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# SYNTHETIC AND STRUCTURAL STUDIES OF PHOSPHONIC AMIDES AND ESTERS

DPhil UP 1992

# Synthetic and structural studies of phosphonic amides and esters

Submitted by

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# ABBREVIATIONS

| | |
|---|---|
| Ac | Acetate or Acyl |
| $Bu^n$ | Normal butyl |
| $Bu^s$ | *Sec*-butyl |
| $Bu^t$ | *Tert*-butyl |
| Bz | Benzyl |
| chxn | *Trans*-1,2-cyclohexanediamine |
| LDA | Lithium diisopropylamide |
| MCPBA | Meta-chloroperbenzoic acid |
| Ms | Mesyl |
| OTFA | Trifluoroacetate ($OCOCF_3$) |
| $Pr^i$ | Isopropyl |
| RC | Reaction coordinate |
| tart | Tartrate |
| THF | Tetrahydrofuran |
| TMS | Tetramethylsilane |

## SUMMARY

The research contained herein is of twofold nature. Firstly, we aimed to obtain a mechanistic understanding of the thermal fragmentation reaction of ß-acyloxyphosphonates, and in the process we secondly aimed to develop synthetic methodology for phosphonic diamides.

We showed that the fragmentation of ß-acyloxyphosphonates proceeds with metaphosphate extrusion preceded by a novel type of molecular rearrangement. It is, to our knowledge, the first example in which alkyl migration from the oxygen of the phosphorus ester function to another centre (in this case carbonyl oxygen of the substrate) has to take place in order to allow metaphosphate extrusion.

We succeeded in developing synthetic methodology by which alkylphosphonic and ß-hydroxyalkylphosphonic diamides can be obtained in good yields using simple procedures. Reaction of the anion of $HP(O)(NEt_2)_2$ with either alkyl halides or epoxides was used to obtain these compounds. In making alkyl- and ß-hydroxyalkylphosphonic diamides more easily accessible than before, more of the chemistry of these compounds can be studied.

# SAMEVATTING

Die navorsing wat hierin vervat is, is tweërlei van aard. Ten eerste het ons onsself ten doel gestel om die meganisme van die termiese fragmentasie van ß-asieloksifosfonate op te klaar en sodoende het ons tweedens ten doel gehad om sintetiese metodologie vir fosfoonsuur diamiede te ontwikkel.

Ons het aangetoon dat die fragmentasie van ß-asieloksifosfonate plaasvind met metafosfaat uitsplyting wat vooraf gegaan word deur 'n ongekende molekulêre omskikking. In soverre ons kennis strek is dit die eerste voorbeeld van 'n reaksie waar alkiel-migrasie vanaf die suurstof van die fosforester groep na 'n ander sentrum (in hierdie geval die karboniel suurstof van die substraat) in die molekuul moet plaasvind voordat die metafosfaat spesie uitgesplyt kan word.

Ons het daarin geslaag om 'n sintetiese strategie te ontwikkel waarmee alkiel- en ß-hidroksiealkielfosfoonsuur diamiede in hoë opbrengs verkry kan word. Die reaksie van die anioon van $HP(O)(NEt_2)_2$ met òf alkielhaliede, òf epoksiede is gebruik om bogenoemde klasse verbindings te sintetiseer. Deur hierdie verbindings meer toegangklik te maak, kan meer van hulle chemie te wete gekom word.

# CONTENTS

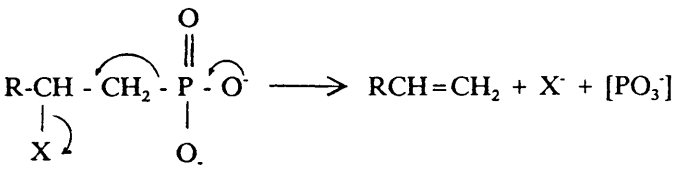
# INTRODUCTION

This project originated from a desire to investigate the possible synthetic applications of the Conant-Swan fragmentation. This reaction, (eq. 1), although already discovered and studied in 1920 by Conant and co-workers,[1-4] has never to our knowledge been investigated as a synthetic route to olefins.

$$RCH(Br)CH_2PO_3^{2-} \longrightarrow RCH=CH_2 + Br^- + [PO_3^-] \qquad (1)$$

Maynard and Swan[5,6] "rediscovered" the reaction in 1962. They were interested in the reaction as a source of metaphosphate ion, $[PO_3^-]$, and thus as a source of a powerful phosphorylating agent.

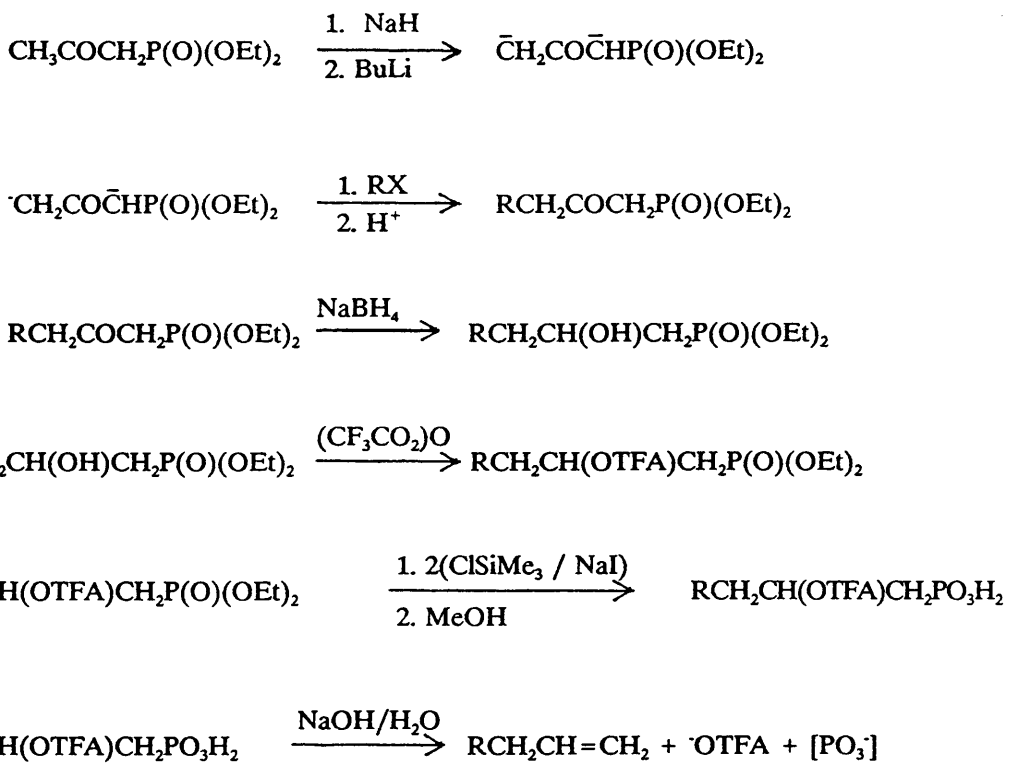
The mechanism of the reaction was finally determined by Calvo and Westheimer,[7-9] who confirmed the prior speculations that the reaction proceeds by a simple 1,2-fragmentation pathway, (eq. 2).




(2)

With this mechanism in mind it is clear that the reaction should be facilitated by increasing the leaving group ability of X. As a synthetic procedure for the preparation of ß-trifluoroacetoxyphosphonates, $RCH(OCOCF_3)\ CH_2P(O)(OR)_2$, has recently been developed in our laboratories[10] we decided to test the Conant-Swan fragmentation where X = $OCOCF_3$.

With X = $OCOCF_3$ we could envisage the following interesting synthetic scheme starting with 2-oxopropyl-phosphonate diester, which offers the useful possibility of skeleton alkylation[11], (scheme 1).

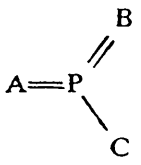



**SCHEME 1 (TFA = $COCF_3$)**

Although all the reactions shown above are known, we had to investigate the effect of the OTFA group on the ester dealkylation step using $ClSiMe_3$. (We later showed that it indeed adversely affects the reaction.) We intended to test this reaction using $PhCH_2CH(OTFA)CH_2P(O)(OEt)_2$, 15a as a substrate. However, when we attempted to distill 15a from the reaction mixture in which it formed, we collected such unexpected products such as allylbenzene and ethyl trifluoroacetate in the collection flask. Since that observation clearly indicated some new, and possibly important, type of fragmentation, we decided to carry out a detailed study of the reaction in order to elucidate its mechanism and scope. In the course of this study we required as a substrate the phosphonic diamide of the structure: $PhCH_2CH(OTFA)CH_2P(O)(NEt_2)_2$, 15e. This need led us into a related quest for a simple and general synthetic route to phosphonic diamides. The results of this research are reported in this thesis.

## METAPHOSPHATES AS INTERMEDIATES

Although quantum mechanical calculations[14,15] have shown that the simplest member of the series having structure A,



A

$PO_3^-$ - the metaphosphate ion, should be thermodynamically more stable than the nitrate ion, metaphosphate species are in general very reactive electrophiles - reacting with weak nucleophiles like *tert*-BuOH[6] or even with themselves, lacking the presence of other nucleophiles. This high reactivity has been ascribed[12] to the even greater thermodynamic stability of the "orthophosphate type" of products which the metaphosphate species form, (e.g. eq. 3 and 4).

$$[PO_3^-] \xrightarrow{H_2O} H_2PO_4^- \qquad (3)$$

$$n[PO_3^-] \longrightarrow -O-\left[\begin{array}{c} O \\ \| \\ P-O \\ | \\ O^- \end{array}\right]-_n \qquad (4)$$

It is this high reactivity which has made it impossible in nearly all cases to obtain direct evidence for the existence of such species. There is, however, a large and convincing amount of indirect evidence that metaphosphate species do indeed play an important role as intermediates in many reactions of phosphorus compounds.

Sodium metaphosphate, $NaPO_3$, has been trapped in an argon matrix at low temperature and shown to be trigonal planar[16] as was expected. Certain nitrogen analogues have been isolated by Niecke and co-

workers.[17-19] The structures of these metaphosphate-type compounds are shown in Figure 1.


B (R = $SiMe_3$) R = $SiMe_3$; R' = Me, Et, $Pr^i$, $Bu^t$

**Figure 1**

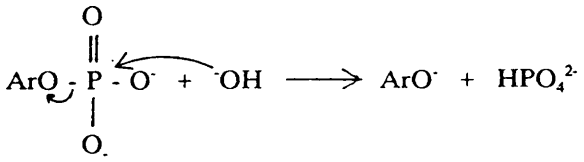
X-ray crystallography showed[18] that B has the expected planar geometry.

The reaction which has probably been the most studied as far as the intermediacy of metaphosphates are concerned, is the hydrolysis of anions of arylphosphoric monoesters, (eq. 5).[20-28]

$$\begin{matrix} ArOPO_3H^- + H_2O \\ \\ ArOPO_3^{2-} + H_2O \end{matrix} \rightarrow ArO^- + H_nPO_4^{-3+n} \qquad (5)$$

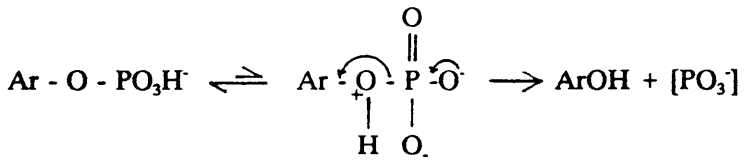
The evidence for metaphosphate intermediacy in these reactions can be summarized as follows:

a. For phenols having a pKa higher than 5,5 the monoanion of the phosphoric monoester, $ArOPO_3H^-$ is more reactive than the dianion. If the pKa of the phenol is less than 5,5 then the dianion, $ArOPO_3^{2-}$, is more reactive.[22] Since removing the proton from the monoanion should not result in phosphorus being more electrophilic (rather the opposite should take place), rate determining attack of hydroxide ion at phosphorus in a bimolecular mechanism, (eq. 6), is highly unlikely.



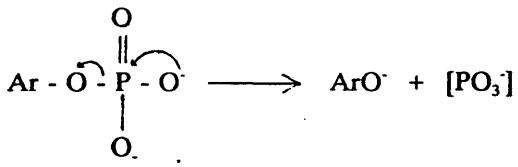

(6)

For phenols with pKa > 5,5 it seems likely that pre-equilibrium protonation allows heterolysis to generate metaphosphate ion, (eq. 7).




(7)

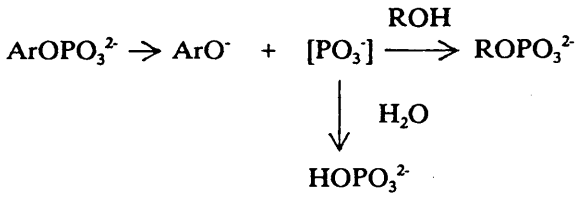
For phenols with pKa < 5,5 the phenolate anion is already a good leaving group and reaction proceeds most readily for the dianion, (eq. 8).




(8)

b. Monoester hydrolyses have $\Delta S^{\ddagger}$ values close to 0 eu.[22,29] This is consistent with a dissociative pathway.

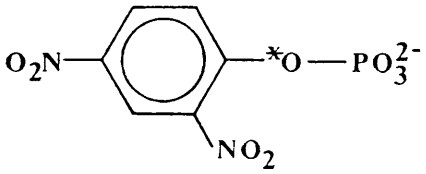
c. The presence of a reactive and thus non-discriminating phosphorylating agent in these reactions is suggested by the fact that there is a correlation between the mole fraction of alcohol in the solvent and the mole fraction of alkyl phosphate in the product if these solvolyses are carried out in mixed aqueous-alcoholic solutions[30] (scheme 2).




**Scheme 2**

d. $\beta_{lg}$ (the measure of the sensitivity of the reaction to the nature of the leaving group) for substituted phenolic monoesters is -1,2 for dianions and -0,27 for monoanions.[22] $\beta_{nuc}$ (the measure of the sensitivity of the reaction to the nature of the nucleophile) for attacking nucleophiles in the aminolysis of 4-nitrophenylphosphate is 0,13.[20] This indicates a transition state with a high degree of bond cleavage to the leaving group with little or no bond forming to the nucleophile.

e. For the hydrolysis of compound C, k ($^{16}$O)/k ($^{18}$O) = 1,020 ± 0,004,[25] again indicating

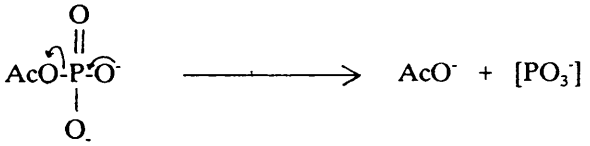


C

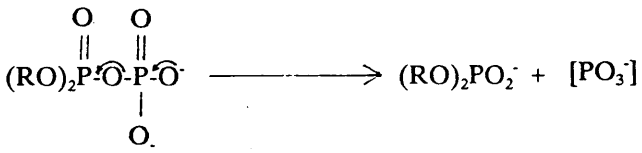
considerable P-O bond cleavage in the transition state.

f. C undergoes alcoholysis by *tert*-BuOH in acetonitrile at a rate similar to that of hydrolysis.[26,27] The monoanion gives no *tert*-butylphosphate. It therefore seems likely that the metaphosphate ion is involved as a reaction intermediate.

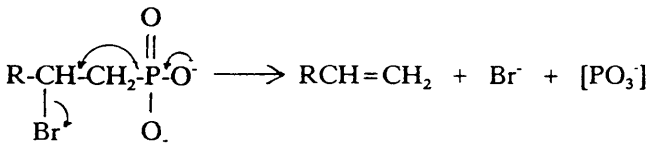
Similar evidence exists for the unimolecular expulsion of the metaphosphate ion in the hydrolysis of acetylphosphate, (eq. 9),[29,31,32] pyrophosphate ions, (eq. 10),[33-35] and the Conant-Swan reaction, (eq. 11).[7-9]



(9)

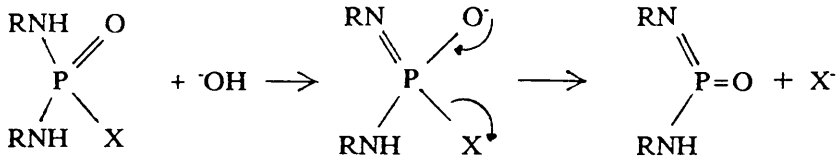


(10)




(11)

Other metaphosphate species have been implicated in the hydrolysis of phosphorodiamidic chlorides, (eq. 12),[36,37] and in the aminolysis of certain phosphonamidic chlorides, (eq. 13).[38-41]

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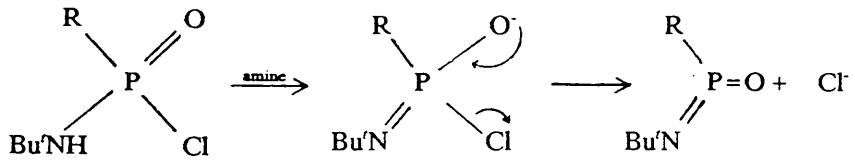
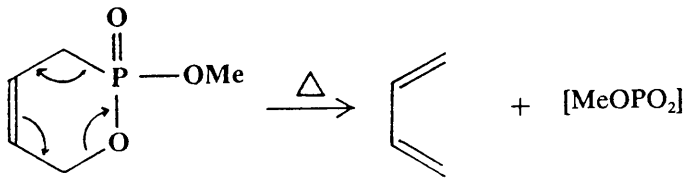



(13)

The mechanism represented by eq. 13 applies only when the amine is bulky, i.e. $Bu^tNH_2$ or $Pr^iNH_2$. With amines that are not sterically hindered the more usual $S_N2(P)$ mechanism applies.

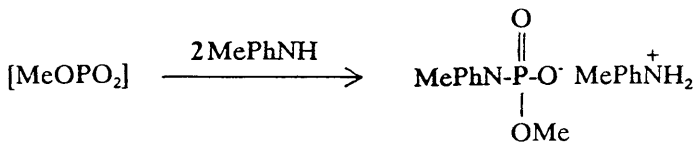
Other metaphosphate species that have been intensively studied are neutral esters, such as methyl metaphosphate, [$MeOPO_2$], and ethyl metaphosphate, [$EtOPO_2$]. A short discussion of these species will be given as they are relevant to our own work herein.

Clapp[42] generated methyl metaphosphate by pyrolysis of methyl 2-butenylphostonate, (eq. 14).

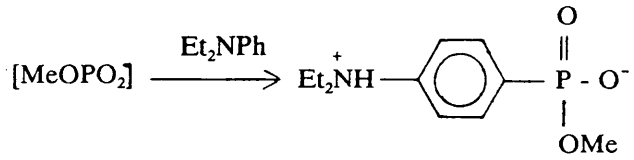



(14)

That the [$MeOPO_2$] species had indeed been generated was confirmed by several trapping experiments, (eq. 15 and 16).[43,44]

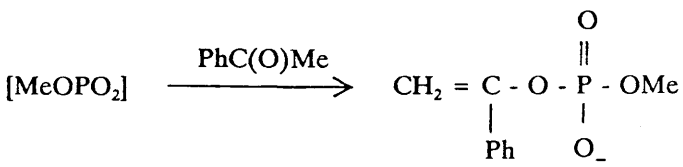



(15)




(16)

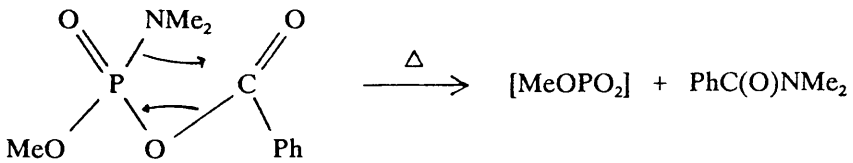
Methyl metaphosphate generated from a Conant-Swan fragmentation has been trapped by acetophenone yielding enol phosphate, (eq. 17).[45]




(17)

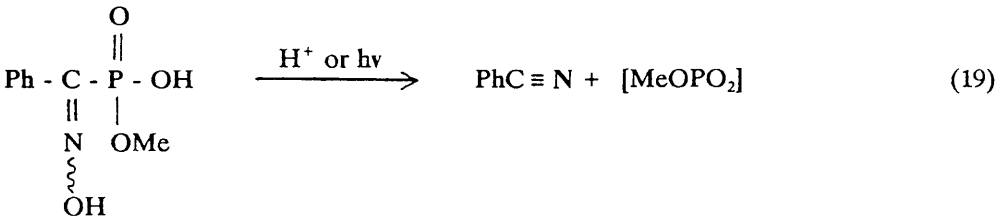
The reactions represented by equations 16 and 17 again illustrate the powerful electrophilic nature of metaphosphate species.

Methyl metaphosphate has also been observed as one of the products of the thermal fragmentation of mixed anhydrides carrying an amino group at phosphorus, (eq. 18).[46]




(18)

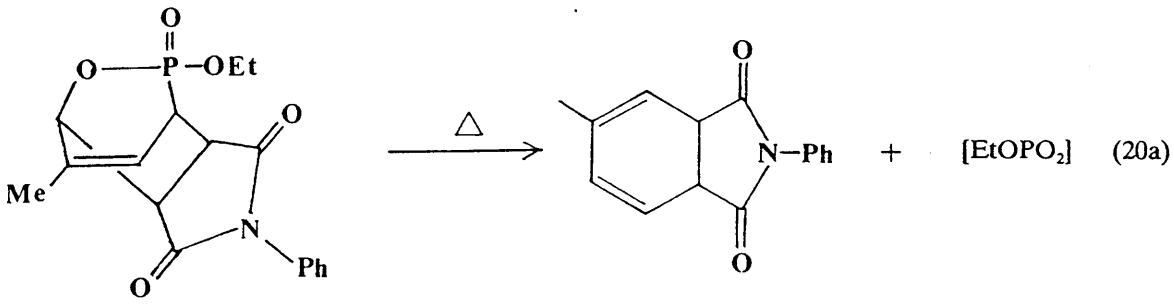
In recent work[47-49] methyl metaphosphate was generated from α-oxyiminophosphonates, (eq. 19).




(19)

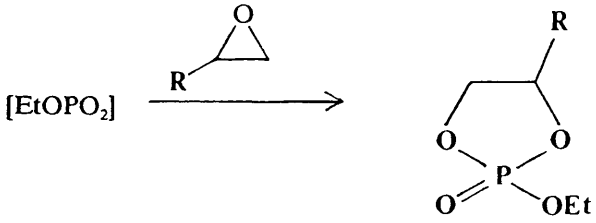
The metaphosphate so generated was trapped using a variety of alcohols and also on the surface of silica gel. Quin[51] has shown the hydroxyl groups on the surface of silica gel to be efficient in trapping metaphosphate species.

Ethyl metaphosphate has been generated using a method developed by Quin and his group similar to that of Clapp, (eq. 20a)[50,51] and



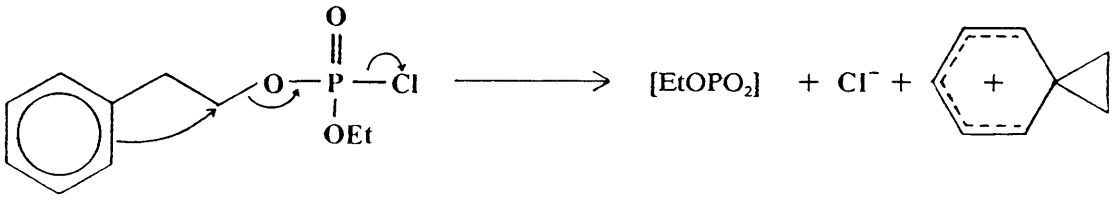

(20a)

trapped with epoxides, (eq. 20b).[52]




(20b)

Ethyl metaphosphate has also been implicated in the fragmentation of (2-arylethyl)phosphorochloridates, (eq. 21).[53]




(21)

This discussion illustrates that although seldom directly observed, metaphosphates are well established as highly reactive, electrophilic intermediates in many reactions and can be generated from a variety of organophosphorus precursors.

