphosphine oxide



(215) (181) (204)

Scheme 93

and 2-(2-methylanilino)phenol. The same benzoxazaphosphole had survived high temperature isolation from a deoxygenation reaction (see Experimental section 4.1(ii)), but rapidly decomposed to a mixture of phosphine oxide and anilinophenol in deuteriochloroform solution. It must be concluded, therefore, that the likelihood of forming and isolating potentially less stable benzoxazaphospholes is not enhanced under the milder reaction conditions offered by this alternative synthesis. Furthermore, the anilinophenols used as starting materials are difficult to obtain in good yield (see Experimental section 6). Attempts to prepare 2-(2-tert-butylanilino)phenol by various methods were thwarted by the tertiary butyl group's tendency to act as a leaving group. The best synthesis found for this anilinophenol still used a deoxygenation method. Thus, in situ acidification of the benzoxazaphosphole derived from 2-nitrophenyl 2-tert-butylphenyl ether and trimethyl phosphite, followed by chromatographic

separation of the hydrolysis products, eventually gave the required 2-(2-tert-butylanilino)phenol in 22% yield.

5.2 Flash vacuum pyrolysis of 2,3-dihydro-2-methyl-2-phenyl-2-sec-butoxy-3-(2-tert-butylphenyl)-1,3,2-benzoxazaphosph(v)ole

The sole product from pyrolysis of the title compound (181) was found to be 2-(2-tert-butylanilino)phenyl methylphenylphosphinate (204). This observation casts some doubt over the conditions under which acyclic phosphinates can arise in deoxygenation reactions. However, the balance of evidence from low temperature formation of benzoxazaphospholes from anilinophenols (see chapter 5.1), and the stability of these pentacoordinate compounds at high distillation temperatures suggests that hydrolysis remains the most likely cause of phosphinic amide formation under normal deoxygenation reaction conditions.

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Direct Observations of Diastereoisomers in Chiral Oxazaphosphoranes [3-Aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles] by ^{1}H and ^{31}P Nuclear Magnetic Resonance Spectroscopy

By J. I. G. Cadogan,* R. Stewart Strathdee, and Neil J. Tweddle
(Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ)

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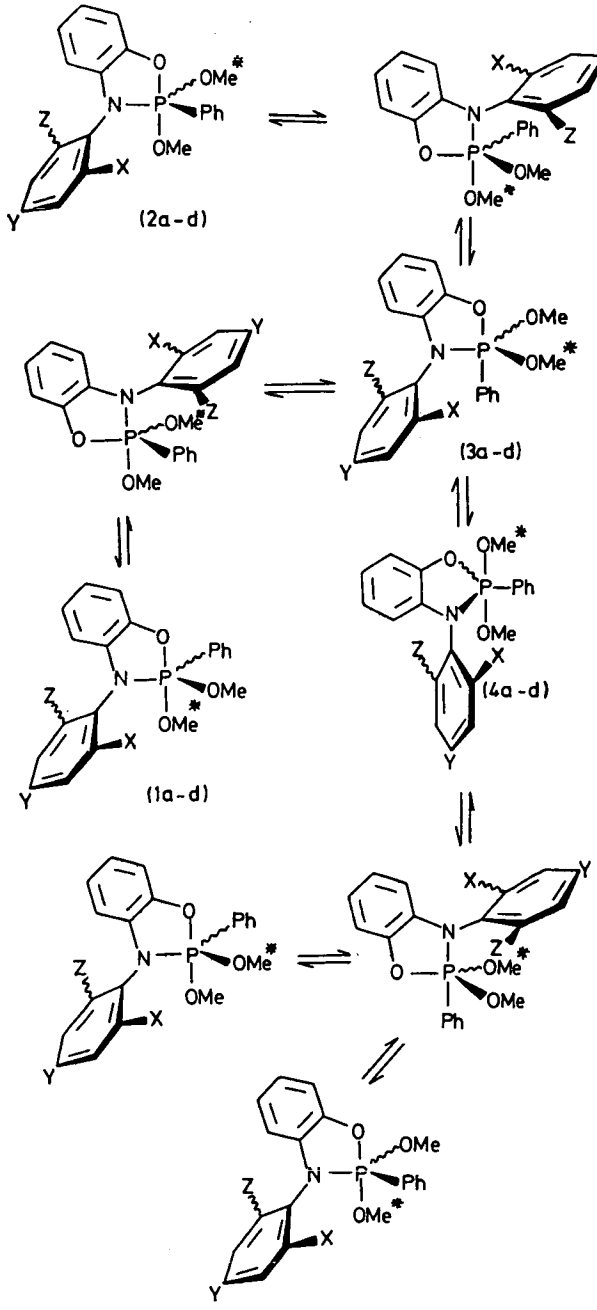
By J. I. G. CADOGAN,* R. STEWART STRATHDEE, and NEIL J. TWEDDLE
(*Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh* EH9 3JJ)