A matter that has lately been receiving more attention concerns how "free" metaphosphate intermediates are, i.e. are they long lived enough to escape the solvent cage in which they are formed before reacting further. The concept of the lifetime of an intermediate has proved a useful tool in probing the mechanisms of reactions.[54,55]

In short, the lifetime of an intermediate can be used to distinguish between mechanisms in a qualitative manner. Eg. nucleophilic substitution reactions have classically been classified as either $S_N2$ or $S_N1$ with a "grey" area of mixed mechanism in between. Using the lifetime of an intermediate as criterion, a sharp distinction can now be made between the possible mechanisms. If the intermediate is long-lived or stable enough to escape the solvent cage in which it is formed, it becomes a free intermediate which then reacts further. This represents the classical $S_N1$ mechanism. If, however, the intermediate is too unstable to escape the solvent cage or is not formed the reaction must proceed through a preassociation mechanism in which the reactants are assembled or preassociated before any bond-making or -breaking processes occur. Here a further distinction between pre-associative concerted and stepwise mechanism can be made. In a preassociative concerted mechanism bond-making and -breaking take place simultaneously (the classical $S_N2$ mechanism). In the preassociative stepwise mechanism the bond-breaking is far advanced but the intermediate cannot escape from the solvent cage before bond-making to the preassociated "spectator" nucleophile takes place. Distinction between the preassociation mechanisms must necessarily be arbitrary. E.g. when we can decide that if bondbreaking is more than 80% complete before bond-making starts then the reaction is preassociative stepwise. Similarly for a preassociative concerted mechanism we would require a certain degree of bond-making to have taken place. In fact a lifetime of $10^{13}$ $s^{-1}$ (roughly one vibration) has been suggested as a borderline between preassociative stepwise and concerted mechanisms.[55] These ideas are somewhat crudely but simply illustrated in Figure 2.

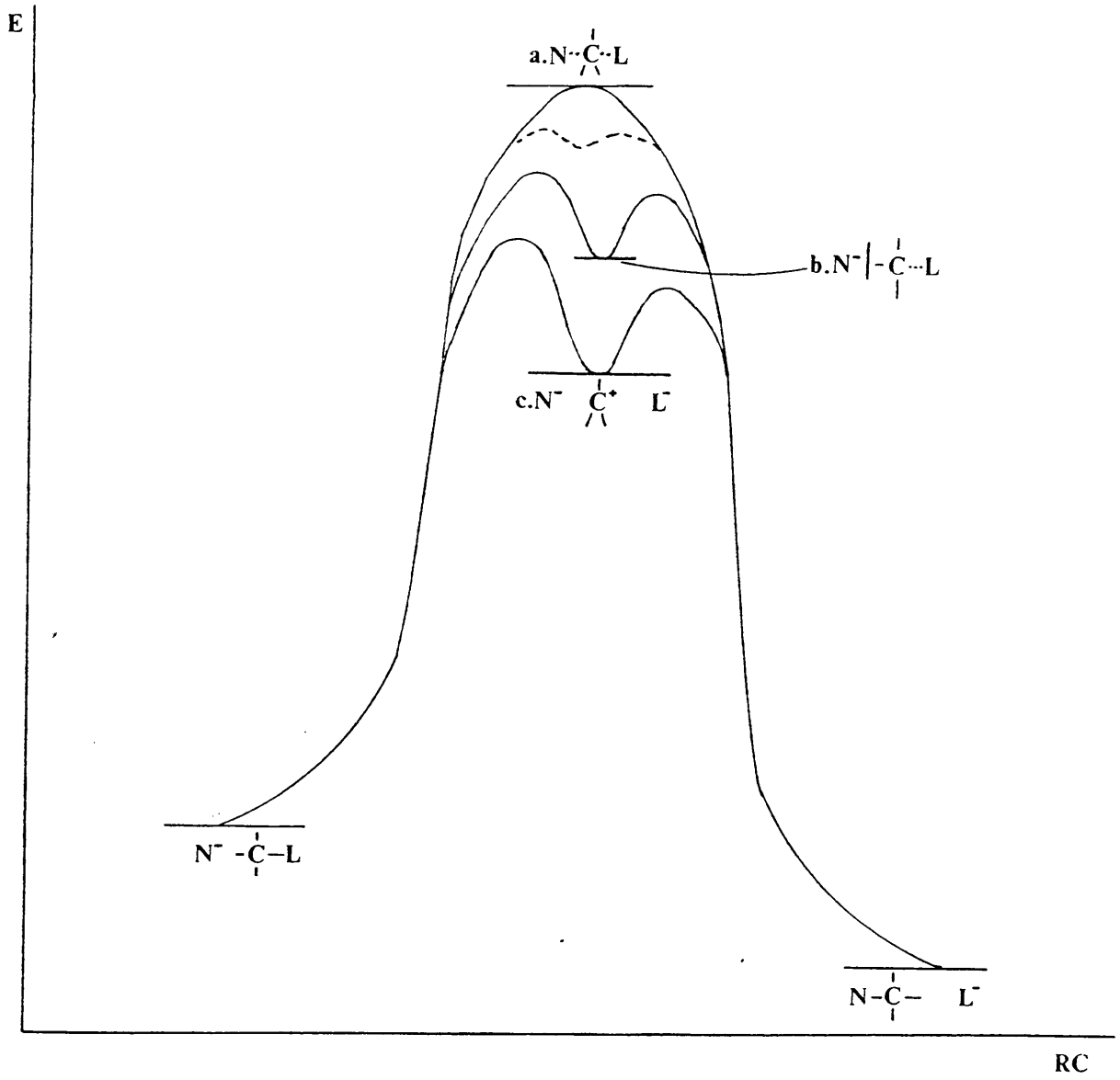



Figure 2

a. Represents the $S_N2$ transition state.

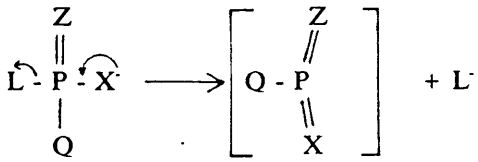
b. Represents an intermediate with a large degree of bond breaking having taken place but little or no bond making. $-\overset{|}{\underset{|}{C^+}}$ never becomes free but reacts with the preassociated nucleophile $N^-$ before escaping the solvent cage. The dashed line would indicate an arbitrary distinction between the two preassociative mechanisms.

c. Classical free carbocation intermediate.

The concept of the lifetime of an intermediate as mechanistic probe can also be extended to nucleophilic substitution at phosphorus and has proved useful in the study of the metaphosphate ion. Modern isotopic labelling techniques have made it possible to prepare chiral and optically pure [$^{16}O$, $^{17}O$, $^{18}O$]-phosphates[28] to study the stereochemical outcome at phosphorus in the hydrolysis of such compounds. The argument being that if the metaphosphate ion is long lived enough to escape the solvent cage in which it is formed, a racemic product mixture can be expected due to the planar geometry of the metaphosphate ion. In fact methanolysis of isotopically labelled, chiral phenyl phosphate monoanion and 2,4-dinitrophenyl phosphate dianion was shown to proceed with complete inversion at phosphorus.[28] Since kinetic evidence clearly shows that reaction doesn't proceed via a $S_N2(P)$ mechanism, the metaphosphate ion must be so short lived that it cannot escape from or rotate in its solvent cage before reacting further with methanol. The reaction, by the classification of Jencks,[55] therefore must proceed by a preassociative mechanism.

Using a similar approach Calvo[7] has shown that the Conant-Swan reaction also proceeds via a preassociative mechanism. Based on these two examples it would appear that metaphosphate species cannot exist as free intermediates in most cases. Obviously much more experimental confirmation of this is required.

All known reactions that involve metaphosphate species, including those shown above, can, from the point of view of the electronic changes, be represented by either equation 22 or 23, where L is a good leaving group.

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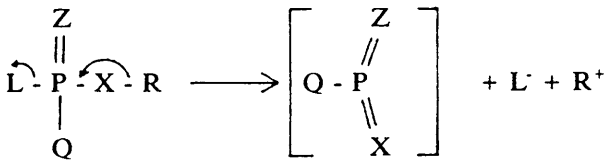



(23)

We shall demonstrate in this work that we were able to add to a wide spectrum of the reactions involving a metaphosphate species a new type of process that differs from all others not only in the sense of a new precursor, but, in the first place, in terms of a new sequence of the necessary bond-making and -breaking steps.

**Phosphonic diamides**

As already mentioned, the phosphonic diamide, $PhCH_2CH(OH)CH_2P(O)(NEt_2)_2$, 4a, was required in our mechanistic studies of the reaction outlined in scheme 3. In our work reported previously[56] we studied the prototropic equilibrium in unsaturated phosphonic diamides. We, however, experienced problems in the synthesis of these compounds, like for example in attempts to synthesize compound D from its dichloride, (eq. 24).

$$CH_2=CHCH_2P(O)Cl_2 + 4HNEt_2 \longrightarrow \underset{D}{CH_2=CHCH_2P(O)(NEt_2)_2} \qquad (24)$$

When the reaction was carried out with 2 mol-equiv. of diethylamine and 3 mol-equiv. of triethylamine in carbon tetrachloride at room temperature for two hours, it gave only the product of mono-substitution, i.e. $CH_2=CH\text{-}CH_2\text{-}P(O)(NEt_2)Cl$. Prolonging reaction time to 19 hours still gave the mono-substituted compound as major product, 64%, along with 12% of $CH_2=CHCH_2P(O)(NEt_2)_2$, 2% $CH_3CH=CH\text{-}P(O)(NEt_2)Cl$ and 14% $CH_3CH=CHP(O)(NEt_2)_2$. Similar problems were experienced in our attempts to synthesize the diamide $PhCH_2P(O)(NEt_2)_2$.

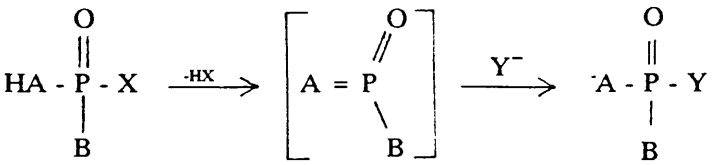
We therefore decided to develop a general method for the synthesis of phosphonic diamides. A survey of the literature revealed that although two phosphonic diamides were prepared by Michaelis[57] in 1903, the real pioneering was done by Doak and Freedman[58,59] and Kosolapoff and Payne[60] in the 1950's. Since then "their" approach, i.e. synthesis via dichlorides has been used almost exclusively. Other reactions have also been reported to yield phosphonic diamides. A brief discussion of each follows.

i) **From dichlorides**

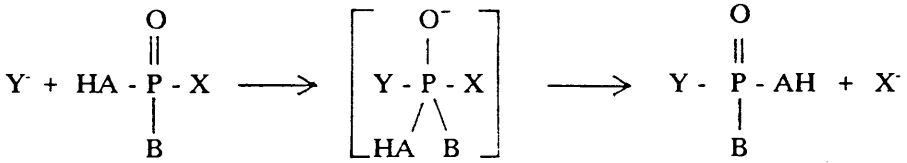
This is the generally used method and the reaction is described by equation 25.

$$RP(O)Cl_2 + 4HNR'_2 \longrightarrow RP(O)(NR'_2)_2 + 2H_2\overset{+}{N}R'_2Cl^- \qquad (25)$$

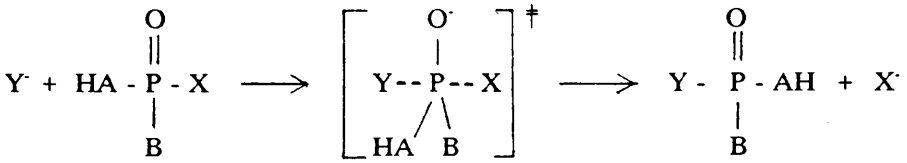
Reaction usually require several hours of reflux in carbon tetrachloride or benzene. Ether has also been used as a solvent. The reaction involves nucleophilic substitution at tetracoordinate phosphorus, and there are three possible mechanisms which can operate - $S_N1(P)$, addition-elimination or $S_N2(P)$ which can be represented in general terms by equations 26, 27 and 28, respectively.




(26)




(27)




(28)

It must be added that evidence for the addition-elimination mechanism, (eq. 27), is scarce and in general has only been found for a few reactions - notably involving cyclic systems where relief of ring strain by the formation of a pentacoordinate phosphorane intermediate is energetically favourable.[61,62]

The $S_N1(P)$ mechanism, (eq. 26), requires a good leaving group at phosphorus and a group able to leave

without its electrons at a centre α to phosphorus. If we consider the first step of attack at dichlorides by amines, (eq. 29),

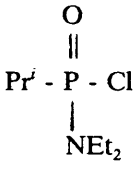
$$RP(O)Cl_2 \xrightarrow{HNR'_2} RP(O)(NR'_2)Cl \qquad (29)$$

the $S_N1(P)$ mechanism is unlikely due to the low acidity of the α-protons. $S_N2(P)$ is therefore likely for this step. For the second step, (eq. 30),

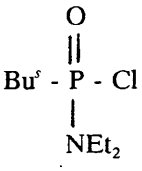
$$RP(O)(NR'_2)Cl \xrightarrow{HNR'_2} RP(O)(NR'_2)_2 \qquad (30)$$

Harger has demonstrated[38-41] that if there is a proton on nitrogen, the reaction with sterically hindered amines proceeds by a $S_N1$ (P) mechanism. Since we were interested in amides derived from secondary amines, the $S_N1$ (P) process is again unlikely. There are several factors that have to be taken into account when considering the reaction represented by equation 30 - all of which complicate the reaction and in certain cases can completely inhibit it. The electrophilicity of phosphorus in phosphonamidic chlorides is lower than that of phosphorus in phosphonic dichlorides; not only due to nitrogen being less electron withdrawing than chlorine, but it is also likely that nitrogen is forming pπ-dπ bonds to phosphorus using its lone pair.[63-66]

The reactivity of the phosphonamidic chloride to amines is further reduced by the steric requirements of the amide functionality. This in combination with a relatively bulky amine nucleophile can seriously retard the reaction. Razvodovskaya[67] for instance reported that compounds E and F failed to react with secondary amines, and even with aniline, in benzene.



**E**



**F**

By mixing compound G and the amine without any solvent and heating at 100°C for 1 hour they obtained the diamide, (eq. 31).

$$Pr^{i}P(O)(NMe_2)Cl \quad + \quad HNR_2 \longrightarrow Pr^{i}P(O)(NMe_2)(NR_2) \qquad (31)$$

**G**

Even such treatment of E and F failed to give the diamides.

Bearing these facts in mind and considering the $S_N2$ (P) mechanism for equation 32 it can be seen that

$$RP(O)(NR_2')Cl \quad + \quad HNR_2' \longrightarrow RP(O)(NR_2')_2 \qquad (32)$$

such a mechanism would require entry of the amine on a face already severely sterically hindered by the groups R and $R_2'N$, (Fig. 3).

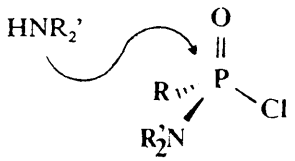
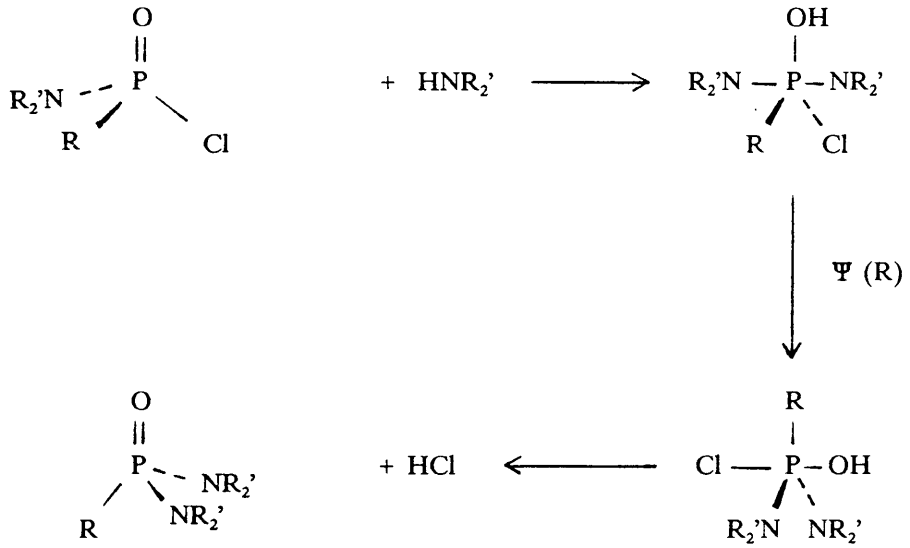



**Figure 3**

Considering an addition-elimination mechanism with apical entry and apical departure* allows the nucleophile to enter along a less hindered face - in this case the face formed by O, R and Cl is the least demanding sterically. The intermediate phosphorane can then pseudorotate in such a fashion to place chlorine apical from whence it can depart, (scheme 4; proton transfers not indicated.)

* Apical entry and departure is generally accepted for reactions involving intermediate phosphoranes. Equatorial entry and apical departure violates the principle of microscopic reversibility[68,69] and equatorial entry and departure is regarded to be unlikely as it involves attack on the edge instead of the face of the tetrahedron.[70,71]




**Scheme 4**

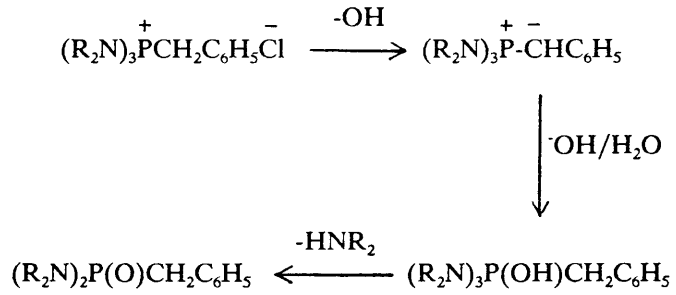
In the first place, the P(V)-intermediate initially formed would contain two $R_2N$ groups in apical positions, while it is known that these substituents have very low relative apicophilicities.[72] Pseudorotation, Ψ (R), may be hampered by N(pπ) → P(dπ) bonding.[73-75] The energy gained in having the hydroxyl and chlorine groups apical instead of the amine groups should overcome this. Although above arguments are only conjectures they do help to rationalize our results and the data contained in the literature. Thus a long list of references (eg. 76-78) can be supplied to show that despite the relatively harsh conditions used in the reactions (several hours of reflux), the yields of phosphonic diamides are seldom good. Yields are good in the case of primary aromatic amines being used; the formed phosphonamidic chlorides being much less sterically hindered than is the case with secondary dialkylamines.

The synthesis of phosphonic diamides from the corresponding dichlorides, although generally used, is complicated by several factors and we therefore sought a different route to these compounds.

**ii) From phosphonium salts**

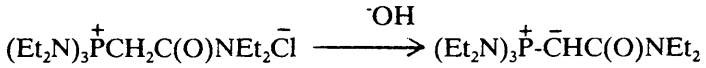
Mizrakh[79] gives the only report in the literature of a synthesis of phosphonic diamides from phosphonium

salts. They reported that the alkaline hydrolysis of benzyltris(dialkylamino)phosphonium salts lead to the corresponding P-benzylphosphonic diamides, (scheme 5), in good yields (75-80%).



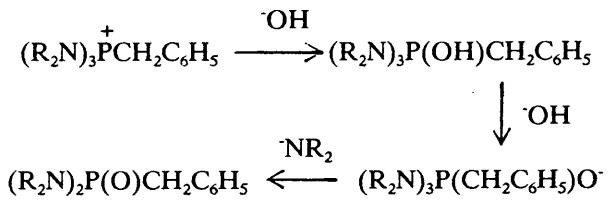
**Scheme 5**

The reaction is therefore apparently limited to phosphonium salts having acidic protons on the carbon α to phosphorus. In the case of reactions leading to stabilized ylids the reaction can stop at the ylid stage as was illustrated[79] for the reaction below, (eq. 33).



(33)

Clearly isolation of the ylid in above reaction would seem to suggest that the mechanism as outlined in scheme 5 is correct. However, in cases leading to unstabilized ylids it is conceivable that the first step is attack of the hydroxide anion at phosphorus,(scheme 6).



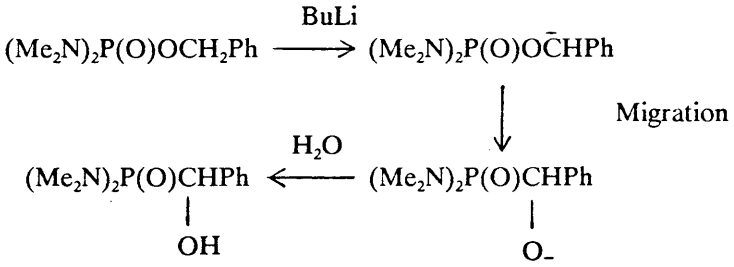
**Scheme 6**

Many reactions of this type are known for phosphonium salts.[80] If this was the case then the reaction

could be a potentially useful source of phosphonic diamides. For lack of further information we decided not to follow this approach.

**iii) From diamidophosphates**

It was reported by Sturtz and Corbel[81,82] that diamidophosphates having benzyl or allyl groups attached to oxygen rearrange upon treatment with n-butyllithium to give α-hydroxyphosphonic diamides. The proposed mechanism again involves acidic protons α to oxygen, (scheme 7).




**Scheme 7**

**iv) From $(R_2N)_2P(O)X$**

Reaction of anilidophosphoric chlorides with aryl Grignard reagents,[83] (Eq. 34), gave the phosphonic diamides in poor yields.

$$(PhHN)_2P(O)Cl \xrightarrow{ArMgX} ArP(O)(NHPh)_2 \quad (34)$$

18-40%

**v) From ylids**

P-chloro-P,P-bis(dialkylamino)ylids give phosphonic diamide when treated with aldehydes or ketones,[84,85] (eq. 35, 36).

$$(R_2N)_2(Cl)P{=}CHR' + R_2"C{=}O \longrightarrow (R_2N)_2P(O)CR'{=}CR_2" \quad (35)$$

$$(R_2N)_2(Cl)P=CHSiMe_3 + R_2'C=O \longrightarrow (R_2N)_2P(O)CH=CR_2' \quad (36)$$

These reactions appear to be of general scope. Several examples were prepared and yields varied from 50-80%.

vi) **From P(III) derivatives**

A number of reactions of P(III) derivatives have been reported that lead to phosphonic diamides - albeit mostly as side products. Most of these reactions are of the Arbuzov type, e.g. eq. 37.[86]

$$(Et_2N)_2POEt + BzCl \longrightarrow (Et_2N)_2P(O)Bz \quad (37)$$

30-50%

As with reaction between phosphites and α-chloroketones the "Perkow product" predominates when diamidophosphites are used, (eq. 38).[87]

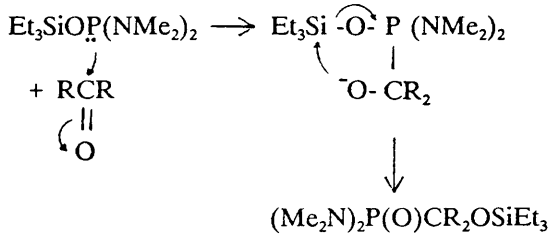
$$(Et_2N)_2POEt + CH_3C(O)CH_2Cl \longrightarrow (Et_2N)_2P(O)OC(CH_3) = CH_2 \quad (40\%)$$
$$+ \quad (38)$$
$$(Et_2N)_2P(O)CH_2C(O)CH_3 \quad (8\%)$$

Similar examples can be found.[88,89] Evans[90,91] reacted silyl phosphorodiamidites with a wide range of aldehydes and ketones to give α-siloxyphosphonic diamides in high yields, (eq. 39).

$$R_2C=O + (Me_2N)_2 POSiEt_3 \longrightarrow (Me_2N)_2P(O)CR_2OSiEt_3 \quad (39)$$

>90%

In this case the reaction is formally similar to the Arbuzov reaction, dealkylation taking place intramolecularly, (scheme 7).




**Scheme 7**

**vii) From $(R_2N)_2PO^-$**

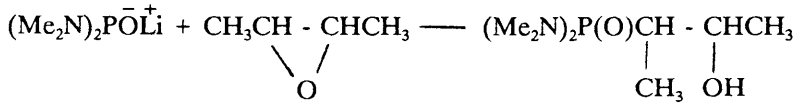
Although the diamidophosphite anions are ambident nucleophiles, $[(R_2N)_2\ P\text{-}O^- \leftrightarrow (R_2N)_2\bar{P}=O]$, attack at electrophilic centres predominantly takes place via phosphorus, as is also the case for dialkylphosphite anions, $(RO)_2P\text{-}O^-$. The diamidophosphite anions should be more nucleophilic than their dialkylphosphite analogues due to the lessened ability of nitrogen to stabilize the negative charge relative to oxygen. This gain in nucleophilic character due to electronic factors can however be offset by the larger bulk of diamidophosphite anions when compared to dialkylphosphite anions.