Summary Low- and variable-temperature studies of the ^{1}H and ^{31}P n.m.r. spectra of 3-(2-substituted-phenyl)-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles (1) show the presence of unequally populated diastereoisomeric forms (1) and (2) corresponding to two possible orientations of the *N*-aryl ring, interconversion of isomers occurring solely *via* ligand reorganisation (pseudorotation) about the phosphorus atom and not by rotation about the *N*-aryl bond, leading, in principle, to a resolvable phosphorane system.

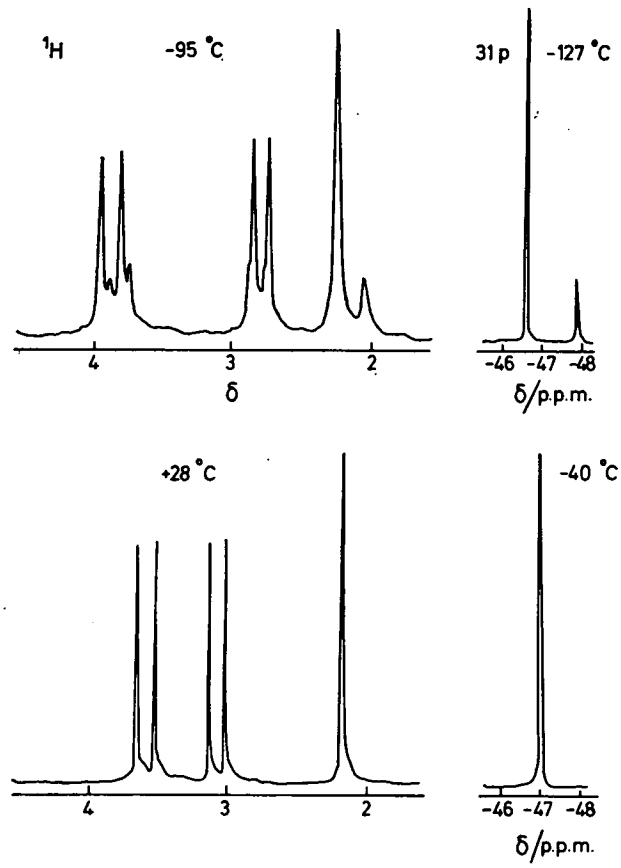
IN principle, many classes of phosphoranes carrying unlike ligands are chiral, but in practice this is usually impossible to demonstrate because such species racemise too easily by ligand reorganisation, *e.g.* by pseudorotation. Exceptions are bicyclic spirophosphoranes derived from chiral aminoalcohols.[1] We now report a demonstration of chirality in monocyclic phosphoranes *via* the direct observation of diastereoisomers, achieved by imposition of an asymmetric steric restraint in a phosphorane nevertheless still able to undergo pseudorotation.

This demonstration follows from the case of 3-mesityl-2,2-dimethoxy-2-phenyl-2,3-dihydro-1,3,2-oxazaphosph-(v)ole (**1a**) in which rotation about the *N*-mesityl bond is severely restricted[2,3] but in which ligand reorganisation (and hence racemisation) involving the enantiomers (**1a**) and (**2a**) occurs readily, the observed equivalence of the *o*-methyl groups at high temperature being a result of rapid positional exchange of the *P*-methoxy ligands which also averages the *o*-methyl environment. Replacement of *one* of the *o*-methyl groups in (**1a**) by hydrogen would be expected still to present a high steric barrier to *N*-aryl rotation,[2,3] but would now impose an asymmetry on the phosphorane system which could not be averaged by pseudorotation involving the *P*-ligands, thus leading to unequally populated diastereoisomeric forms, *e.g.* (**1c**) and (**2c**). We now present direct evidence of this obtained from the temperature dependence of ^1H and ^{31}P spectra.



SCHEME

	X	Y	Z
a;	Me	Me	Me
b;	Me	H	H
c;	Me	Me	H
d;	MeO	H	H



FIGURE

At −127 °C the proton decoupled ^{31}P n.m.r. spectrum of the racemic mixture represented by (**1b**) and (**2b**) and their enantiomers consists of two unequal singlets at δ −46·75 and −47·88 in the ratio of 5·5:1. On warming, these signals coalesce and at −40 °C a single sharp line at δ −46·90 is observed; the ^1H n.m.r. spectrum of (**1b**) and (**2b**) at −95 °C similarly exhibits P–OMe and Ar–Me signals due to major and minor isomers in the ratio of 5·4:1, while at +28 °C a sharp averaged spectrum is

obtained (Figure). Since the *P*-phenyl group of (**1b**) and (**2b**) is expected to be orthogonal to the equatorial plane,[3b] the minor isomer is assigned as (**2b**) on the basis of the shielding of the arylmethyl group of the minor isomer relative to that of the major isomer.

From the positions of the low field equatorial- and high field apical-P–OMe doublets in the averaged ^{1}H n.m.r. spectrum (Figure)† it is apparent that coalescence of the *major* equatorial P–OMe doublet with the *minor* apical P–OMe doublet (and of the *major* apical P–OMe doublet with the *minor* equatorial P–OMe doublet) has occurred.

This observation confirms that rotation about the *N*-aryl link is inhibited because rotation would cause the major and minor equatorial P–OMe doublets to coalesce with each other (and similarly the major and minor apical P–OMe doublets). It therefore follows that the observed coalescences arise from interconversion of (**1b**) and (**2b**) *via* pseudorotation involving the high energy intermediate (**3b**). The introduction of the further element of asymmetry in the form of a single *o*-aryl substituent therefore leads to a pseudorotation which links, not a pair of enantiomers , but a pair of diastereoisomers. Further, there is no pseudorotation process which could cause equilibration of enantiomeric configurations in this chiral system, which in principle is now resolvable, the energy barrier for racemisation being at least 88 kJ mol^{-1} (Table).

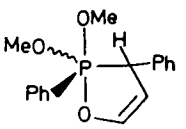
The *N*-2,4-dimethylphenyl- and the *N*-2-methoxyphenyl-analogues (**1c**) and (**2c**) and (**1d**) and (**2d**) behave similarly and it is noteworthy that free energies of activation for the pseudorotation (**1**)→(**2**) (Table) are similar to those observed for analogous systems, *e.g.* (**1a**) and (**2a**).[2]

Complete averaging of the environments of the P–OMe groups in the above phosphoranes is only observed in the cases of (**1d**) and (**2d**) for which process a free energy of activation of 94·9 ± 2·6 kJ mol^{-1} obtains. This value is similar to those obtained[2,4] for pseudorotations proceeding *via* high energy intermediates with a five-membered ring in a diequatorial position, and suggests that complete equilibration of the P–OMe groups of (**1d**) and (**2d**) occurs *via* the intermediate (**4d**) rather than by a combination of pseudorotation *via* (**3d**) and simple rotation of the *N*-aryl group.

TABLE[a]

	$\Delta G_1^{\ddagger}$/kJ mol^{-1}[b]			$\Delta G_2^{\ddagger}$/kJ mol^{-1}[b]
	o-subst.[c]	P–OMe[c]	^{31}P[d]	P–OMe[e]
(**1b**)–(**2b**)	47·1 ± 1·9	46·5 ± 2·8	44·9 ± 2·9	>88
(**1c**)–(**2c**)	48·2 ± 2·0	47·9 ± 3·9	45·8 ± 2·2	>93
(**1d**)–(**2d**)	46·6 ± 2·2	46·8 ± 1·1	44·9 ± 1·1	94·9 ± 2·6

[a] $\Delta G^{\ddagger}$ calculated as in reference 5 from coalescences of *o*-aryl-substituent, P–OMe, and ^{1}H decoupled ^{31}P signals. [b] $\Delta G_1^{\ddagger}$: isomerization (**1**)→(**2**). $\Delta G_2^{\ddagger}$: complete equilibration of P–OMe groups. [c] In CH_2Cl_2. [d] In CH_2Cl_2 + 20% $(CD_3)_2C{=}O$. [e] In Ph_2O.



(5)

Similar arguments account for the previously reported variable temperature ^{1}H n.m.r. phenomena exhibited by the cyclic phosphorane (**5**), which observations were not then discussed in terms of chirality.[6]

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† Complete averaging of the environments of the P–OMe groups does not occur at this temperature.

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