The diamidophosphite anions have been used less often as reagents than the dialkylphosphite anions which have found wide-spread use in the Michaelis-Becker reaction.

Normant,[92] generating the sodium derivative of tetramethyldiamidophosphite from HMPT and sodium amide, obtained phosphonic diamides on reaction with alkyl bromides in 40-60% yield, (eq. 40).

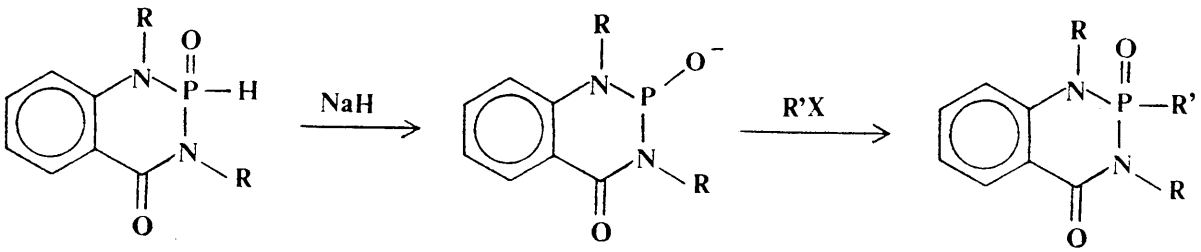
$$(Me_2N)_2P\bar{O}Na^+ \quad + \quad RBr \longrightarrow (Me_2N)_2P(O)R \qquad (40)$$

Corey[93] used the lithium derivative (obtained from reaction of *n*-butyllithium with bis(dimethylaminophosphorous acid) and epoxides to generate ß-hydroxyphosphonic diamides in low yields, (eq. 41).




(41)

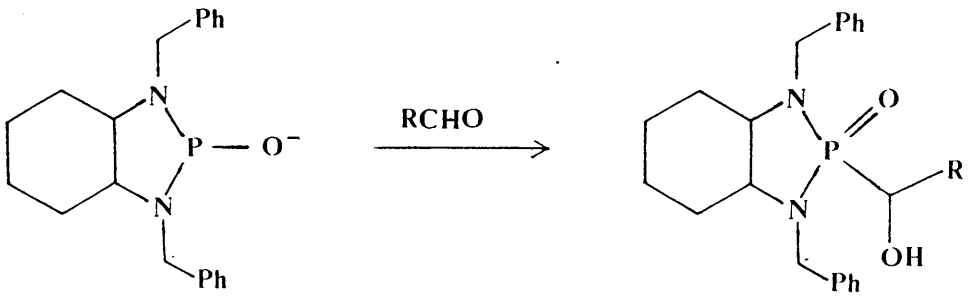
Coppola[94] used a similar route in a synthesis of phosphorus heterocycles, (scheme 8).




**Scheme 8**

There are two notable advantages to this approach. The phosphonic diamide, $(Et_2N)_2P(O)H$, is easily accessible from $PCl_3$. Different phosphonic diamides, $(Et_2N)_2P(O)R$, could easily be prepared using different alkyl halides or epoxides; as will be described below. We have shown $(Et_2N)_2PO^-$ to be an excellent nucleophile, reacting cleanly under suitable conditions with both alkyl halides and epoxides to give high yields of phosphonic diamides and ß-hydroxyphosphonic diamides respectively.

Shortly after publishing our results concerning the reactions of $(Et_2N)_2PO^-$ with alkyl halides, we received a personal communication[95] outlining unpublished results concerning reactions of diamidophosphite anions with aldehydes to give α-hydroxyphosphonic diamides also in high yields, (eq. 42).



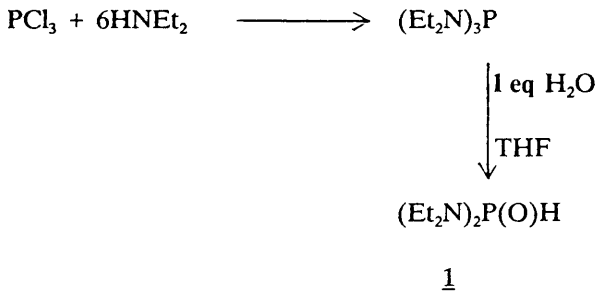

(42)

# RESULTS AND DISCUSSION

## Alkylphosphonic Diamides

### Synthesis of $HP(O)(NEt_2)_2$ (1)

The synthesis of 1 has been previously described[96] and we followed the published procedure, (scheme 1).

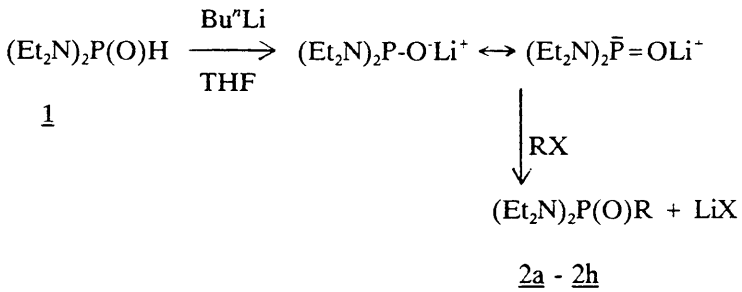



Scheme 1

A point of note here is that the crude 1 so obtained is essentially pure (>99% by $^{31}P$ n.m.r. spectroscopy) and that it cannot be distilled without severe decomposition.

### Synthesis of $RP(O)(NEt_2)_2$ (2a - 2h)

Eight phosphonic diamides, 2a - 2h, were prepared as shown in scheme 2.




| | R | X | Yield (%) |
|---|---|---|---|
| 2a: | $CH_2=CHCH_2$ | Br | 82 |
| 2b: | $CH_3CH_2CH_2$ | Br | 75 |
| 2c: | $PhCH_2$ | Br | 85 |
| 2d: | $CH_3CH=CHCH_2$ | Br | 54 |
| 2e: | $CH_3$ | I | 100 |
| 2f: | $Ph(CH_2)_3$ | Br | 30 |
| 2g: | $CH_3(CH_2)_4$ | Cl | 23 |
| 2h: | $CH_3(CH_2)_5$ | Br | 75 |

**Scheme 2**

The crude products were generally pure (>95% by $^{31}P$ n.m.r. spectroscopy) so that further purification was not necessary. Thus the yields shown for 2a-2c, 2e and 2h are those obtained for the crude products. In the case of 2g the usual reaction time of 2 hours after the addition of chloropentane gave 2g in the poor yield shown. Prolonging the reaction time to 18 hours gave a mixture consisting mostly of 2g (ca. 24% yield). Distillation gave the pure compound in 16% overall yield. Comparing the yield to that of 2h it appears that chloroalkanes were more inferior substrates for the synthesis than bromo- or iodoalkanes.

For 2f a mixture consisting of about 50% of 2f and 50% of starting bromide was obtained. Prolonging the reaction time did not significantly alter this ratio. The product had to be purified by column-

chromotography followed by distillation giving the yield shown.

The yield of 2d is that obtained after distillation. Distillation was necessary to remove an unknown phosphorus product, which we suspect was derived from 3-bromo-1-butene which is the thermal rearrangement product of crotyl bromide, (eq. 1).

$$CH_3 - CH = CH \quad \rightleftharpoons \quad CH_3 - CH - CH = CH_2 \qquad (1)$$
$$\qquad\quad Br \quad CH_2 \qquad\qquad\quad Br$$

The crotyl bromide was essentially an equilibrium mixture of the two isomers.[97]

In all cases THF was used as solvent. Addition of *n*-butyllithium took place at temperatures below -70°C. After 15 minutes the haloalkane was added. Temperature was maintained below -40°C for 1 hour and then allowed to return to room temperature and stirring continued for a further hour. It was found that carrying out the reaction from the beginning at room temperature gave considerable amounts of side-products (~35% by $^{31}P$ n.m.r. spectroscopy). It was also found useful to use slightly less than 1 mol-eq. of high boiling haloalkanes, since an excess of 1 can be easily removed during the aqueous workup.

The reaction failed when RX was 2-bromopropane or propargyl bromide. In both cases n.m.r. spectroscopy showed the reaction product to be a complex mixture of phosphorus-containing products.

Attempts were also made to carry the reaction out using sodium hydride as a base in the place of *n*-butyllithium, (scheme 3).

$$(Et_2N)_2P(O)H \xrightarrow{NaH} (Et_2N)_2\bar{P}{=}O\overset{+}{N}a \xrightarrow{RX} (Et_2N)_2P(O)R + NaX$$

**Scheme 3**

Working at room temperature and using similar reaction times as for the reactions involving *n*-butyllithium, only unchanged 1 was recovered. When the mixture was heated under reflux after addition of RX, a complex mixture of products was obtained. It would therefore appear that the sodium derivatives of 1 is not useful in this synthesis for reasons that are not clear at this stage.

We have shown therefore that the $(Et_2N)_2PO^-$ ion is an excellent nucleophile in substitution reactions with primary bromo- and iodoalkanes, with an apparent change to an E2-mechanism with secondary substrates. It is, however, a sterically hindered nucleophile and this may explain the different reactivity with respect to secondary bromides. Approach to the terminal proton in isopropyl bromide would be much easier than approach to the secondary carbon atom.

**Characterization of the alkyl phosphonic diamides**

**i) Mass spectrometry**

For all compounds 2a - 2h a peak corresponding to $M^{+\cdot} = RP(O)(NEt_2)_2^{+\cdot}$ was observed. There are two major fragmentation pathways for $RP(O)(NEt_2)_2^{+\cdot}$, and which one predominates is determined by the nature of the alkyl group, R. In those cases where $R^\cdot$ is a stabilized radical (benzylic or allylic), loss of $R^\cdot$ takes place predominantly, giving base peaks corresponding to the $(Et_2N)_2PO^+$ phosphorylium ion, (eq. 2).

$$RP(O)(NEt_2)_2^{+\cdot} \longrightarrow R^\cdot + (Et_2N)_2PO^+ \qquad (2)$$

m/z 191 (base peak)

R = $PhCH_2$; $CH_2$ = $CHCH_2$; $CH_3CH$ = $CHCH_2$

In those cases where $R^\cdot$ is not resonance stabilized, i.e. $R^\cdot$ is an ordinary alkyl radical, loss of $NEt_2$ either as a radical or a cation predominates, (eq. 3 and 4).

$$RP(O)(NEt_2)_2^{+\cdot} \longrightarrow RP(O)(NEt_2)^{+} + {}^{\cdot}NEt_2 \qquad (3)$$

base peak

R = Me, Pr

$$RP(O)(NEt_2)_2^{+\cdot} \longrightarrow RP(O)(NEt_2)^{\cdot} + {}^{+}NEt_2 \qquad (4)$$

m/z 72 (base peak)

R = $Ph(CH_2)_3$; $CH_3(CH_2)_4$; $CH_3(CH_2)_5$

There appears to be discrimination between reactions 3 and 4 depending on the size of R. In all cases all three pathways are significant except for 2c and 2d for which reaction 3 was found to be a minor one.

Another fragmentation pathway exhibited by 2a - 2h is shown in scheme 4.

i) $RP(O)(NEt_2)_2^{+\cdot} \rightarrow RP(O)(NEt_2)H^{+\cdot} + CH_3CH{=}NEt$

$\downarrow$

$R^{\cdot} + HP(O)(NEt_2)^{+}$

or ii) $RP(O)(NEt_2)_2^{+\cdot} \longrightarrow R^{\cdot} + P(O)(NEt_2)_2^{+}$

$\downarrow$

$HP(O)(NEt_2)^{+} + CH_3CH{=}NEt$

m/z 120 (12-85%)

**Scheme 4**

Without additional experiments it is impossible to distinguish between the two possible routes, (i) or (ii), as they give rise to the same products, but via different fragmentation sequences.

In those cases in which $R^+$ is resonance stabilized, the heterolysis of the P-C bond offers a further route for fragmentation, (eq. 5).

$$RP(O)(NEt_2)_2^{+\cdot} \longrightarrow R^+ + P(O)(NEt_2)_2^{\cdot} \quad (5)$$

25-82%

R = $PhCH_2$; $CH_3CH=CHCH_2$; $CH_2=CHCH_2$

**ii) N.m.r. spectroscopy**

The $^{31}P$ n.m.r. spectra of 2a - 2h gave single signals in the range of +31 to +38 ppm, which is in the range expected for phosphonic systems.[98] Figure 1 shows the $^{31}P$ n.m.r. spectrum obtained for crude 2a and is representative of the $^{31}P$ spectra generally obtained for crude products 2 - the spectrum clearly shows the high purity of the crude product obtained using our procedure. (The $^{31}P$ n.m.r. spectrum shown was recorded relative to trimethyl phosphate as a standard. The $^{31}P$ chemical shifts reported in the experimental section are given relative to 85% $H_3PO_4$).

The $^1H$ n.m.r. spectrum of 1 is notable in that it shows the large coupling of 570 Hz which can only be due to $^1J_{HP}$ coupling and results from the P(O)H functional group. The chemical shift of this proton i.e. +6,5 ppm is also remarkable as it clearly indicates the powerful deshielding effect of the phosphoryl group and thus also its electron-withdrawing ability, (figure 2) [e.g. the modified Swain-Lupton F-values for the -$P(O)(NMe_2)_2$, 0,27 and the -C(O)Me, 0,33 groups can be compared[99]].

The $|^2J_{HP}|$ values for the protons in the P-alkyl chains of 2a - 2h are listed in Table 1.

Table 1: Table of $|^2J_{HP}|$ values for the protons in the P-alkyl chains in 2a - 2h

| $RP(O)(NEt_2)_2$ | $\|^2J_{HP}\|$ /Hz |
|---|---|
| 2a | 17,3 |
| 2c | 16,6 |
| 2d | 16,6 |
| 2e | 14,6 |
| 2h | 14,7 |

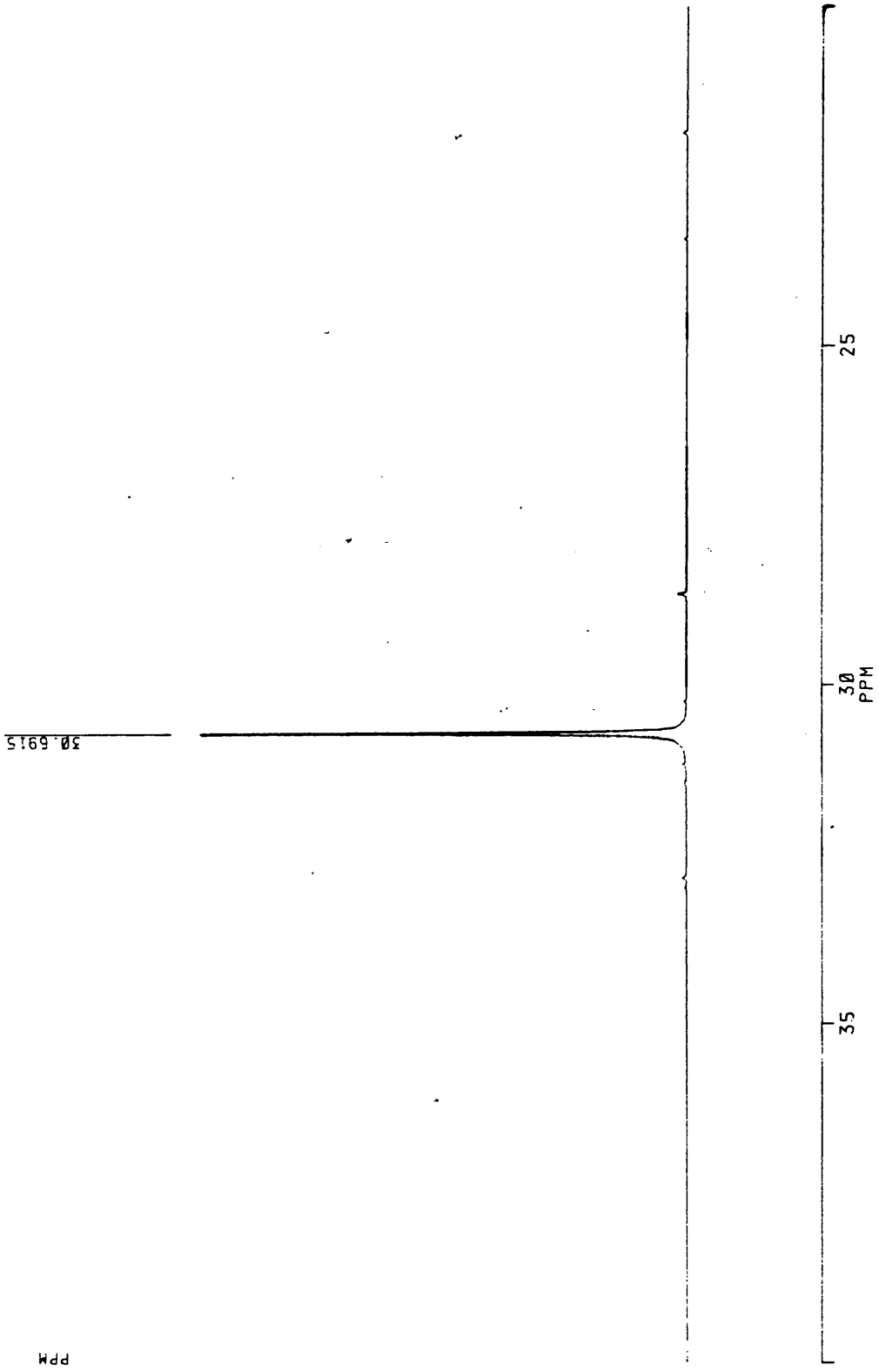



Figure 1 $^{31}P$ n.m.r. spectrum of crude 2a

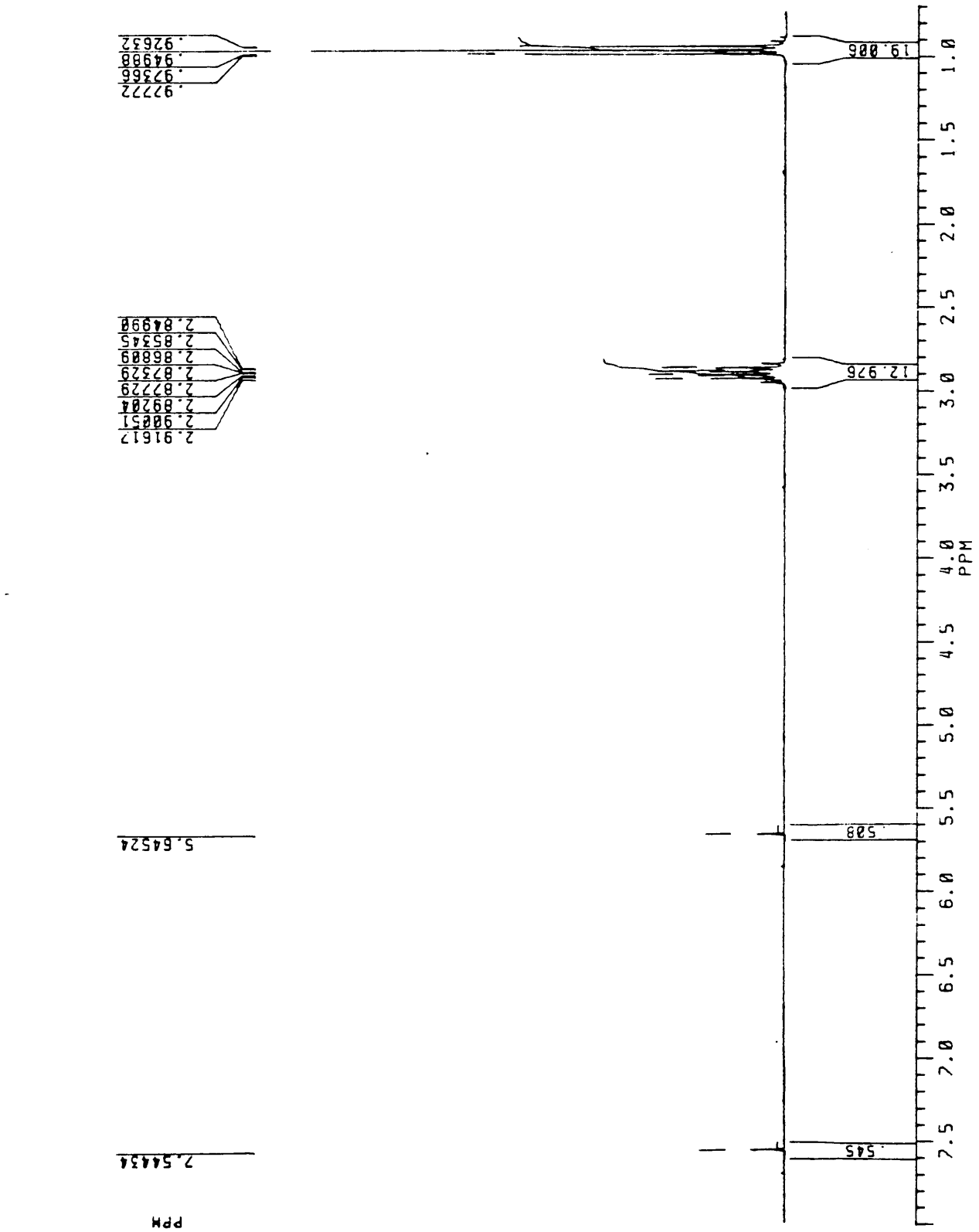
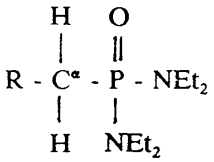



Figure 2 $^{1}$H n.m.r. spectrum of 1

In the discussion that follows we will be considering the α-protons of the phosphonic diamides, 2, which can be represented by the structure A.



A

The Newman projections shown are taken from the side of phosphorus down the P-$C^{\alpha}$ axis. The $|{}^{2}J_{PH}|$ values for these α-protons indicate certain conformational preferences as they have been found[100] to be influenced by the relationship of the hydrogen atom to the phosphoryl oxygen. Studies[101-104] indicated the range of $^{2}J_{PH}$ values possible for certain OPCH dihedral angles to be as indicated in Figure 3.

-14 to -18 Hz | 0 to -5,3 Hz | -13,5 to -16,5 Hz | -6 to -9 Hz

Figure 3

As we can ignore eclipsed conformations due to the bulky amide functionalities in structure A, we have only two conformations (I and II) to consider, (Fig. 4).

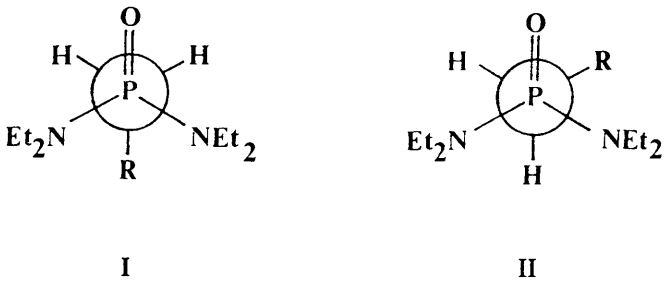



Figure 4

In conformation I both H atoms are gauche with respect to the phosphoryl oxygen, while in II one is gauche and one is anti. For I thus, the $|^2J_{PH}|$ values should be 14 to 18 while for II it should be 7 to 12 Hz (the average value for one gauche and one anti H atom). Our results ($|^2J_{PH}|$ = 15 to 17 Hz) clearly indicate that I represents the most populated conformation of phosphonic diamides 2 in $CDCl_3$ solution.

When R in $RP(O)(NEt_2)_2$ is a bulky group (i.e. R = $PhCH_2$; $Ph(CH_2)_3$; $CH_3(CH_2)_4$ or $CH_3(CH_2)_5$), the rotation around the P-N bond may be restricted. This can be seen when the $NCH_2$ regions of the $^1H$ n.m.r. spectra of 2e (R = methyl, free rotation) and 2h (R = hexyl, restricted rotation) are compared, (Fig. 5). Normally, the $NCH_2$ methylene hydrogens form a $A_2B_3X$ system and as such should give rise to a pair of quartets ($^3J_{HP}$, $^3J_{HH}$). Such a pattern is indeed observed for 2e (Fig. 5(a)). If we consider the expected stable conformations with respect to one of the P-N bonds, (Fig. 6: Newman projections drawn as viewed from N to P),

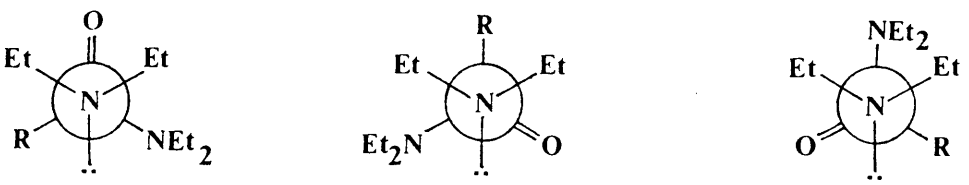



Figure 6

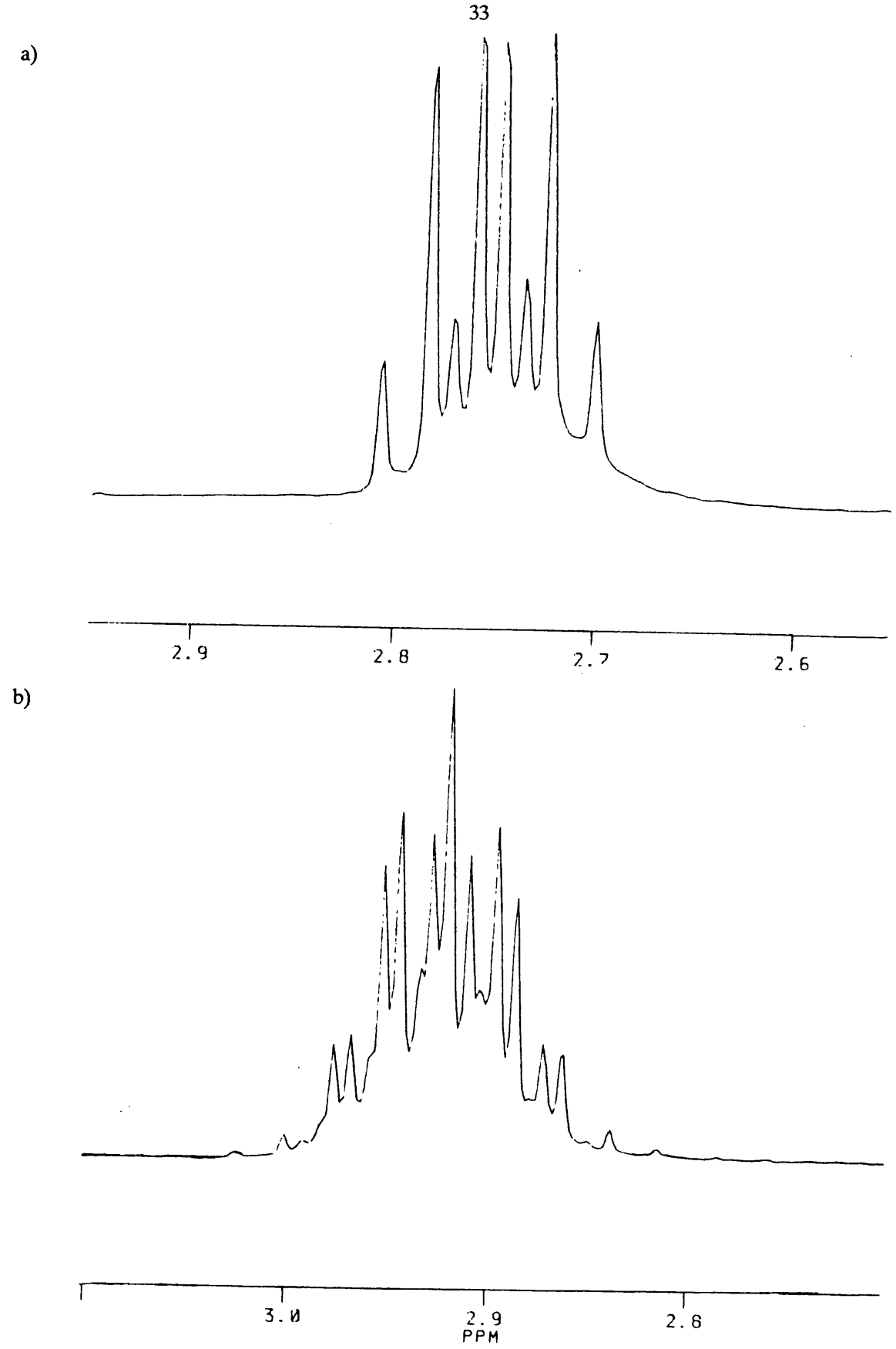



Figure 5 $NCH_2$ region of the $^1H$ n.m.r. spectra of a) 2e and b) 2h.

we can see that if rotation is restricted around the P-N bond the protons of the two methylene groups of a single $NEt_2$ function will find themselves in different environments and will therefore exhibit different chemical shifts. Irrespective of which of the above conformations is "frozen out", the same applies to the other $NEt_2$ group, so we arrive at two pairs of methylene protons with different chemical shifts, which is exactly what we observe when R becomes sufficiently bulky as in 2c, 2f, 2g and 2h.

The $^{13}C$ n.m.r. spectra of 2a - 2h showed all expected signals. The $^{13}C$ n.m.r. spectrum of 2b is shown in Figure 7 as an example. The previous arguments concerning the non-equivalence of the $NCH_2$ protons when the alkyl groups R is bulky also pertains to both carbon atoms of the N-ethyl chains. The $^{13}C$ n.m.r. spectra, however, do not give clear evidence that this is the case. For 2a (R = allyl) the $N\underline{C}H_2$ and $NCH_2\underline{C}H_3$ carbon atoms are observed as singlets while for 2e (R = methyl) they give doublets with $|J_{CP}|$ coupling constants of 4,6 and 2,7 Hz respectively. If we ignore restricted rotation around the P-N bond for 2c, 2f, 2g and 2h, which exhibited the non-equivalence of the $NCH_2$ protons, and determine $J_{CP}$ values for the relevant carbon atoms, we obtain values similar to those given for 2e. It is therefore not clear whether the splitting for the signals of the carbon atoms in the N-ethyl chains of 2c, 2f, 2g and 2h are due to C-P spin-spin coupling or to the restricted rotation. As these compounds exhibit non-equivalence of the $NCH_2$ protons it is likely that the non-equivalence will also be exhibited by the carbon atoms of the N-ethyl chains. For 2c, 2f, 2g and 2h these carbon atoms are thus reported in the experimental section as giving two singlets with no C-P coupling.

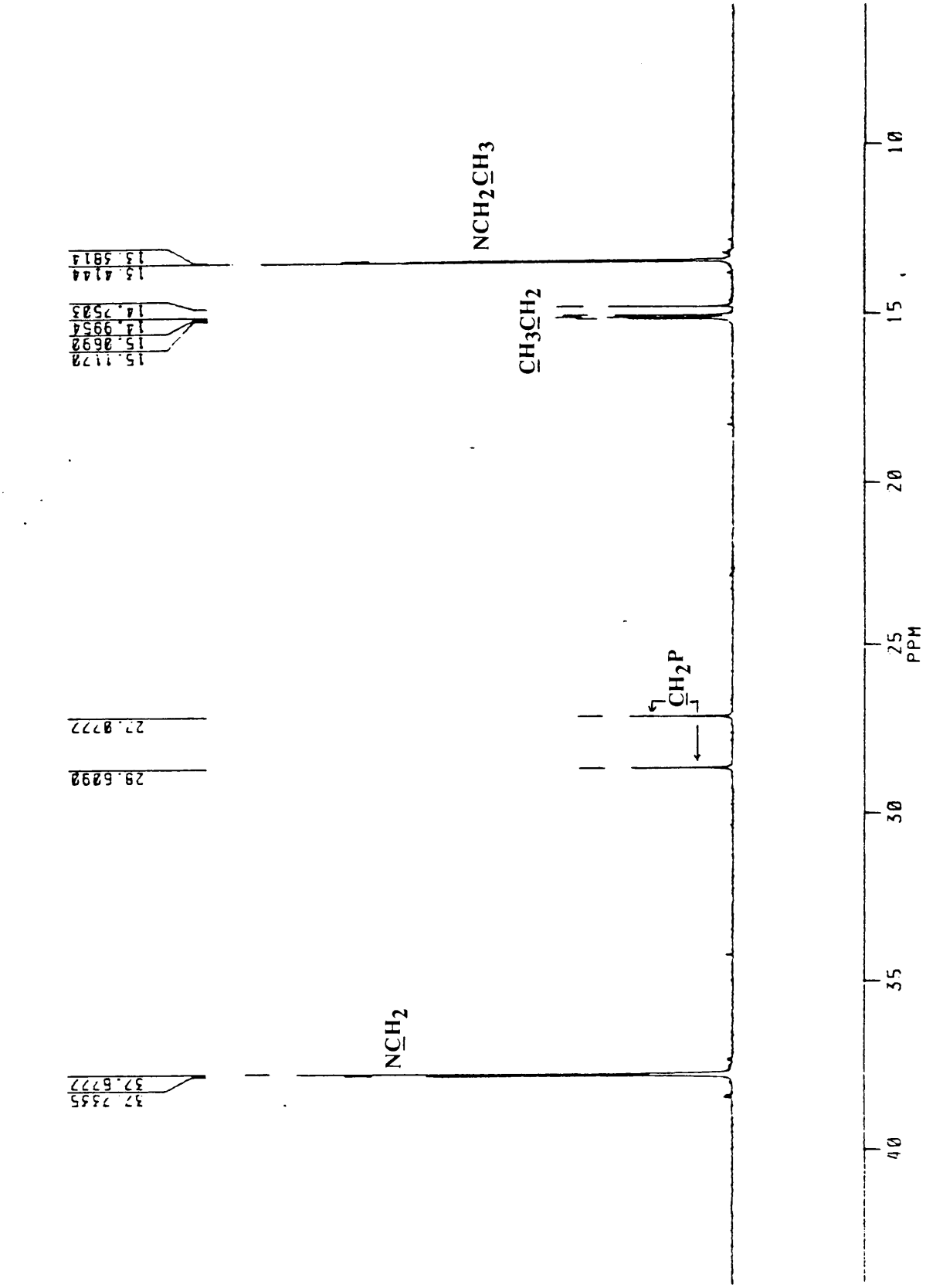


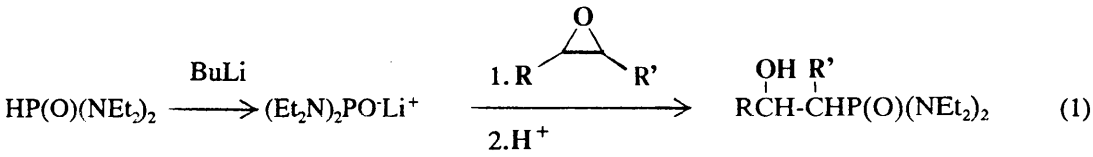

Figure 7 $^{13}C$ n.m.r. spectrum of 2b.

# RESULTS AND DISCUSSION:

## ß-hydroxyalkylphosphonic diamides

### Synthesis of $RCH(OH)CHR'P(O)(NEt_2)_2$, (4a - 4g)

ß-hydroxyalkylphosphonic diamides, (4a - 4g), were synthesized according to the reaction represented by equation 1.




(1)

1 4

| | R | R' | Yield (%) |
|---|---|---|---|
| 4a: | $PhCH_2$ | H | 79 |
| 4b: | Ph | H | 99 |
| 4c: | Et | H | 65 |
| 4d: | $-(CH_2)_4-$ | | 76 |
| 4e: | $-(CH_2)_3-$ | | 62 |
| 4f: | $CH_3$ | $CH_3$(RR/SS) | 50 |
| 4g: | $CH_3$ | $CH_3$(RS/SR) | 56 |

The reaction was carried out in THF and the anion of 1 generated at -94°C. The epoxide was added at the same temperature. Depending on the epoxide, different reaction conditions have to be used thereafter. The epoxides can be divided into four groups based on their reactivities toward the anion of 1:

a. Most reactive are terminal epoxides i.e. 1,2-epoxy-3-phenylpropane, 1,2-epoxybutane and styrene

oxide.

b. 1,2-disubstituted epoxides having a cis-configuration i.e. cyclohexene oxide, cyclopentene oxide and cis-2,3-epoxybutane.

c. 1,2-disubstituted epoxides with a trans-configuration i.e. trans-2,3-epoxybutane.

d. Epoxides that do not react with the anion of 1 even under harsh conditions e.g. exo-2,3-epoxynorbornane.

**i. Terminal epoxides**

The anion of 1 reacted smoothly with terminal epoxides within two hours at room temperature. The yields shown are for the crude products which are pure according to $^{31}P$ n.m.r. spectroscopy. The epoxides of this group are the only ones we used where regiochemistry was at issue; all the other epoxides used being symmetrically substituted. These epoxides gave exclusively the products (4a - 4c) of attack of the nucleophile at the less hindered carbon. This is in accord with the known reactivity of epoxides in $S_N2$-type reactions in basic media.[105-106]

**ii. cis-Disubstituted epoxides**

In contrast to the mild conditions under which the opening of terminal epoxides takes place, harsher conditions were required for 1,2-disubstituted epoxides. This is clearly an indication of how steric hindrance influences the approach of the bulky nucleophile, $(Et_2N)_2PO^-$. To obtain products (4d - 4f) it was necessary to heat the reaction mixture for several hours under reflux after addition of the epoxides.

Various conditions were used in attempts to optimize the yield of 4d and these highlight the different reactivities of the terminal and disubstituted epoxides toward the anion of 1.

a. Under the same conditions as used for terminal epoxides mostly 1 was recovered.

b. Prolonging reaction time to 22 hours at room temperature gave a mixture of several phosphorus

containing products including 4d and 1.

c. Using the same reaction time as for terminal epoxides and carrying the reaction out in the presence of copper(I)iodide, again gave a mixture of phosphorus containing compounds, with 4d as a major product. The mixture was less complex than that obtained under the conditions indicated in b.

d. Upon reflux on an oilbath at 80°C after 2 hours a mixture of 4d and 1 in a ratio of ca. 85:15 was obtained. This mixture was separated by distillation to give pure 4d in the yield shown above.

An important feature of the reactivity of the ß-hydroxyalkyl phosphonic diamides must be mentioned here. These compounds can undergo thermal elimination as indicated in equation 2.[92,108,109]


(2)

Corey and co-workers[92] demostrated that a syn-configuration of the hydroxy and phosphorus groups is required for this reaction to take place. They prepared compound A as in equation 3.


(3)

A

Compound A has a trans-configuration and cannot attain the syn-geometry required for the elimination, and indeed it doesn't undergo the reaction. 4d could therefore be distilled, as could 4e.

That A, 4d and 4e have a trans-geometry is a consequence of the fact that ring opening of cyclic epoxides nearly always proceeds in a trans-fashion, (fig. 1).[105]

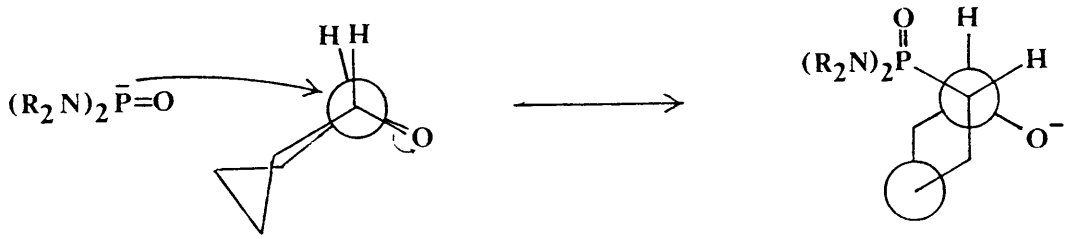


**Figure 1**

Spectroscopic studies have indicated that cyclohexene oxide has the structure shown in figure 1. It is also interesting to note that A was obtained by Corey after 44 hours at room temperature in only 20% yield.[92]

Under exactly the same conditions as used for 4d, cyclopentene oxide gave a mixture of 4e and 1 in a ratio of ca. 59:41. Refluxing for 6 hours after addition of the epoxide resulted in almost complete conversion to 4e. It therefore appears that cyclopentene oxide is with respect to the $(Et_2N)_2PO^-$ ion somehow more sterically hindered than cyclohexene oxide.

Cis-2,3-epoxybutane also required 6 hours of reflux for complete conversion to 4f. The tetramethyl analogue of 4f was prepared by Corey using 72 hours of stirring at room temperature in 23% yield.[92] Assuming the $S_N2$ mechanism is applicable, cis-2,3-epoxybutane must give the RR/SS diastereomeric pair of 4f, (fig. 2).

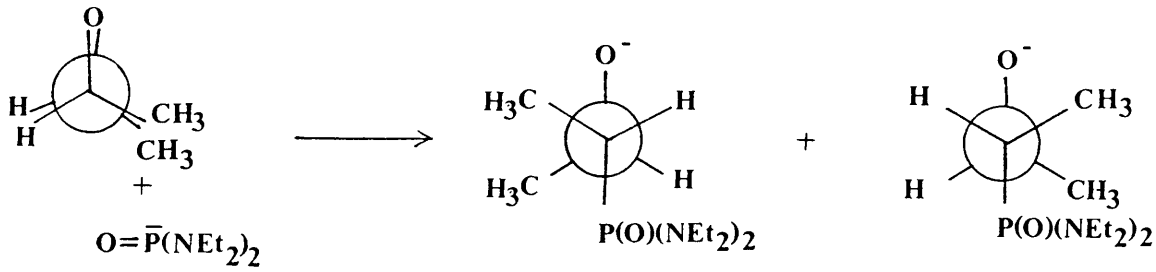


**Figure 2**

$^{31}P$ n.m.r. spectroscopy indeed showed that only one diastereomer pair was derived. A full discussion of the stereochemistry of the products follows later.

### iii. Trans-2,3-epoxybutane

In marked contrast to the cis-isomer, trans-2,3-epoxybutane required 22 hours of reflux to be fully converted to 4g. Again we may compare it with the results obtained for the tetramethyl analogue of 4g. After stirring at room temperature for 5 days this compound was obtained in only 14% yield.[92]

Trans-2,3-epoxybutane should give the RS/SR diastereomer pair of 4g, (fig. 3).

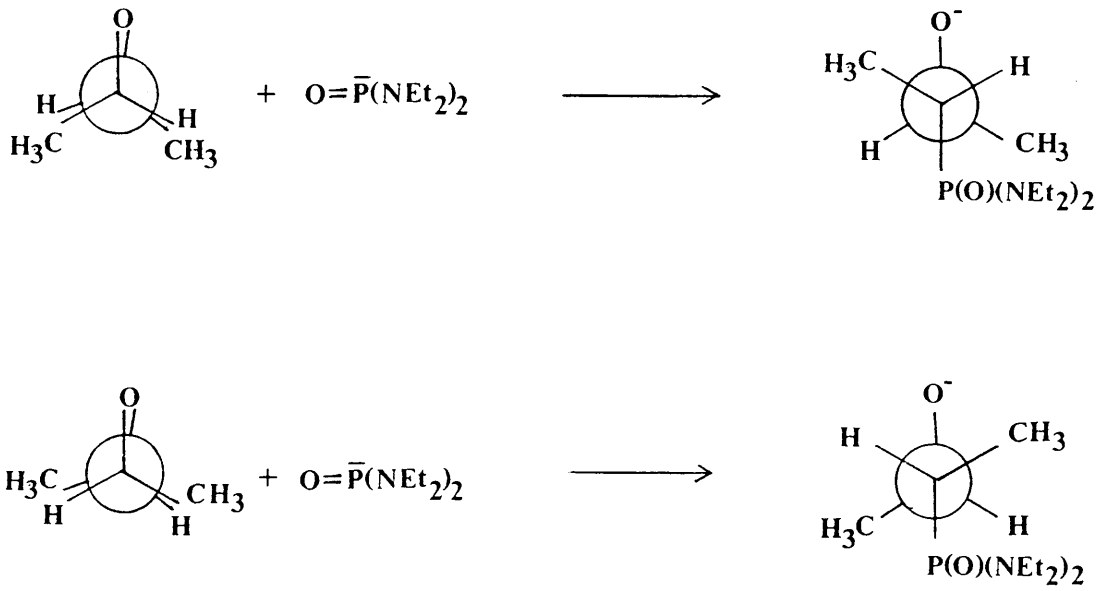
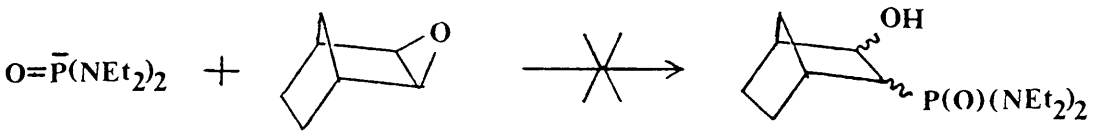



**Figure 3**

Two explanations can be proposed to account for the different reactivities of the trans- and cis-isomers of 2,3-butene oxides. Nucleophilic attack in the cis-isomer should be energetically more favourable due to the removal of eclipsing interactions between the two methyl groups. Attack may also be easier in the cis-isomer as the one side of the molecule is more accessible than it is in the case of the trans-isomer.

### iv. Exo-2,3-epoxynorbornane

Exo-2,3-epoxynorbornane failed to give any product with the anion of 1 even after 24 hours of reflux. Steric hindrance completely impeeds the reaction, (eq. 4).




(4)

### Characterization of ß-hydroxyalkylphosphonic diamides

### i. Mass spectrometry

In the mass spectra, $M^{+\cdot}$ was observed only for 4a and 4c. Compounds 4a - 4g exhibit very similar fragmentation pathways giving rise to common ions. The more important ones are indicated in equations 5 to 8.

$$\underset{\underline{4}}{RP(O)(NEt_2)_2^{+\cdot}} \equiv M^{+\cdot} \longrightarrow \underset{\text{m/z 191}}{(Et_2N)_2PO^+} + R^{\cdot} \qquad (5)$$

$$M^{+\cdot} \longrightarrow \underset{\text{m/z (72)}}{NEt_2^+} + RP(O)(NEt_2)^{\cdot} \qquad (6)$$

$$M^{+\cdot} \longrightarrow CH_3CH{=}NEt + RP(O)(NEt_2)H^{+\cdot} \longrightarrow \underset{\text{m/z 120}}{HP(O)(NEt_2)^+} \qquad (7)$$

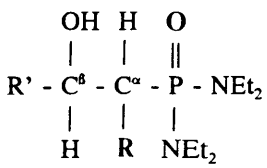
$$M^{+\cdot} \longrightarrow NEt_2^{\cdot} + \underset{\substack{| \quad | \\ HO \quad \overset{+}{P}(O)(NEt_2)}}{R'CH\text{-}CH_2} \longrightarrow R'CH{=}CH_2 + \underset{\text{m/z 136}}{(HO)P(O)(NEt_2)^+} \qquad (8)$$

The relative importance of each of these reactions varies from compound to compound, without any simple correlation with structure. The more usual fragmentation pathways associated with alcohols are unimportant for 4a - 4g. More relevant to structure elucidation is the observance of peaks corresponding to $M^{+\cdot}$ -$NEt_2^{\cdot}$ for all seven compounds 4a - 4g.

## ii. N.m.r. spectroscopy

$^{31}P$ n.m.r. spectroscopy showed that compounds 4a - 4g give signals with the chemical shifts in the range of +37 to +45 ppm. Again, $^{31}P$ n.m.r.spectroscopy can be used as a probe of the purity of the synthesized compounds; e.g. the $^{31}P$ n.m.r. spectrum of crude 4b is shown in figure 4. The effect of the hydroxy group is clear upon comparison of the $^{31}P$ chemical shifts of 2f, ($Ph(CH_2)_3P(O)(NEt_2)_2$; $\delta$ = 37,5) and 4a ($PhCH_2CH(OH)CH_2P(O)(NEt_2)_2$ ; $\delta$ = 38,3). The higher chemical shift of 4a relative to 2f is expected due to the deshielding effect of the hydroxy group.

The $^1H$ n.m.r. spectra of compounds 4a - 4g contain a wealth of interesting information. The most important feature of compounds 4a - 4g, as far as $^1H$ and $^{13}C$ n.m.r. spectroscopy is concerned, is the chirality of the carbon bearing the hydroxy group. This chirality induces diastereotopicity of other centres which is observed as far away as the terminal methyl groups of the amide functions. The compounds can in general be written as having structure B.




**B**

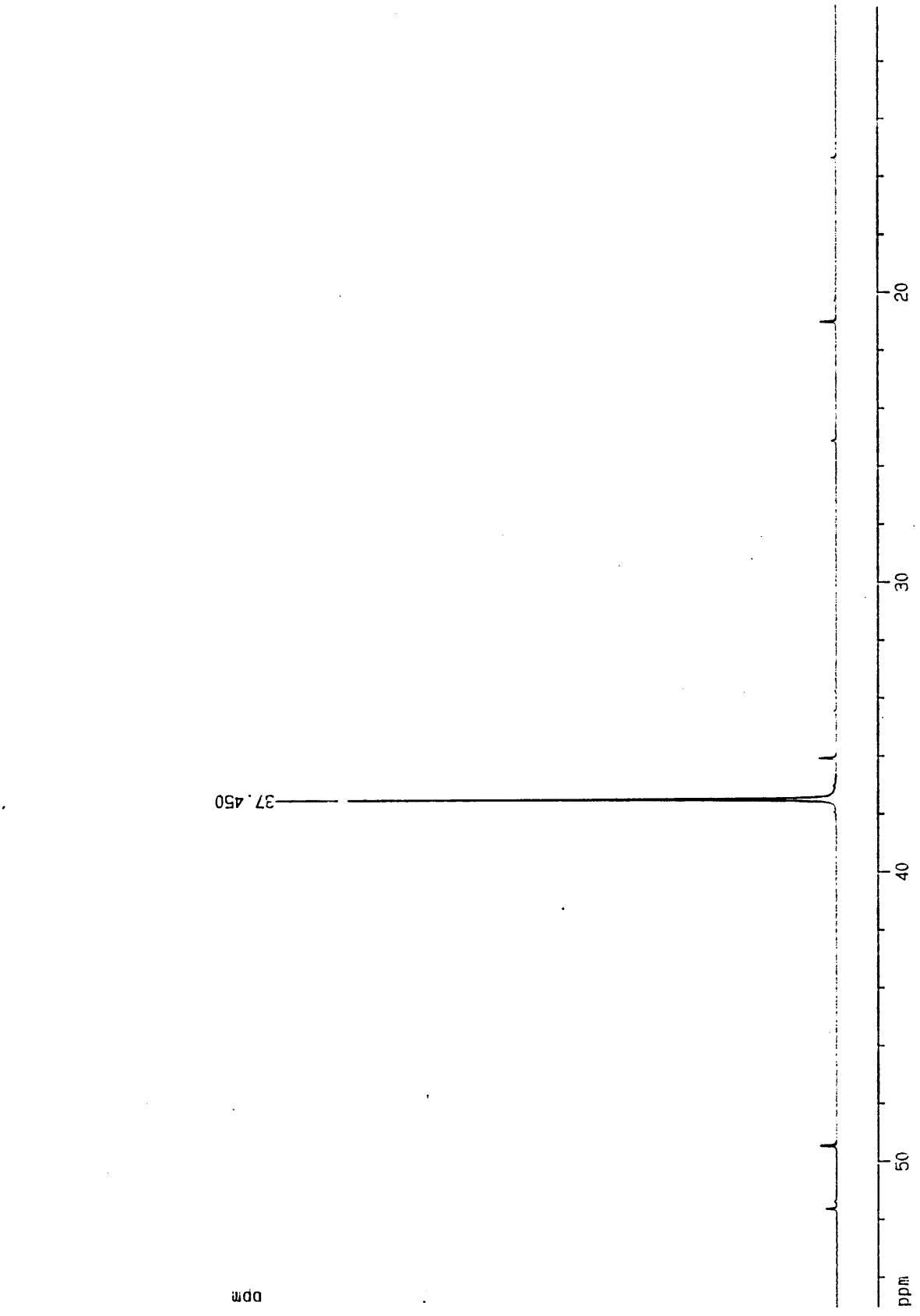
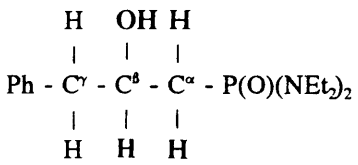



Figure 4 $^{31}P$ n.m.r. spectrum of 4b

For 4a - 4e, where R=H, the two $\alpha$-protons are diastereotopic. Considering the ethyl groups of the amide $NEt_2$ functions, it is easy to see that the two ethyl groups attached to the same nitrogen are spectroscopically equivalent, but in a diastereotopic relation to the two ethyl groups attached to the other nitrogen atom. The chirality that would be introduced by changing one of the methyl groups of the $NEt_2$ function to some other group doesn't occur at the adjacent centre to a chiral carbon, but at the remote phosphorus centre. The same holds for the methylene groups attached to nitrogen. These diastereotopic groups have different chemical shifts, as is clearly observed in all the $^1H$ and $^{31}C$ n.m.r. spectra of 4a - 4g. The difference is most marked for the terminal methyl groups of the amide functions. The $^1H$ n.m.r. spectrum of 4b is shown as an example, (fig. 5).

For 4a, there is an additional pair of diastereotopic protons in the molecule, that is at the $\gamma$-carbon. The




4a

most revealing structural information can be obtained from the $^3J_{HH}$ (vicinal) coupling constants of the $\alpha$- and ß-protons. These protons form an AA'BX sytem and thus eight lines (ddd) should be observed for each of these protons with the respective coupling constants $^2J_{HH}$, $^3J_{HH}$ and $^2J_{HP}$. This pattern is indeed experimentally observed. Considering the three stable staggered conformations with respect to the rotation around the $C^{\alpha}$-$C^{ß}$ bond, (fig. 6; Newman projection as viewed from $C^{\alpha}$ to $C^{ß}$; (P) = $P(O)(NEt_2)_2$), we would expect conformation I to be the most populated, as it offers the possibility of intramolecular hydrogen bonding between the hydroxy hydrogen atom and either phosphoryl oxygen or the nitrogen atoms, as well as it releases the unfavourable steric interactions between the benzyl and phosphorus groups in an anti configuration. (4a is a racemic mixture. We consider only one enantiomer, in this case the S-isomer as the same result will be obtained when considering the other enantiomer.)

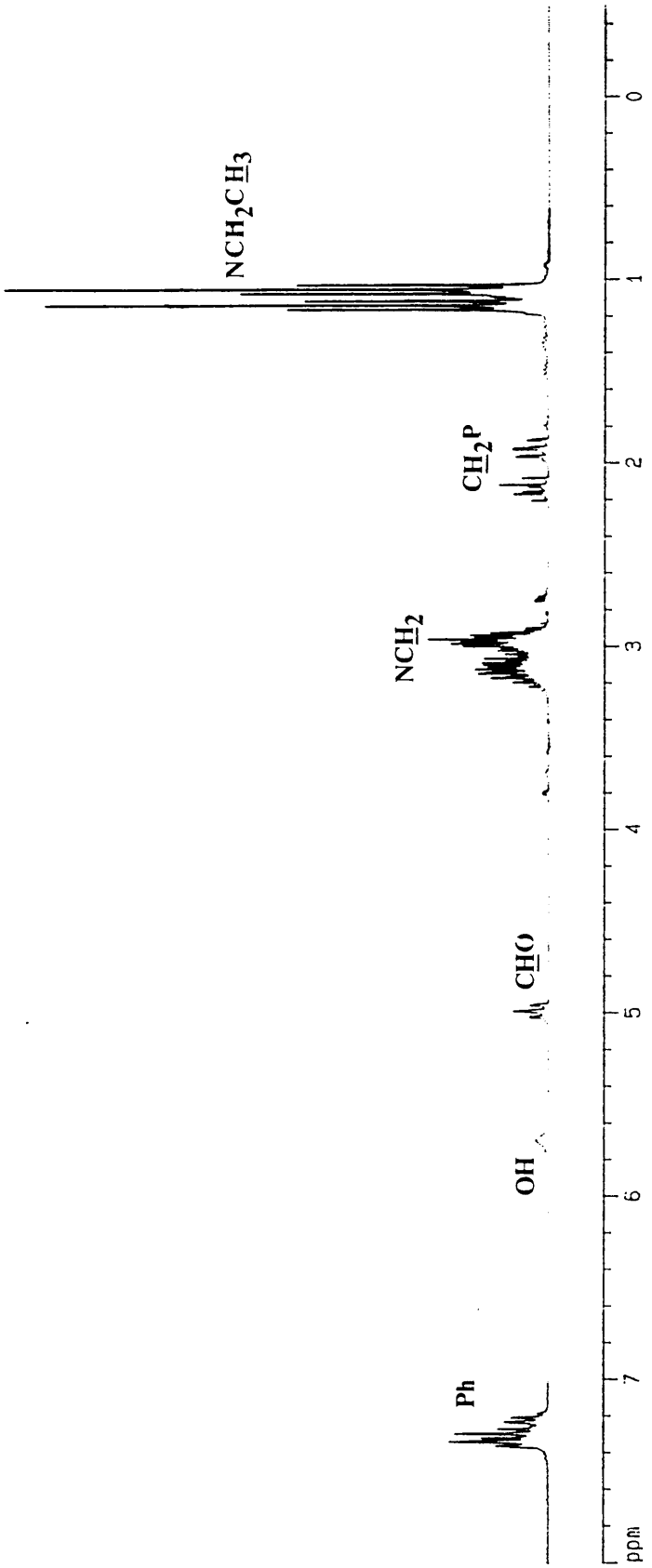
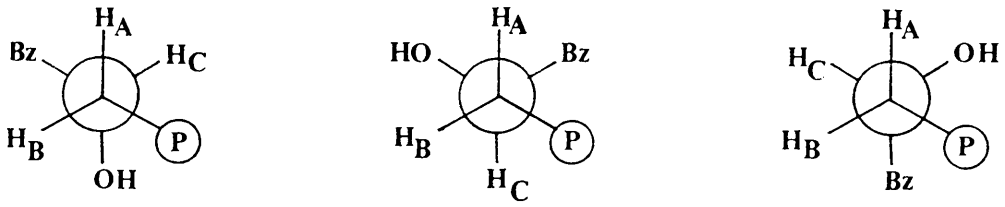



Figure 5: $^{1}H$ n.m.r. spectrum of 4b




I II III

**Figure 6**

By using the observed coupling constants, $^3J_{AC}$ and $^3J_{BC}$, for 4a and the Haasnoot-equation[110] (for a description of this equation and the relevant calculations see the appendix) we have calculated the populations of the three conformations (I, II and III in figure 6) in $CDCl_3$ as being 82% of I, -4% of II and 22% of III. The small error of -4% can be attributed to the fact that we used as group electronegativity for $P(O)(NEt_2)_2$ the group electronegativity of $P(O)(OR)_2$[111], as the former was not available. We assumed that the group electronegativity is largely determined by the P=O function at both $P(O)(OR)_2$ and $P(O)(NR_2)_2$ groups. Dividing the deviation equally between conformation I and III, we then have 80% of I and 20% of III. This result confirms what we would expect and indicates the importance of intramolecular hydrogen bonding for 4a, at least for a chloroform solution. We can thus conclude that 4a exists largely as one of the forms shown in figure 7.

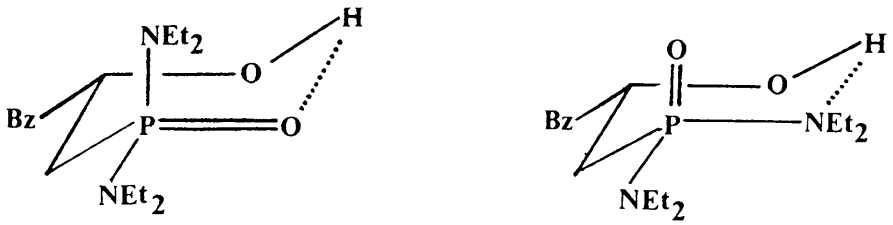
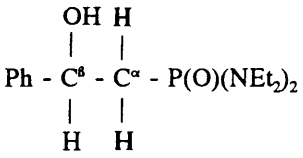



**Figure 7**

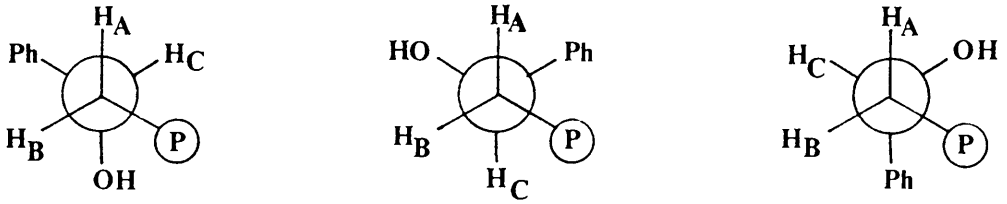
Evidence for hydrogen bonding in 4a in $CDCl_3$ can also be found in the fact that the hydroxy proton resonance occurs at 5,3 ppm.[112] The IR spectrum of 4a recorded in a $CCl_4$ solution also confirms this, as the O-H stretching band occurs at 3363 $cm^{-1}$, which is typical of hydrogen bonded OH.[113]

The same conformational analysis was carried out for 4b.




4b

Again the staggered conformations are as shown in figure 8 (Newman projections viewed from $C^{\alpha}$ to $C^{\beta}$).




I II III

**Figure 8**

We obtained population percentages of 93% of I and 7% of III. Again, further evidence of intramolecular hydrogen bonding could be found in the $^1H$ n.m.r. resonance of the hydroxy proton, as well as in the IR spectrum. In fact, all compounds 4 show these features characteristic of intramolecular hydrogen bonding.

Unfortunately the $CH_2P$ region of the $^1H$ n.m.r. spectra of 4c - 4e are obscured by overlapping resonances and no analogous calculations were possible. However, with the information at hand, it is easy to predict that the most preferred conformation of 4d (SS isomer) should be one of those shown in figure 9.


**Figure 9**

Firstly, the attack of the anion of 1 is likely to result in trans-opening of the epoxide (which gives us the

RR/SS diastereomeric pair of 4d). 4d must therefore have the phosphorus and hydroxy groups either diaxial or diequatorial. If the groups were diaxial, intramolecular hydrogen bonding would be impossible and it is also a well known fact that most groups prefer to adopt equatorial positions.[114] Similar arguments apply to the cyclopentyl phosphonic diamide, 4e.

For 4f we claimed to have obtained the RR/SS diastereomer pair resulting from $S_N2$ attack of the anion of 1 on cis-2,3-epoxybutane. We now present evidence in support of this claim. The staggered conformations of (1R,2R)-4f are shown in figure 10, (Newman projections viewed from $C^{\alpha}$ to $C^{\beta}$).

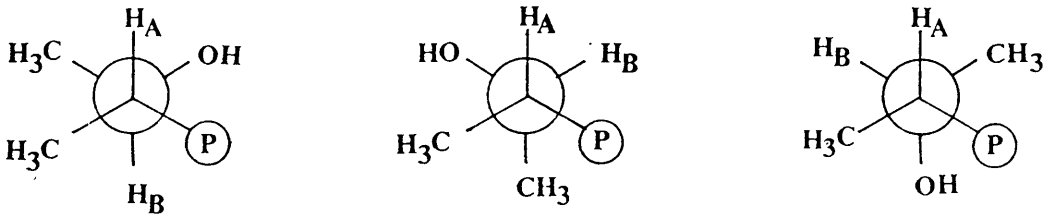



**Figure 10**

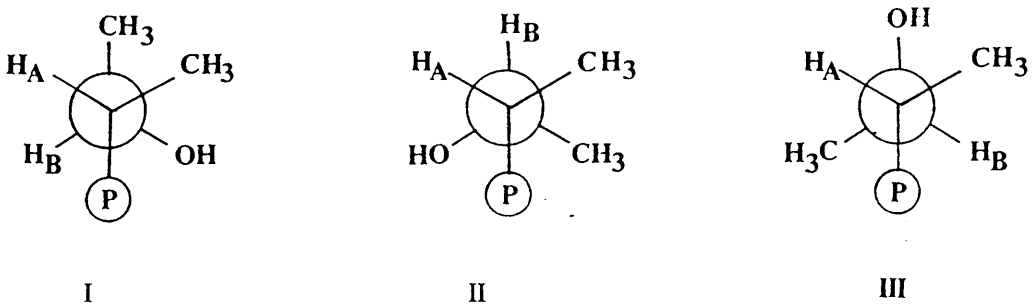
As we have shown for 4a and 4b that the conformation which does not allow intramolecular OH to P=O or P-N hydrogen bonding is not relevant, we can ignore conformation II for (1R, 2R)-4f. We have also shown for 4a and 4b that the almost exclusive conformation is the one that doesn't result in the phosphorus group being gauche with respect to the alkyl group attached to the ß-carbon. Thus as first approximation we may assume that I is the conformation representing the molecule of (1R,2R)-4f. As $^3J^{obs}_{AB} = a\ ^3J^{I}_{AB} + b\ ^3J^{II}_{AB} + c\ ^3J^{III}_{AB}$,[115] where a, b and c are the populations of conformations I, II and III, respectively, and $^3J^{X}_{AB}$ are the calculated coupling constants of the given conformation, we then have $^3J^{obs}_{AB} \sim 1.^3J^{I}_{AB} + 0.^3J^{II}_{AB} + 0.^3J^{III}_{AB}$ or $^3J^{obs}_{AB} = {}^3J^{I}_{AB}$. Thus the observed vicinal coupling constant should equal the theoretically calculated coupling constant for conformation I. Using the Haasnoot equation we obtain $^3J^{I}_{AB} = 12{,}0$Hz. The observed coupling constant is 9,1 Hz. This is in reasonable agreement, as conformation III will certainly be contributing to the observed coupling constant, i.e. $c \neq 0$, and will lower the observed coupling constant. In fact, for conformation III, $^3J^{III}_{AB} = 1{,}9$ Hz. We thus have two equations, [1] and [2].

$$9,1 = 12,0\ a + 1,9\ c \qquad [1]$$

$$1 = a + c \qquad [2]$$

We therefore obtain a = 0,71 and c = 0,29. Thus the contributions of the conformations are 71% of I and 29% of III - in good agreement with that found for 4a and 4b. We thus assign 4f the 1R,2R/1S,2S stereochemistry.

Again we can consider the three possible staggered conformations of (1S,2R)-4g, (fig. 11, Newman projections viewed from $C^{\alpha}$ to $C^{\beta}$).



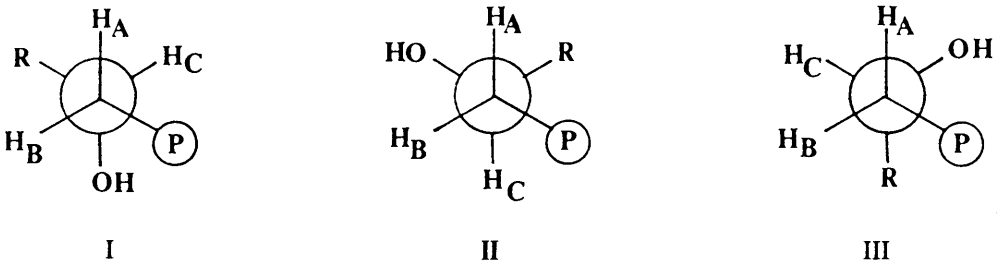

I II III

**Figure 11**

After ignoring conformation III ($P(O)(NEt_2)_2$ and OH groups anti), and assuming conformation I to be the only one populated, we arrive at the calculated coupling constant of $^3J^I_{AB}$ = 1,9 Hz. The observed coupling constant is 1,0 Hz. As the calculated values largely depend on the first two terms of the Haasnoot equation (in this case 13,24 $\cos^2 \varnothing$ - 0,91 $\cos \varnothing$), it is clear that the actual $HC^{\alpha}C^{\beta}H$ dihedral angle for 4g is somewhat larger than the 60° in conformation I, as this would result in a lower calculated value of $^3J_{AB}$. This might be expected as it would help relieve any unfavourable interactions between the two gauche methyl groups. In any case, we expect a small $^3J_{AB}$ coupling constant for the (1S,2R) / (1R,2S) pair of 4g which is indeed observed.

Similar calculations have been done[116] for the dimethyl phosphonic esters corresponding directly to 4a and

4b, i.e. $PhCH_2CH(OH)CH_2P(O)(OMe)_2$, C, and $PhCH(OH)CH_2P(O)(OMe)_2$, D. For C the relative populations of conformations I, II and III (figure 12, Newman projections of C and D as viewed from the phosphorus bearing carbon; (P) = $P(O)(OMe)_2$),




I II III

**Figure 12**

in $CDCl_3$ are 54%, 24% and 22% respectively; for D they are 83%, 5% and 12%. It seems that the greater conformational preference of the diamides for configuration I when compared to the esters reflects the greater hydrogen bonding acceptor ability of the phosphonodiamide functional group. The greater bulk of the $P(O)(NEt_2)_2$ group, as compared with the $P(O)(OMe)_2$ group should additionally favor conformation I (anti orientation of the phosphorus function and the R group at carbon ß).

The situation with regard to the $NCH_2$ protons is much more complex than earlier stated. If we consider only diastereotopicity, we would expect two sets of eight lines in the $^1H$ n.m.r. spectrum (2 x dq). For 4b two sets consisting of considerably more lines are however observed. The exact number in each set could not be determined due to the overlap of the two sets of signals. The total number, however, is less than thirty two. It appears therefore that for 4b some restriction of rotation around the P-N bond is also present. In other cases the two sets are less well separated and the situation is much less clear. The $^{13}C$ n.m.r. spectra of 4a - 4g showed all the expected signals. The $^{13}C$ n.m.r. spectrum of 4f is shown in figure 13. The diastereotopicity of the carbon atoms in the $NCH_2CH_3$ groups is clearly manifested. Two different

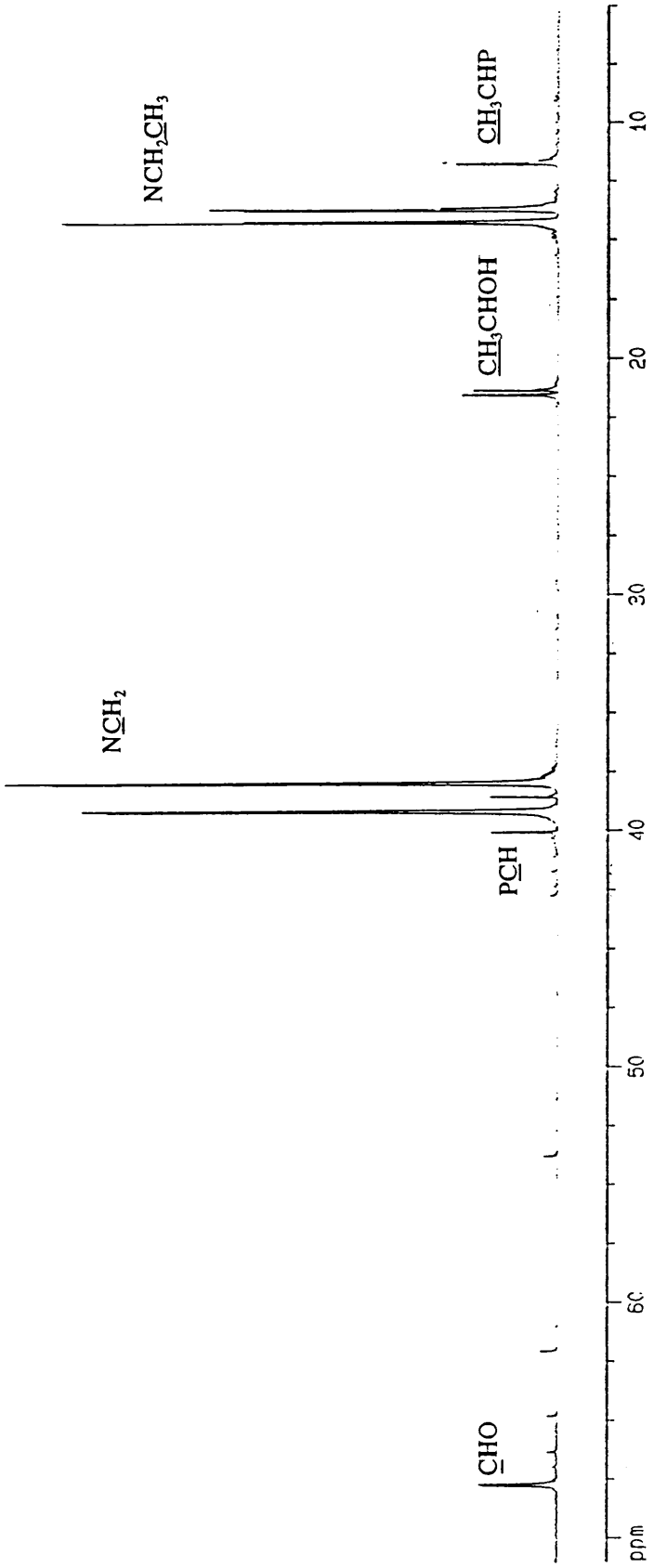



Figure 13: $^{13}C$ n.m.r. spectrum of 4f

signals for the $NCH_2$ carbon atoms are observed. The same applies to the terminal methyl carbons of these groups. This is in accord with our previous discussion.

The $^{13}C$ n.m.r. spectra are also useful in confirming the conformational analysis using data from $^{1}H$ n.m.r. spectroscopy. Several Karplus type equations have been derived for $^{3}J_{CP}$ couplings.[117-119] Using one derived by Thiem,[117] $^{3}J_{CP} = 7,35 - 1,76 \cos \varnothing + 7,86 \cos 2 \varnothing$ ($\varnothing$ = CCCP dihedral angle) and by substituting $\varnothing = 180°$ we obtain $^{3}J_{CP} = 17,0$ Hz. 180° is the dihedral CCCP angle in conformation I previously shown for 4a and 4b in figures 6 and 8 respectively. The observed values are $^{3}J_{CP} = 17,1$ Hz for 4a and $^{3}J_{CP} = 16,7$ Hz for 4b. Thus even such a simple approach confirms the previously discussed conformational analysis for 4a and 4b. The observed $^{3}J_{CP}$ couplings for all compounds 4a - 4g vary from 12,8 - 17,4 Hz. This range can be reduced to 14,0 - 17,4 Hz by excluding 4e ($^{3}J_{CP} = 12,8$ Hz)where the CCCP dihedral angle is necessarily smaller than 180° due to the requirements of the five membered ring. It thus appears that compounds 4 highly prefer conformations around the $C^{\alpha}$ - $C^{\beta}$ bond which has the R group anti and the OH group gauche to the phosphorus group, (fig. 14).

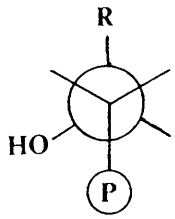


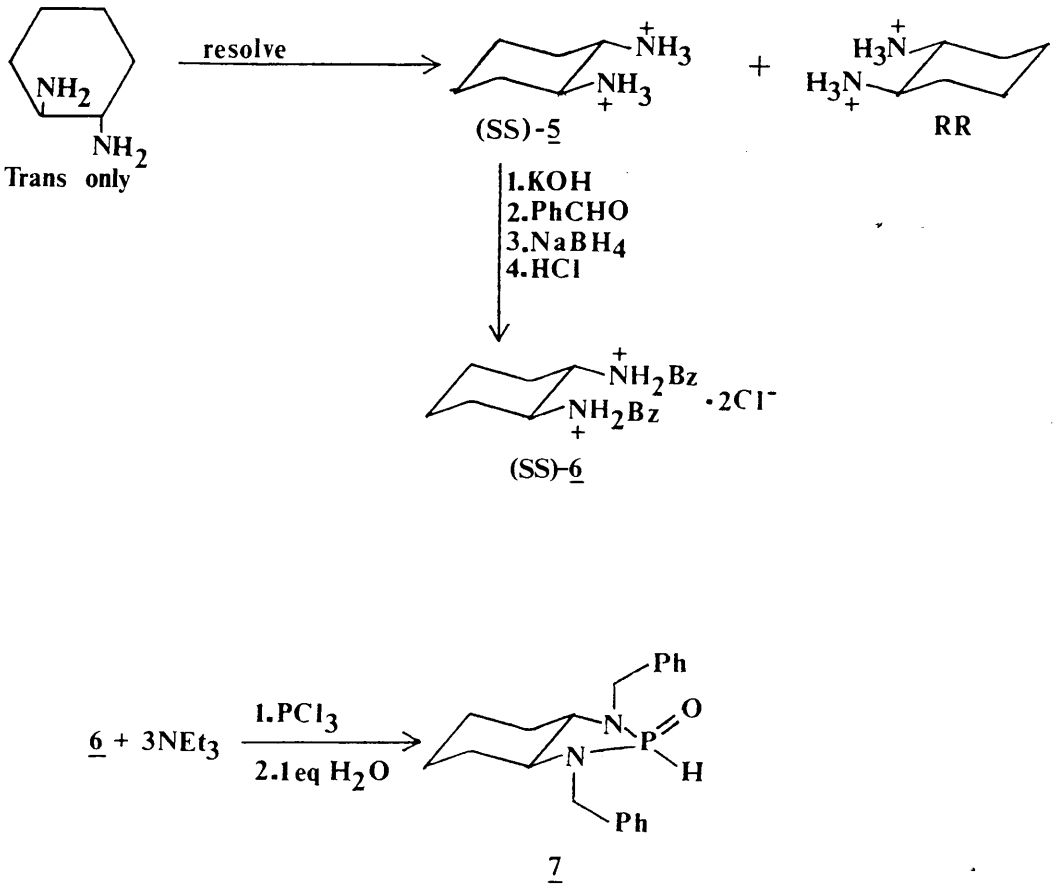

**Figure 14**

**Synthesis and reaction of a chiral phosphonic diamide**

After establishing that lithiated diamidophosphites react with epoxides to give ring opened products containing one or two chiral centres (equation 1), we decided to test the possibility of asymmetric induction in the epoxide ring opening by using a chiral diamidophosphite group. Recently Spilling and coworkers[95]

synthesized a chiral phosphonic diamide, 7, derived from N,N'-dibenzyl-trans-1,2-diaminocyclohexane and studied reactions of the anion of 7 with carbon electrophiles. The reaction with aldehydes gave α-hydroxyphosphonamides in good yield and with diastereoselectivity in the order of 25:1.[95] It seemed therefore worthwhile to apply Spilling's reagent to our reaction with epoxides in order to evaluate its potential in the preparation of optically active ß-hydroxyalkylphosphonic diamides.

The chiral phosphonic diamide, 7, was prepared according to known procedures,[95,120] (sheme 1).




**Scheme 1**

The $^{31}P$ and $^{1}H$ n.m.r. spectrum of 7 was similar to that reported in the literature[95] for the isomer having the RR stereochemistry. It is important to note that the enantiomers comprising 7 are in rapid equilibrium via the phosphite form, (figure 15).

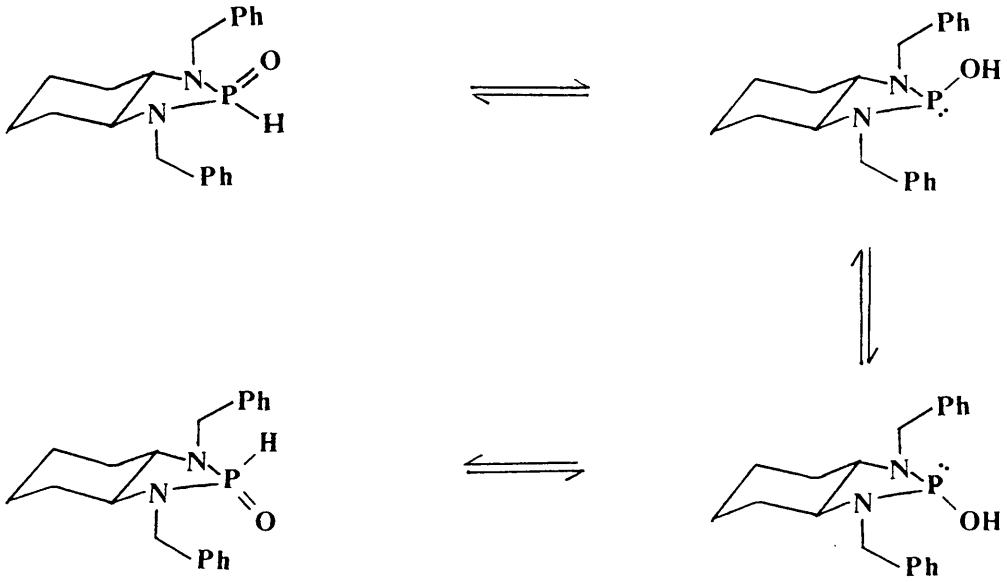
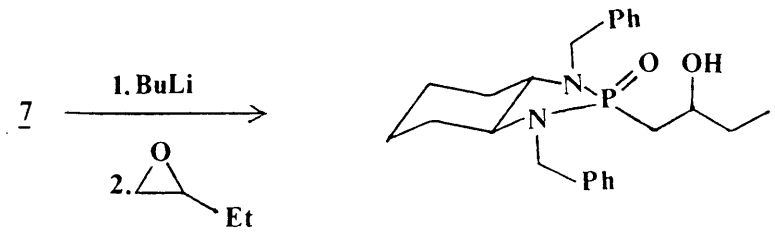


**Figure 15**

The anion of 7 was treated with an excess of 1,2-epoxybutane, (eq. 9),



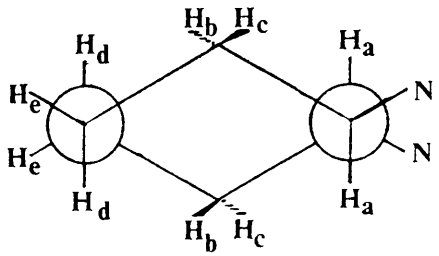
8 (9)

and gave the expected product 8 as a mixture of diastereomers. The $^{31}P$ n.m.r. spectrum of 8 contained two signals at 44,1 and 43,2 ppm in the ratio 64:36. That the two signals do correspond to diastereomers of 8 was confirmed in the following way. The previously obtained product 4c was hydrolyzed in dilute hydrochloric acid to give the free phosphonic acid, 9, (eq. 10).

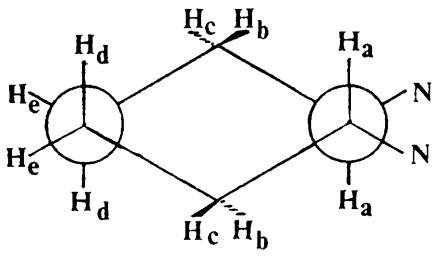
$$\underset{\underline{4c}}{CH_3CH_2CH(OH)CH_2P(O)(NEt_2)_2} \xrightarrow{HCl} \underset{\underline{9}}{CH_3CH_2CH(OH)CH_2PO_3H_2} \qquad (10)$$

When the product 8, consisting of two diastereomers was hydrolyzed in a similar manner the two signals in the $^{31}P$ n.m.r. spectrum of the product disappeared and were replaced by a single signal with the same $^{31}P$ chemical shift, and a similar $^{1}H$ n.m.r. spectrum as those obtained for 9. It is obvious that when the chiral diamine moiety has been removed from a molecule of 8 by hydrolysis, the resulting 2-hydroxybutylphosphonic acid, 9, was produced as a mixture of two enantiomers and hence was homogeneous from a spectroscopic point of view. We demonstrated therefore that chirality introduced to the $(R_2N)_2PO^-$ ion does indeed, albeit with rather poor stereoselectivity, induce chirality at the alcohol centre in the epoxide ring opened product.

The protons of the cyclohexane rings in all compounds involved in this part have been assigned in the experimental section using the notation indicated in figure 16.




SS




RR

**Figure 16**

## MECHANISTIC STUDIES:

### Fragmentation of 2-acyloxyalkylphosphonates

### Synthesis of the substrates

#### i. ß-ketophosphonates

As indicated in the introduction, we intended to access the ß-trifluoroacetoxyphosphonate system via the corresponding ß-ketophosphonates. As we wanted a high boiling olefinic product from the envisaged Conant-Swan fragmentation, we considered as first target the compound $PhCH_2CH_2C(O)CH_2P(O)(OEt)_2$ since a literature procedure[11] claimed the product could be obtained by alkylation of $CH_3C(O)CH_2P(O)(OEt)_2$, (eq. 1).

$$CH_3C(O)CH_2P(O)(OEt)_2 \xrightarrow[\text{2. } Bu^nLi \\ \text{3. } PhCH_2Cl \\ \text{4. } H^+]{\text{1. NaH}} PhCH_2CH_2C(O)CH_2P(O)(OEt)_2 \qquad (1)$$

Our first aim was thus $CH_3C(O)CH_2P(O)(OEt)_2$, which was accordingly prepared as indicated in equation 2.

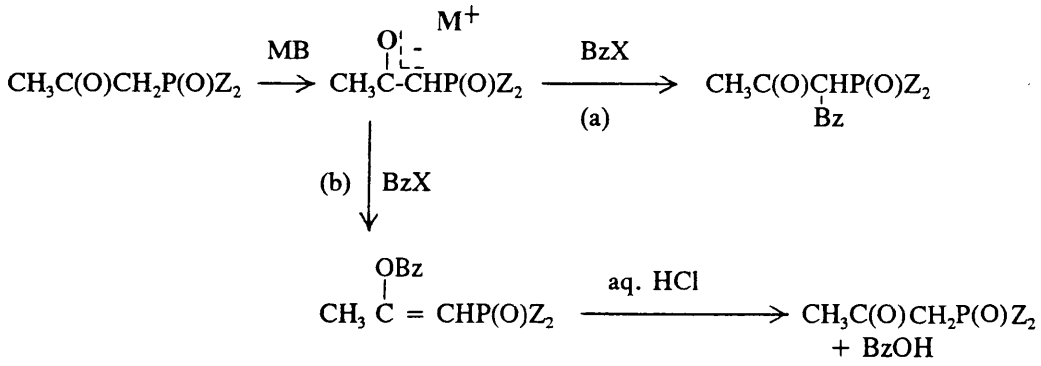
$$CH_3P(O)(OEt)_2 \xrightarrow[\text{2. AcOEt}]{\text{1. } Bu^nLi} CH_3C(O)CH_2P(O)(OEt)_2 \qquad (2)$$

10

However, when we attempted the reaction represented by equation 1, considerable amounts of starting material was recovered. We thus attempted to alkylate the mono-anion of $CH_3C(O)CH_2P(O)(OEt)_2$ rather than the dianion, (eq. 3).

$$CH_3C(O)\bar{C}HP(O)(OEt)_2 \xrightarrow{PhCH_2Cl} CH_3C(O)CH(PhCH_2)P(O)(OEt)_2 \qquad (3)$$

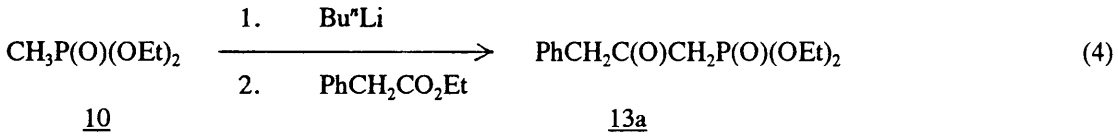
If the mono-anion of $CH_3C(O)CH_2P(O)(OEt)_2$ is generated using NaH at room temperature the desired product, together with starting material, is obtained. If the anion is generated at -94°C using LDA or *n*-butyllithium, reaction with benzyl bromide or chloride returns only starting material. The results can be rationalized as in scheme 1.




**Scheme 1**

The position of attack by ambident nucleophiles like the above enolate anion has been the subject of numerous articles and reviews.[121-123] It appears that path (a) is followed when M = Na and path (b) when M = Li, temperature effects also being important.

Due to the above difficulties we decided to change our target and to use the reaction represented by equation 4 to prepare 13a.




10 13a (4)

This also proved to be unsuccessful due to the formation of considerable amounts of unknown side-products. The desired products, 13, could however be obtained in high yields by using a procedure developed in the laboraties of Savignac[124] and represented by equation 5.

$$CH_3P(O)(OR')_2 \xrightarrow[2.\ CuI]{1.\ Bu^nLi} RC(O)CH_2P(O)(OR')_2 \quad (5)$$
$$\xrightarrow[3.\ RCOCl]{}$$

13a - 13d

| | R | R' |
|---|---|---|
| 13a: | $PhCH_2$ | OEt |
| 13b: | $p\text{-}MeOC_6H_4CH_2$ | OEt |
| 13c: | $PhCH_2CH_2$ | OEt |
| 13d: | $PhCH_2$ | OMe |

The reaction proved to be of general utility and was used to synthesize compounds 13a - 13d. If $CH_3P(O)(NEt_2)_2$ is used in above reaction, appreciable amounts of side-products were formed. This prompted our investigation into other routes by which $PhCH_2(OH)CH_2P(O)(NEt_2)_2$, 4a, could eventually be obtained.

### ii. ß-Hydroxyalkylphosphonates

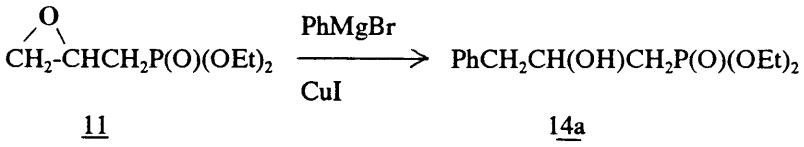
Three routes proved to be feasible to obtained ß-hydroxyalkylphosphonates. In most cases, the reduction of the corresponding ketone was used, (eq. 6).

$$RC(O)CH_2P(O)(OR')_2 \xrightarrow[EtOH]{NaBH_4} RCH(OH)CH_2P(O)(OR')_2 \quad (6)$$

13a - 13d → 14a - 14d

| | R | R' |
|---|---|---|
| 14a: | $PhCH_2$ | OEt |
| 14b: | $p\text{-}MeOC_6H_4CH_2$ | OEt |
| 14c: | $PhCH_2CH_2$ | OEt |
| 14d: | $PhCH_2$ | OMe |

In all cases the reaction proceeded smoothly and in high yield. We showed that 14a could also be obtained using an epoxide opening reaction,[125] (eq. 7).



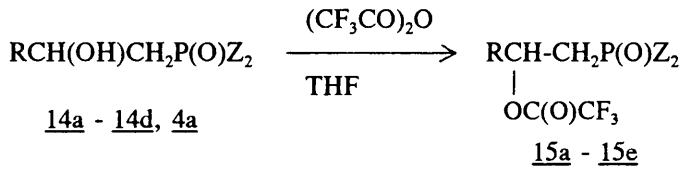
$$\underset{\underline{11}}{CH_2\text{-}CHCH_2P(O)(OEt)_2} \xrightarrow[CuI]{PhMgBr} \underset{\underline{14a}}{PhCH_2CH(OH)CH_2P(O)(OEt)_2} \qquad (7)$$

Although the yield in which 14a was obtained when using reaction 7 was high, the low yield in which 11 is obtained and the necessity of using column-chromatography to purify 14a made us abandon this approach.

The third route by which ß-hydroxyalkylphosphonates can be obtained has been discussed in the previous chapter.

### iii. ß-Acyloxyalkylphosphonates

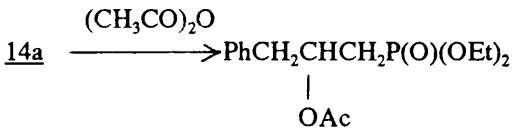
The ß-trifluoroacetoxyphosphonates, 15a - 15e, were prepared using a method developed in our laboratories,[10] (eq. 8).



$$\underset{\underline{14a}\text{ - }\underline{14d},\ \underline{4a}}{RCH(OH)CH_2P(O)Z_2} \xrightarrow[THF]{(CF_3CO)_2O} \underset{\underline{15a}\text{ - }\underline{15e}}{\begin{matrix} RCH\text{-}CH_2P(O)Z_2 \\ | \\ OC(O)CF_3 \end{matrix}} \qquad (8)$$

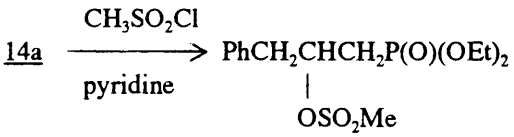
| | R | Z |
|---|---|---|
| 15a: | $PhCH_2$ | OEt |
| 15b: | $p\text{-}MeOC_6H_4CH_2$ | OEt |
| 15c: | $PhCH_2CH_2$ | OEt |
| 15d: | $PhCH_2$ | OMe |
| 15e: | $PhCH_2$ | $NEt_2$ |

The acetate, 15f, and mesylate, 15g, were prepared by standard procedures, (eq. 9 and 10).



$$\underline{14a} \xrightarrow{(CH_3CO)_2O} PhCH_2CH(OAc)CH_2P(O)(OEt)_2 \quad (9)$$

15f



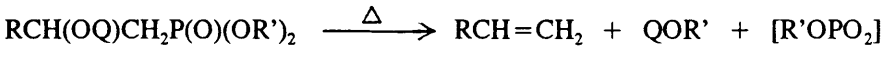
$$\underline{14a} \xrightarrow[\text{pyridine}]{CH_3SO_2Cl} PhCH_2CH(OSO_2Me)CH_2P(O)(OEt)_2 \quad (10)$$

15g

The mesylate, 15g, is thermally unstable and the crude product had to be used for further studies. The carbonyl carbon in the trifluoroacetates, 15a - 15e, is highly electrophilic and can be attacked by even weak nucleophiles, like *tert*-butanol, at higher temperatures, as will be shown later. These compounds could however be kept in a refrigerator for a week before decomposition products were observed.

### iv. Fragmentation products

For these compounds, 15a - 15g, for which the thermal fragmentation products were observed, (eq. 11),



$$\underset{\underline{15}}{RCH(OQ)CH_2P(O)(OR')_2} \xrightarrow{\Delta} \underset{\underline{16}}{RCH{=}CH_2} + \underset{\underline{17}}{QOR'} + [R'OPO_2] \quad (11)$$

| | 16 | 17 |
|---|---|---|
| 15a: | R = $PhCH_2$ (16a) | $CF_3CO_2Et$ (17a) |
| 15b: | R = p-$MeOC_6H_4CH_2$ (16b) | 17a |
| 15c: | R = $PhCH_2CH_2$ (16c) | 17a |
| 15d: | 16a | $CF_3CO_2Me$ (17b) |
| 15g: | 16a | $MeSO_3Et$ (17c) |

the olefinic, 16a - 16c, and ester, 17a - 17c, products were independently synthesized by standard procedures for comparison purposes.

Compound 18, $PhCH=CHCH_2P(O)(OEt)_2$, was prepared as possible intermediate in the fragmentation reaction of 15a, due to the known thermal 1,2-elimination of acetates, (eq. 12).

$$PhCH_2CH(OTFA)CH_2P(O)(OEt)_2 \xrightarrow{\Delta} PhCH=CHCH_2P(O)(OEt)_2 + CF_3CO_2H \qquad (12)$$

Gas chromatography and n.m.r. spectroscopy showed that 18 was not formed during the fragmentation of 15a.

**Characterization of compounds**

**i. Mass spectrometry**

**a) ß-ketophosphonates:** In all cases, for substrates 13a - 13d, molecular ion peaks were observed. The major fragmentation pathway appears to be one that involves loss of tropylium ions, (eq. 13-15).

$$PhCH_2C(O)CH_2P(O)(OR)_2^{+\cdot} \longrightarrow C_7H_7^+ \qquad (13)$$

m/z 91 (R = Et 100%; R = Me 91%)

$$PhCH_2CH_2C(O)CH_2P(O)(OEt)_2^{+\cdot} \longrightarrow C_7H_7^+ \qquad (14)$$

m/z 91 (100%)

$$p\text{-}MeOC_6H_4CH_2C(O)CH_2P(O)(OEt)_2^{+\cdot} \longrightarrow MeOC_7H_6^+ \qquad (15)$$

m/z 121 (100%)

Further fragmentation pathways differ significantly from compound to compound, and are listed below for each substrate.

<u>13a</u>: $M^{+\cdot} \xrightarrow{-C_7H_7^{\cdot}} {}^{+}O \equiv CCH_2P(O)(OEt)_2$ (16)

m/z 179 (90%)

$M^{+\cdot} \xrightarrow{-C_2H_4} PhCH_2C(O)CH_2P(O)(OEt)(OH)^{+\cdot} \xrightarrow{-C_7H_7^{\cdot}} {}^{+}O \equiv CCH_2P(O)(OEt)(OH)$ (17)

A m/z 151 (69%)

$A \xrightarrow{-C_2H_4} PhCH_2C(O)CH_2P(O)(OH)_2^{+\cdot} \xrightarrow{-C_7H_7^{\cdot}} {}^{+}O \equiv CCH_2P(O)(OH)_2$ (18)

m/z 123 (67%)

$A \xrightarrow{-PhCH_2COCH_2^{\cdot}} {}^{+}O=P(OEt)(OH)$ (19)

m/z 109 (57%)

$M^{+\cdot} \xrightarrow{-PhCH_2COCH_2^{\cdot}} {}^{+}O=P(OEt)_2$ (20)

m/z 137 (23%)

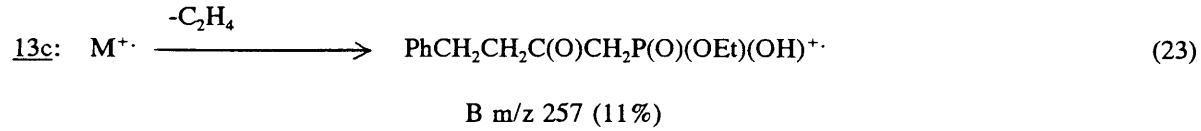
<u>13b</u>: $M^{+\cdot} \xrightarrow{-PhCH=C=O} CH_3P(O)(OEt)_2^{+\cdot}$ (21)

m/z 152 (37%)

$M^{+\cdot} \xrightarrow{-P(O)(OEt)_2^{\cdot}} MeOC_6H_4CH_2\text{-}C{=}O \longrightarrow MeOC_6H_4CH_2CH_2^{+} + CO$ (22)

$CH_2^{+}$

m/z 135 (71%)

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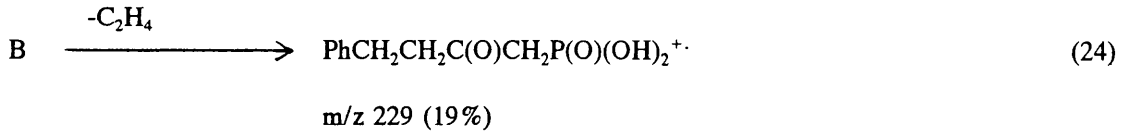


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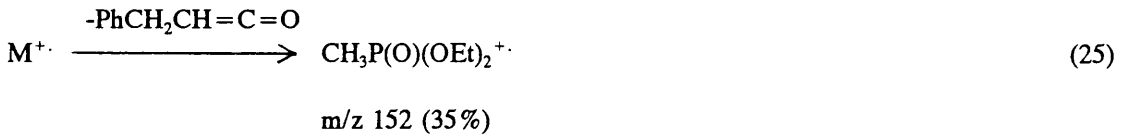


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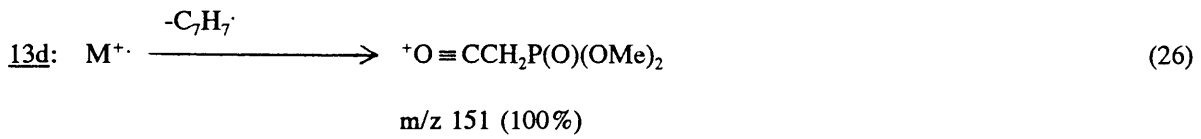


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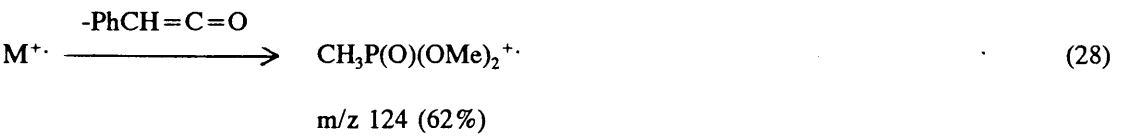
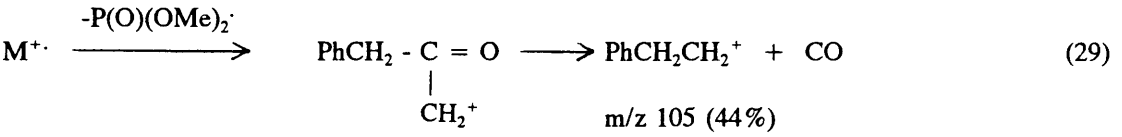
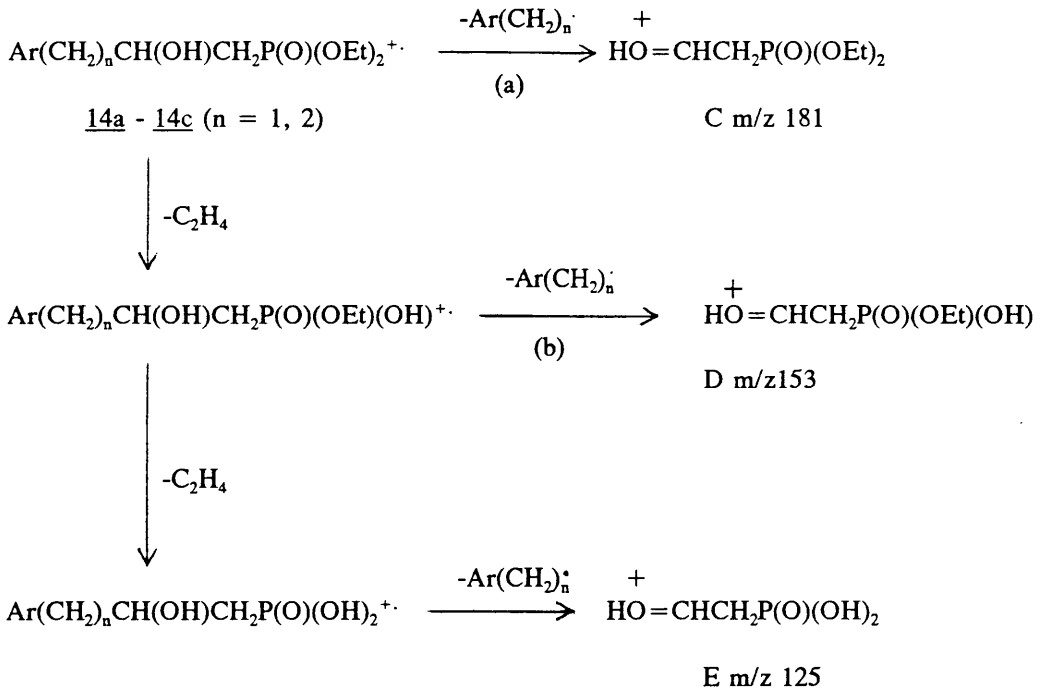



(28)

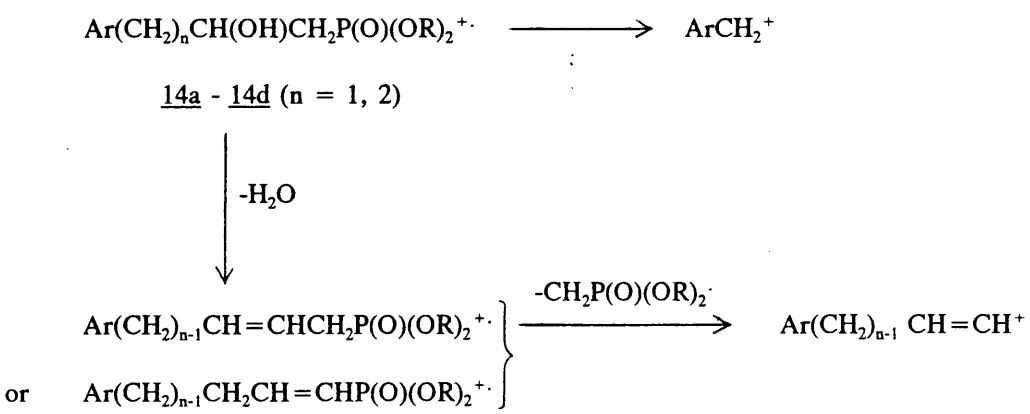



(29)

**b) ß-hydroxyphosphonates:** The most common fragmentation pathways of compounds 14a - 14d are summarized in schemes 2 and 3.




**Scheme 2**




**Scheme 3**

Obviously the pathways represented in scheme 2, except (a), do **not** operate for the methyl diester, 14d. $M^{+\cdot}$ is not always observed but $M^{+\cdot}$-$H_2O$ is. The products C, D and E in scheme 2 are normal fragments observed for alcohols.

The mass spectrum of 18 will be discussed here as it serves to confirm the pathways outlined in

scheme 3. The main pathways are summarized by equations 30 to 33.

$$M^{+\cdot} \equiv PhCH{=}CHCH_2P(O)(OEt)_2^{+\cdot} \xrightarrow{-C_2H_4} \begin{matrix} PhCH{=}CHCH_2P(O)(OEt)(OH)^{+\cdot} \\ \text{or } PhCH_2CH{=}CHP(O)(OEt)(OH)^{+\cdot} \\ F \text{ m/z } 226 \ (18\%) \end{matrix} \quad (30)$$

$$F \xrightarrow{-C_2H_4} \begin{matrix} PhCH{=}CHCH_2P(O)(OH)_2^{+\cdot} \\ \text{or } PhCH_2CH{=}CHP(O)(OH)_2^{+\cdot} \\ \text{m/z } 198 \ (27\%) \end{matrix} \quad (31)$$

$$M^{+\cdot} \xrightarrow{-P(O)(OEt)_2^{\cdot}} C_9H_9^{+} \quad \text{m/z } 117 \ (100\%) \quad (32)$$

$$M^{+\cdot} \xrightarrow{-CH_2P(O)(OEt)_2^{\cdot}} C_7H_7^{+} \quad \text{m/z } 91 \ (48\%) \quad (33)$$

**c) ß-acyloxyalkylphosphonates:** The major fragmentation pathways for compounds 15a -15g are outlined in equations 34 and 35.

$$ArCH_2CH(OQ)CH_2P(O)Z_2^{+\cdot} \equiv M^{+\cdot} \xrightarrow{-HOQ} \begin{matrix} ArCH{=}CHCH_2P(O)Z_2^{+\cdot} \\ \text{or } ArCH_2CH{=}CHP(O)Z_2^{+\cdot} \\ \Big\downarrow -P(O)Z_2^{\cdot} \\ ArCH{=}CHCH_2^{+} \\ \text{or } ArCH_2CH{=}CH^{+} \end{matrix} \quad (34)$$

$$M^{+\cdot} \longrightarrow ArCH_2^{+} \quad (35)$$

Peaks corresponding to $M^{+\cdot}$ - HOQ are always observed. Further peaks which were useful in structure determination are listed in the equations below.

<u>15a</u> and <u>15d</u>: $M^{+\cdot} \longrightarrow CF_3^+$ (36)

m/z 69 (97% and 100%)

$$M^{+\cdot} \xrightarrow{-CF_3^{\cdot}} PhCH_2CH(OC{\equiv}O)CH_2P(O)Z_2 \longrightarrow HOC{\equiv}O^+ \quad (37)$$

m/z 45 (100%; 99%)

<u>15e</u>: $M^{+\cdot} \longrightarrow NEt_2^+ + PhCH_2CH(OQ)CH_2P(O)NEt_2^{\cdot}$ (38)

m/z 72 (29%)

$$M^{+\cdot} \longrightarrow PhCH_2CH(OQ)CH_2^{\cdot} + O{=}P(NEt_2)_2^+ \quad (39)$$

m/z 191 (10%)

<u>15f</u>: $M^{+\cdot} \longrightarrow PhCH_2CH(O.)CH_2P(O)(OEt)_2$ (G) $+ CH_3C{\equiv}O^+$ (40)

m/z 43 (100%)

<u>15g</u>: $M^{+\cdot} \longrightarrow G + CH_3SO_2^+$ (41)

m/z 79 (46%)

### ii. $^{31}$P n.m.r. spectroscopy

$^{31}$P n.m.r. spectroscopy of compounds <u>13</u>, <u>14</u> and <u>15</u> always gave the expected signals. As can be expected when changes in the structure occur far from the nuclei studied, (at the aryl centre in a given series e.g. <u>13a</u> - <u>13d</u>) this doesn't affect the $^{31}$P chemical shift significantly. Thus <u>13a</u>, <u>13b</u> and <u>13c</u> have

$^{31}P$ chemical shifts 20,3, 20,3 and 20,4 respectively. The same holds true for the hydroxy compounds 14a - 14c and the esters 15a - 15c. Comparison of structurally similar diethyl and dimethyl phosphonates e.g. 14a and 14d have $^{31}P$ chemical shifts of 30,3 and 33,4 respectively. This is in accord with the better electron withdrawing ability of the OMe group when compared to the OEt group. When comparing the 2-oxo compounds to the 2-hydroxy compounds there is a downfield shift of ca. 10 ppm in going from oxo- to hydroxy-substituted phosphonates. In fact we can compare the influence of the ß-substituent on the $^{31}P$ chemical shift in the series of compounds 13a, 14a, 15a, 15f and 15g. The phosphorus nuclei are shielded in these compounds as follows: Most shielded 2-oxo (20,3 ppm) > 2-OMs (25,5) ~ 2-OTFA (25,6) > 2-OAc (27,2) > 2-OH (30,3).

There is however, an apparent anomaly as far as $^{31}P$ n.m.r. spectroscopy is concerned. Comparison of the $^{31}P$ chemical shift of 4a and 14a, and, 15a and 15e shows that phosphorus is significantly more deshielded in the amides than in the esters. This is not in accord with the fact that nitrogen groups are better electron-donors than their oxygen analogues. The phosphorus centres in aminophosphines are more shielded than in the corresponding phosphites e.g. the $^{31}P$ chemical shift of $P(NMe_2)_3$ is 123 ppm while that of $P(OMe)_3$ is 141 ppm.[126] However, comparison of the $^{31}P$ chemical shifts of $OP(NMe)_3$, (24,8 ppm), and $OP(OMe)_3$, (-2,4 ppm),[126] shows the same effect as previously mentioned. The effect is probably due to stronger resonance interactions of the $R_2N$ groups with the phosphorus atom, which in turn modify the bond order of the phosphoryl group, P=O.

### iii. $^{1}H$ n.m.r. spectroscopy

The $^{1}H$ n.m.r. spectra of compounds 13a - 13d showed no unusual features. These compounds also don't contain any diastereotopic groups, which are again characteristic of the $^{1}H$ and $^{13}C$ n.m.r. spectra of compounds 14a - 14d and 15a - 15g due to the chiral centre ß to phosphorus in these compounds. The $^{1}H$ n.m.r. spectrum of 15a is shown in figure 2 as an example.

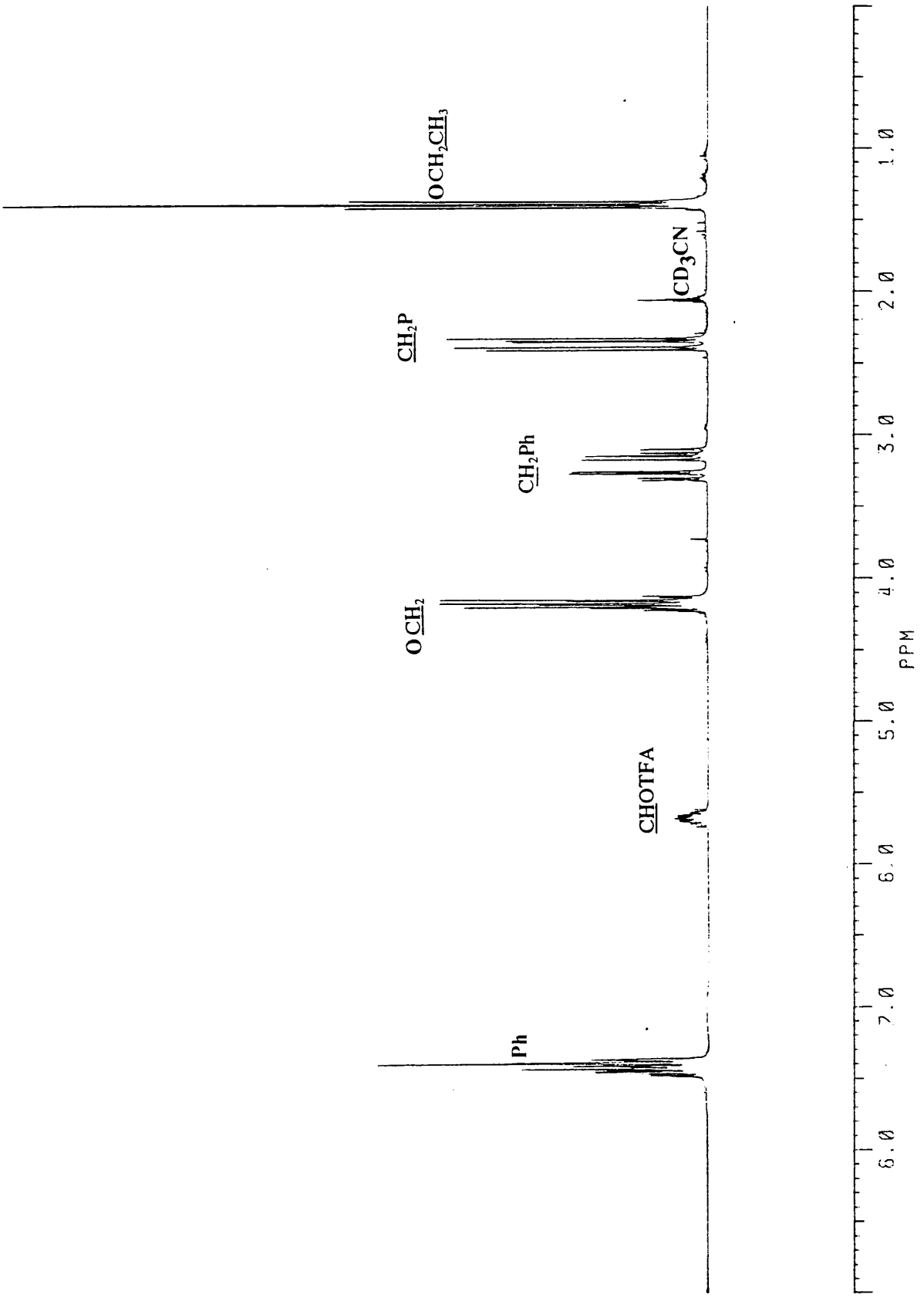
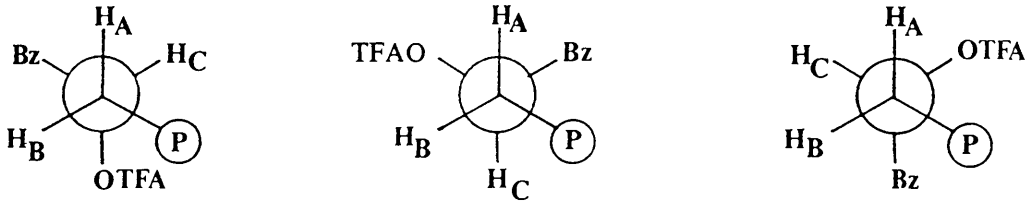



Figure 2: $^{1}H$ n.m.r. spectrum of 15a

Again, if the required coupling constants can be extracted from the $^1$H n.m.r. spectra, calculations using the Haasnoot equation can be done. However, the effect of structural features and external factors e.g. solvent and the presence of metal ions on the conformation of ß-hydroxyphosphonates very similar to compounds 14a - 14d, has been extensively studied in our laboratories.[116] Compounds of type 15 were not included in this study and we required an indication of the spatial proximity of the ß-oxyester and phoshorus groups as part of the study of the fragmentation reaction of compounds 15. Calculation for 15a gave the population of conformations I, II and III, (figure 3; (P) = $P(O)(OEt)_2$; Newman projections viewed from $C_\alpha$ to $C_ß$), as 45%, 32% and 22% respectively.




I II III

**Figure 3**

Clearly the absence of hydrogen bonding allows 15a much more conformational freedom than is the case for the corresponding ß-hydroxy derivative. Important is that at least 67% of the population has a conformation in which the ß-oxyester group is in a gauche relationship to the phosphorus group.

A characteristic feature of the $^1$H n.m.r spectra of 15a - 15d, the ß-trifluoroacetates, is the low field at which the ß-CH proton resonates - typically 5,2 - 5,4 ppm. This clearly illustrates the powerful electron withdrawing ability of the trifluoroacetoxy group.

### iv. $^{13}$C n.m.r. spectroscopy

The diastereotopicity of carbon atoms in the ethyl and methyl chains of the phosphorus ester function is

again an important feature of the $^{13}C$ n.m.r. spectra of compounds of the type 14 (ß-hydroxyphosphonates) and 15 (ß-acyloxyphosphonates). Interesting are the quartets observed for both the CO and $CF_3$ carbons in the trifluoroacetates, 15a - 15e, as a result of C-F coupling. The $CF_3$ area of the $^{13}C$ n.m.r. spectrum of 15c is shown in figure 4.

## Mechanistic studies

We first observed the fragmentation reaction of 15a, when we attempted to distill 15a from the mixture in which it had been formed, and instead observed allylbenzene and ethyl trifluoroacetate in the receiving flask. Since some trifluoroacetic acid was then present in the product we initially considered the possibility that the reaction involves an acid catalyzed reaction of either the alcohol 14a or of 15a itself. A sample of the ß-hydroxyphosphonate, 14a, as a $CF_3CO_2D$ solution was prepared in a n.m.r. tube. After 69 hours $^{31}P$ and $^{1}H$ n.m.r. spectra showed the ß-trifluoroacetoxyphosphonate, 15a, to be the only phosphorus containing product present. 15a is, of course formed in this experiment by direct esterification of 14a by the sufficiently strong acid i.e. trifluoroacetic acid. No fragmentation products were, however, observed. Heating the sample at 70°C for 44 hours showed no further change, so clearly acid catalyzed reactions of 14a or 15a were not responsible for the observed fragmentation products. Repetition of the original experiment still gave allylbenzene and ethyl trifluoroacetate in the receiving flask. As 15a was obtained by first evaporating solvent on a rotary evaporator, and then distilling the product, it became clear that the factors required for the fragmentation are high temperatures and possibly the presence of a solvent.

We proposed four different possible mechanisms by which the fragmentation could take place. These are shown in the equations below, (eq. 42-46). Furtheron these mechanisms will only be referred to as mechanism A, B, C or D.

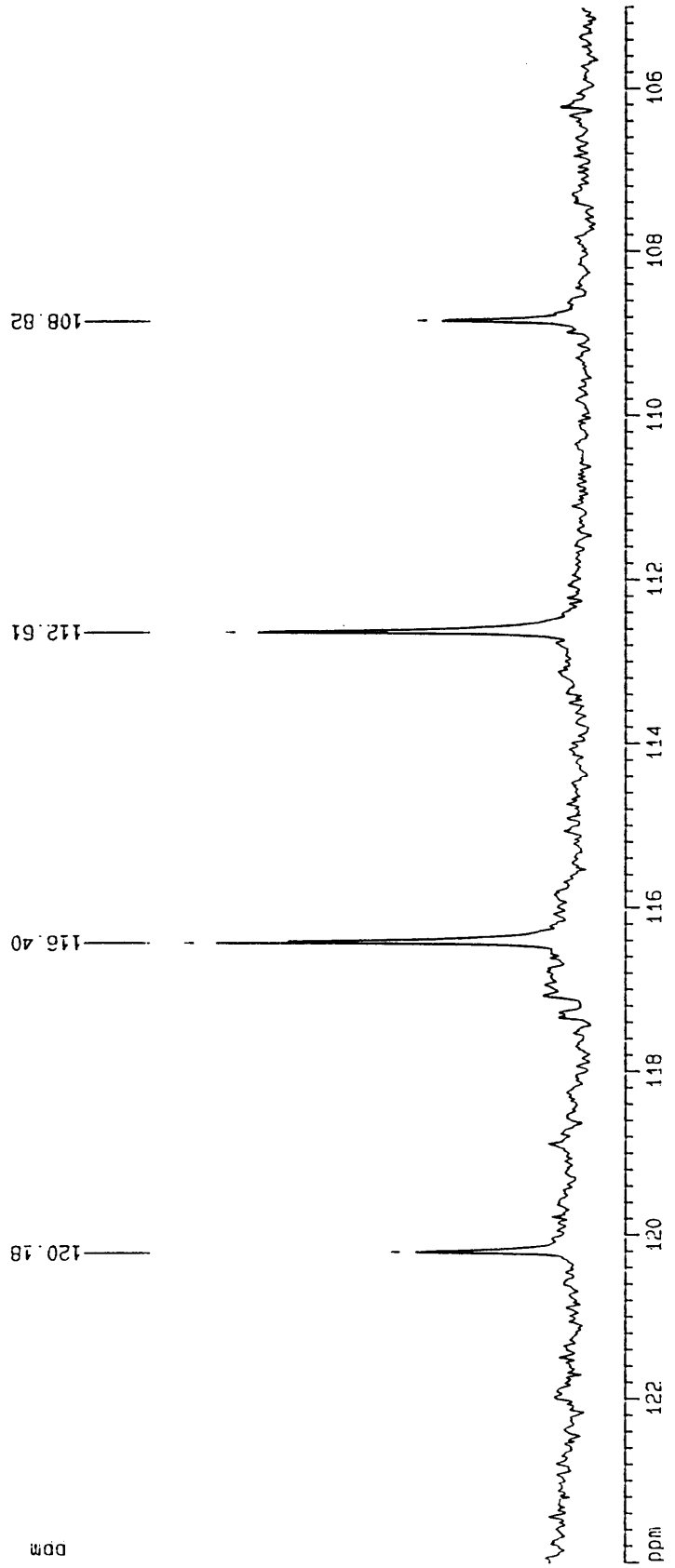
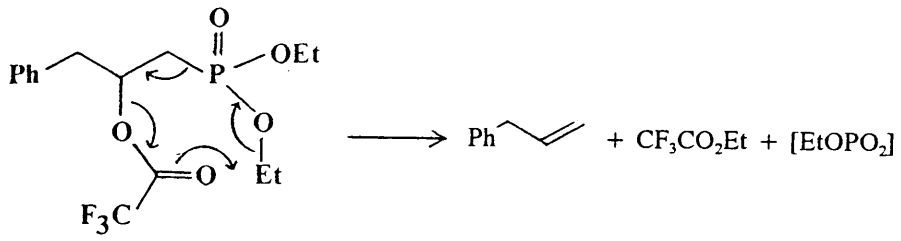


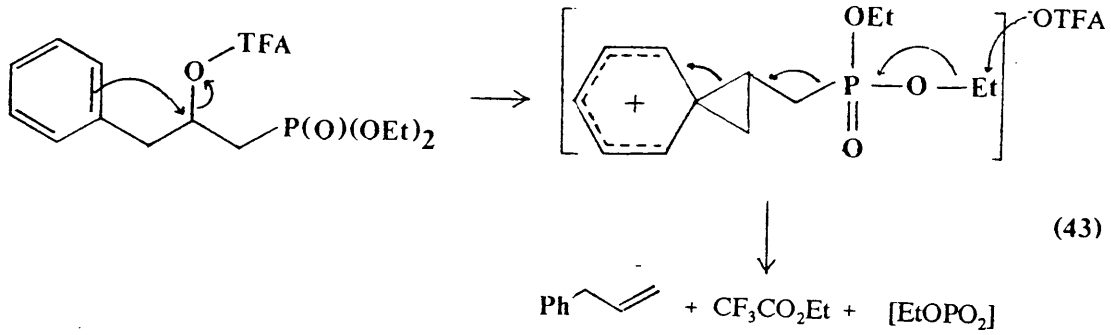

Figure 4: $CF_3$ area of the $^{13}C$ n.m.r. spectrum of 15c

A



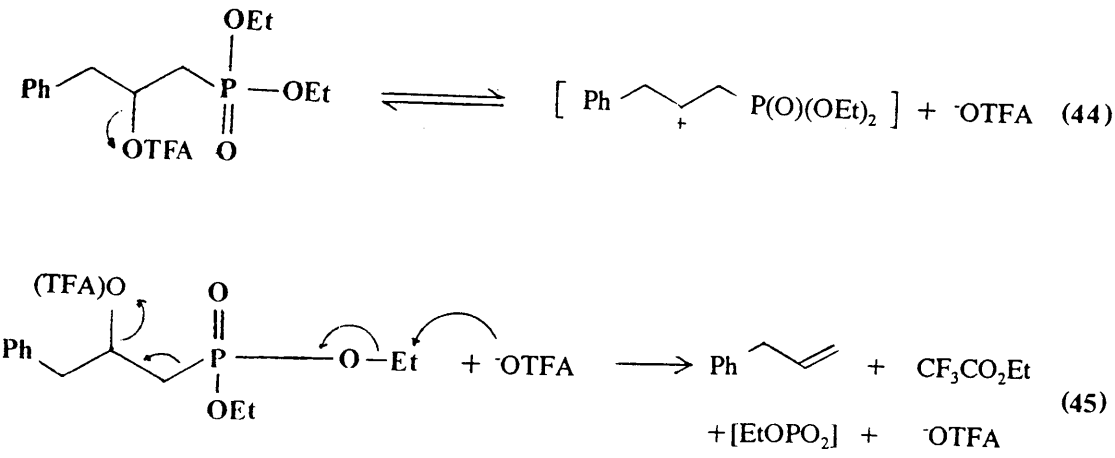

(42)

B




(43)

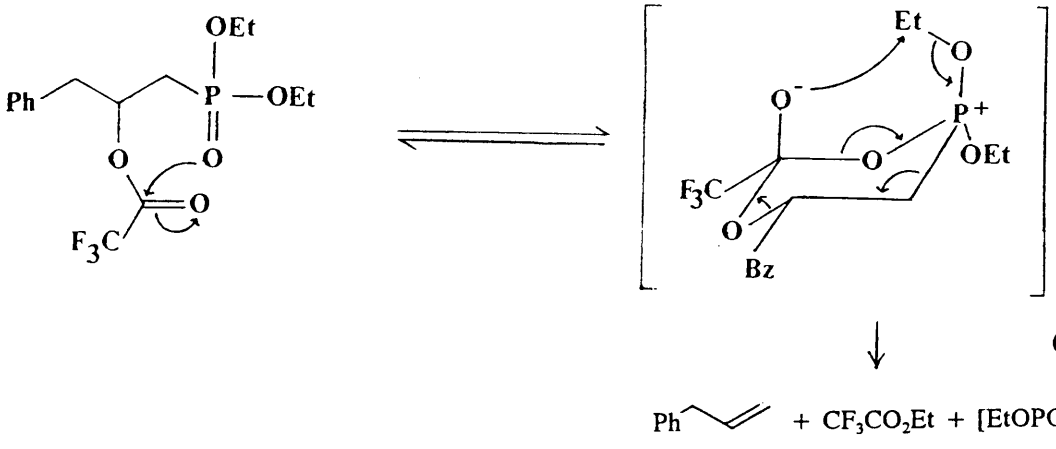
C




(44)

(45)

D




(46)

We also had to consider the possible involvement of the styrene derivative $PhCH=CHCH_2P(O)(OEt)_2$, 18, as intermediate in some way, due to the known thermal fragmentation reactions of acetates[127] previously mentioned. The substrates, of which the syntheses has already been discussed, had thus been prepared in order to differentiate between the above mentioned mechanisms. The kinetics of fragmentation of compounds 15a - 15g were studied using gas-chromatography as analytical technique.

A typical kinetic run will be described here rather than in the experimental section as several points about the method have to be discussed. Special micro test-tubes, 2 mm in diameter and 2 cm long, were used. Several of these, typically 12, would be sealed with rubber septa. A concentrated solution of the required substrate in a given solvent was prepared and a few drops of this solution injected into each micro test-tube. One of the test-tubes would be inserted into an oilbath at the required temperature for ca. 15 minutes and then dropped into ice-water. Analysis of the contents of this test-tube and the original solution by gas-chromatography would enable a rough estimate of $t_{1/2}$ of the reaction to be made. With this information the time intervals at which tubes should be removed from the oilbath could be calculated. The tubes were placed in a rack which allows the bottom halves of the tubes to be immersed in the oilbath without immersing the top rubber sealed halves. The tubes were then heated in the oilbath and at the previously estimated time intervals, a vial was quickly removed and cooled in ice-water. The contents was then analysed by gas-chromatography. The vial was not opened but the contents withdrawn with the GC syringe prior to injection into the gas-chromatograph. A value for k was then calculated as will be described.

The points to be noted are:

a) First order kinetics are observed. $k_{obs}$ is obtained from a least squares fitting of a plot of $\ln (X_0/X_t)$ versus t, i.e. $\ln(X_0/X_t) = k_{obs}\, t$. $X_0$ is the ratio of the area of the peak of the substrate to the area of the peak of the solvent in the gas-chromatogram of the original solution. $X_t$ is the same ratio for the contents of a tube removed from the oilbath after time t has elapsed.

b) The relative peak areas of the substrate and the solvent were used to determine the rate constant as this eliminated the need for using standard solutions of exact known concentration.

c) Very concentrated solutions were used as we wanted, for accuracy purposes, changes in the peak area of the peak in question to be comparable with that of the solvent.

d) As mentioned, for those compounds, 15a - 15g, for which the fragmentation reaction does take place, the olefinic and ester products were independently synthesized. The presence of these products in the fragmentation mixture was therefore confirmed by injecting the authentic samples into the gas-chromatograph.

e) The relative yields of the olefinic and ester products could not be determined accurately from the gas-chromatogram as it is likely that some of these volatile products can be lost through the puncture hole in the septum of the test-tubes at the high temperatures (typically 190 - 200°C) at which the kinetic runs are conducted.

f) The presence of the ester and olefinic products were further confirmed by subjecting the contents of one of the test-tubes to n.m.r. spectroscopy.

g) With care the temperature of the oilbath could be maintained within a two degree range throughout a run. At the high temperatures used this should not seriously influence the kinetic plots obtained.

h) The contents of each test tube was injected into the gas-chromatograph three times and the average value of the ratio of peak areas used.

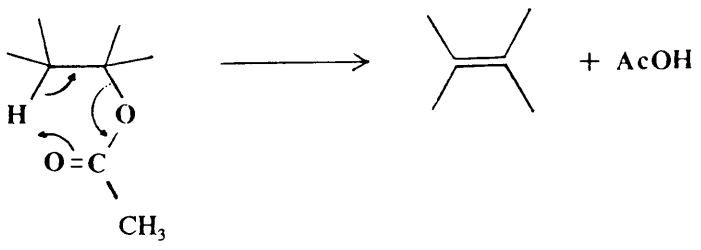
Despite this being a "rough-and-ready" procedure, excellent first order kinetic plots were obtained, with the correlation coefficients, r, generally having values larger than 0,99. Typical chromatograms obtained

during a kinetic run are shown in figure 5. A table of the retention times of substrates, solvents and products can be found in the experimental section. The kinetic results are listed in table 1.

Table 1: Table of rate constants, $k_{obs}$, for the fragmentation of various substrates in various solvents and at various temperatures. $k_{rel}$ is calculated using $k_{obs}$ for the fragmentation of 15a in sulfolane at 195°C as reference. r is the correlation coefficient of the least squares fitting used to obtain $k_{obs}$.

| Compound | Solvent | Temperature/°C | $10^4 \times k_{obs}/s^{-1}$ | $k_{rel}$ | r |
|---|---|---|---|---|---|
| 15a | Diglyme | 162 | 0,21 | 0,06 | 0,976 |
| 15a | Sulfolane | 178 | 2,35 | 0,69 | 0,993 |
| 15a | Sulfolane | 195 | 3,41 | 1,0 | 0,991 |
| 15a | Sulfolane | 212 | 14,8 | 4,3 | 0,991 |
| 15a | Sulfolane satd. NaI | 195 | 8,34 | 2,4 | 0,998 |
| 15b | Sulfolane | 195 | 4,69 | 1,4 | 0,993 |
| 15c | Sulfolane | 195 | 3,96 | 1,2 | 0,997 |
| 15d | Sulfolane | 195 | 10,2 | 2,9 | 0,995 |
| 15f | Sulfolane | 195 | ≤0,73 | ≤0,2 | 0,998 |
| 15g | Sulfolane | 192 | 200 | 59 | 0,993 |
| 15a | Sulfolane satd. LiF | 192 | 10,2 | 3,0 | 0,999 |

Acetates undergo thermal fragmentation reactions following the mechanism shown in equation 47.[127]




(47)


i. Sulfolane

ii. 15a


i. $CF_3CO_2Et$

ii. Allylbenzene

iii. Sulfolane

iv. 15a


i. $CF_3CO_2Et$

ii. Allylbenzene

iii. Sulfolane

iv. 15a

Figure 5: Chromatograms obtained during the fragmentation of 15a in sulfolane at 178-9°C. Column stationary phase; SE30. Oven temperature; 180°C. Carrier gas; Nitrogen 1 $kg.cm^{-3}$.

a) Initial solution, t = 0. b) t = 3 300 s. c) t = 6 000 s.

Typically these reactions are carried out at very high temperatures, 300-500°C, while our kinetic studies were done mostly at 190-200°C. We could, however, not simply preclude the possibility that this reaction takes place for 15a to give 18, either as stable product or as intermediate in the observed fragmentation of 15a, (eq. 48).

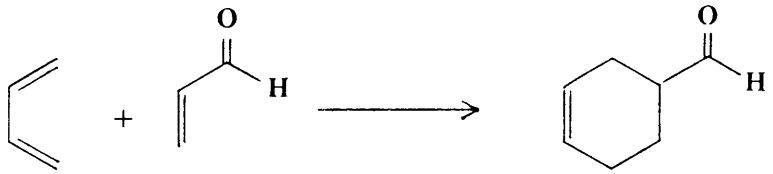
$$\underset{\text{15a}}{PhCH_2CH(OTFA)CH_2P(O)(OEt)_2} \longrightarrow \underset{\text{18}}{PhCH=CHCH_2P(O)(OEt)_2} \qquad (48)$$

18 was therefore independently prepared from triethyl phosphite and cinnamyl bromide. In none of the fragmentation mixtures could 18 be observed in the gas-chromatograms or $^{31}P$ n.m.r. spectra. 18 is thus, under the conditions used, not formed as intermediate in the fragmentation reaction of 15a, nor as product in a competitive reaction to the fragmentation of 15a.

The concerted mechanism A should be characterized by a large negative entropy of activation as demanded by a more rigid arrangement of atoms in the transition state. Several known concerted reactions do exhibit such negative entropies of activation. The acetate fragmentation represented by equation 47 typically have $\Delta S^{\neq}$ = -3 to -5 eu.[127] Pyrolysis of sulfoxides, (eq. 49), has $\Delta S^{\neq}$ = -12 to -15 eu.[128]


$$+ \quad \text{R-S-OH} \qquad (49)$$

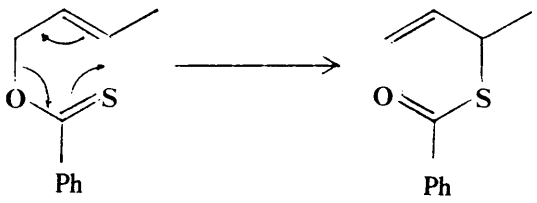
We can also compare our reaction with the Diels-Alder reaction which exhibits very large negative entropies of activation, e.g. the reaction in equation 50 has $\Delta S^{\neq}$ = -35 eu.[129]



(50)

Using the data in table 1 and the Arrhenius equation we have calculated the entropy of activation for the fragmentation of 15a to be $\Delta S^{\neq}$ = -103 $J.mol^{-1}.K^{-1}$ = -24 eu (in the temperature range 178-213°C). However, we could expect negative activation entropies for mechanism D (more rigid arrangement of atoms in the transition state than in the ground state) and for mechanism B and C (ordering of solvent molecules to accommodate charged intermediates[130]).

We would expect for mechanism A neglible solvent effects as no charge is being developed in the course of the reaction.[131] This is typical of a large variety of pericyclic reactions. For example, the reaction outlined in equation 51 exhibits only a fourfold rate increase in going from cyclohexane to acetic acid as a solvent.[132]



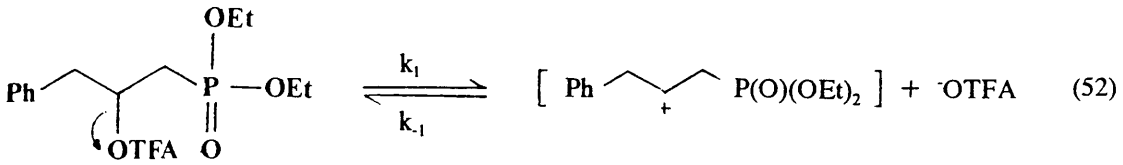
(51)

The fragmentation reaction of 15a exhibits marked solvent effects. Changing the solvent from sulfolane to diglyme results in a 17-fold decrease in the rate. In fact, no reaction was observed when 15a was refluxed in sym-tetrachloroethane for 23 hours. The difference in reactivity in sym-tetrachloroethane (bp 146°C) and in diglyme (bp 162°C) must most likely be ascribed to temperature effects. 15a was heated at the boiling point of these solvents and solvent polarity parameters indicate that sym-tetrachloroethane is slightly more polar than diglyme.[131] The increase in rate going from these solvents to the more polar sulfolane is not likely to be due to temperature effects only. Further evidence against

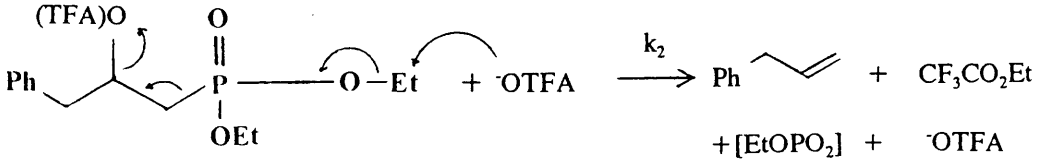
the concerted mechanism A can be found in the fact that the acetate 15f reacts at least 5 times more slowly than the trifluoroacetate 15a under the same conditions. We would expect the trifluoromethyl group to be more electronwithdrawing than the methyl group and thus the π-electrons in the carbonyl bond should be less available in the trifluoroacetate than in the acetate. In the case such a concerted mechanism is operating we would thus expect the acetate to react faster than the trifluoroacetate. We believe that mechanism A is therefore not responsible for the fragmentation reaction of 15a.

Mechanism B, that is, the one involving anchimeric assistance of the 3-aryl group, would be characterized by substituent effects for groups attached to the phenyl ring. Groups on the aromatic ring capable of stabilizing the developing positive charge on the ring should accelerate the reaction. If mechanism B were operating we would expect the p-methoxy-substituted derivate 15b to react much faster than the unsubstituted derivative 15a.* The absence of any significant effects on the rate for the p-methoxy-substituted compound thus precludes this mechanism. This is confirmed by the fact that 15c, with an extra methylene group between the aryl ring and acyl-bearing carbon, reacts at a similar rate to 15a and 15b. Anchimeric assistance in 15c is highly improbable.

For the carbocationic mechanism C, we can have either the ionization step or the fragmentation step rate determining, (eq. 52 and 53).




(52)

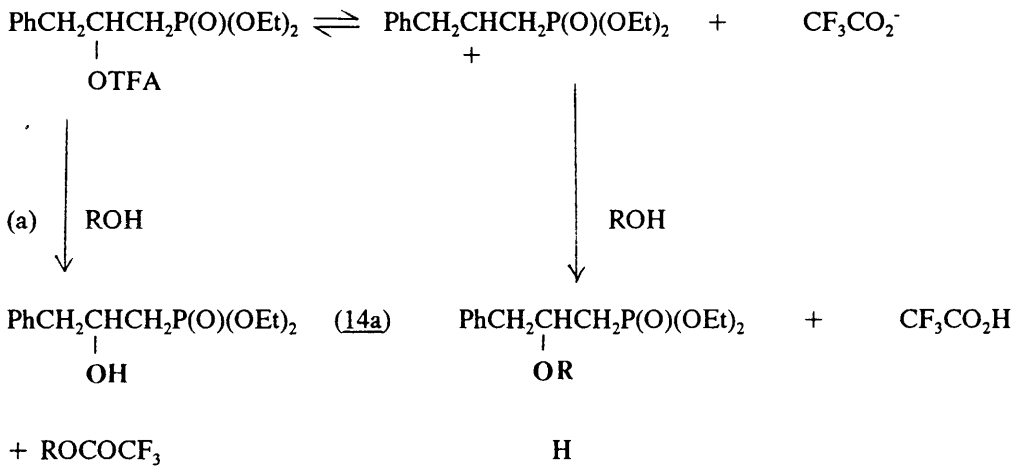



(53)

* In a related system, in which the anchimeric assistance of the 2-arylgroup was responsible for the fragmentation, the p-methoxyphenyl substrate was found to be ca. hundred times more reactive than the phenyl derivative.[53]

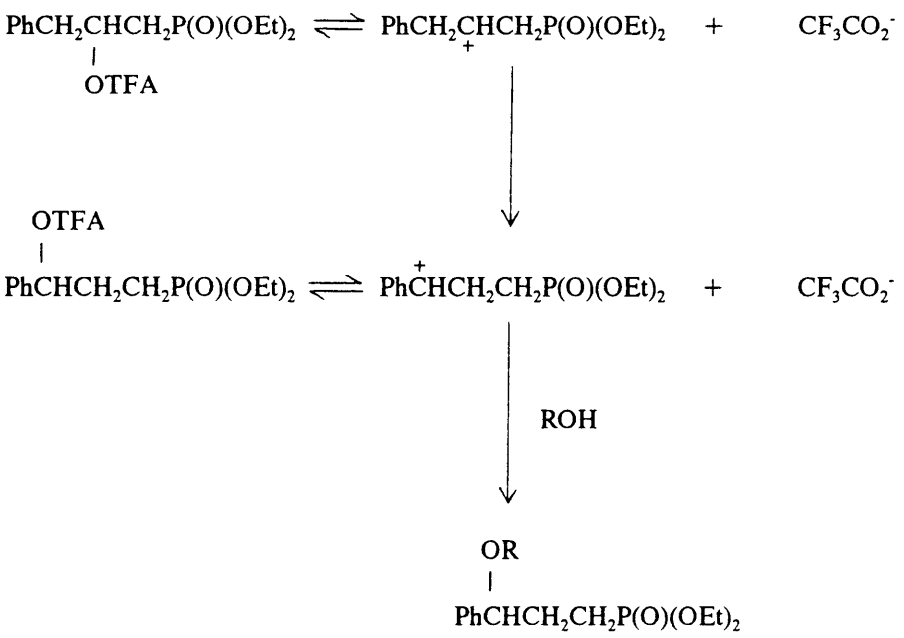
If the second step is rate determining we would expect the addition of an external nucleophile to accelerate the reaction. In the presence of sodium iodide, which is known to be an excellent nucleophile for dealkylation of phosphonic esters, the rate of fragmentation of 15a is not significantly increased. We could also expect for such a mechanism a rate increase in going from the diethyl ester, 15a, to the dimethyl ester, 15d, as it is known that dealkylation of phosphonic methyl esters proceeds more smoothly than that of the corresponding ethyl esters. That no such rate increase is observed also serves to eliminate mechanism C having the second step rate determining.

Mechanism C having the first step rate determining can be discounted on the following grounds. Mechanism C, which is in fact, an "open carbocation" version of B, should still have the p-methoxy-substituted substrate, 15b, more reactive than 15a. Another experiment gives additional evidence against mechanism C. In a protic, nucleophilic solvent we can expect the reaction scheme outlined below, (scheme 4).




**Scheme 4**

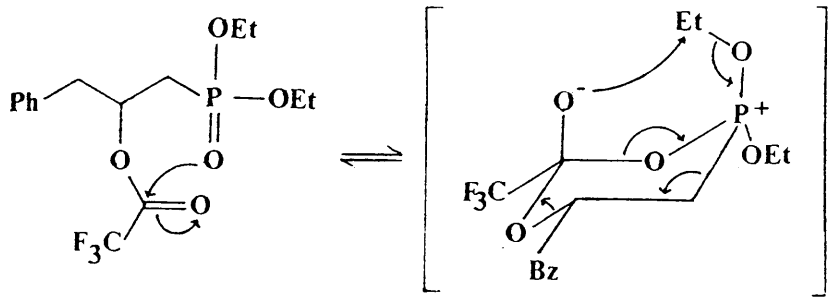
We would expect transesterification, (a), but we should also obtain some of the ether product, H, formed by trapping of the carbocation by the solvent. We can also envisage the following rearrangement, (scheme 5), to be operating.




**Scheme 5**

When 15a was heated under reflux in isoamyl alcohol, only alcohol 14a was obtained. The absence of the other products expected in schemes 4 and 5 rules out the ionic mechanism C.

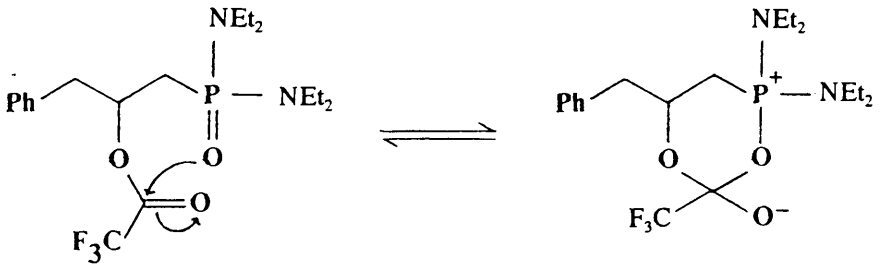
By elimination, we are left with mechanism D, (eq. 54), which is in accord with all the known experimental facts.




(54)

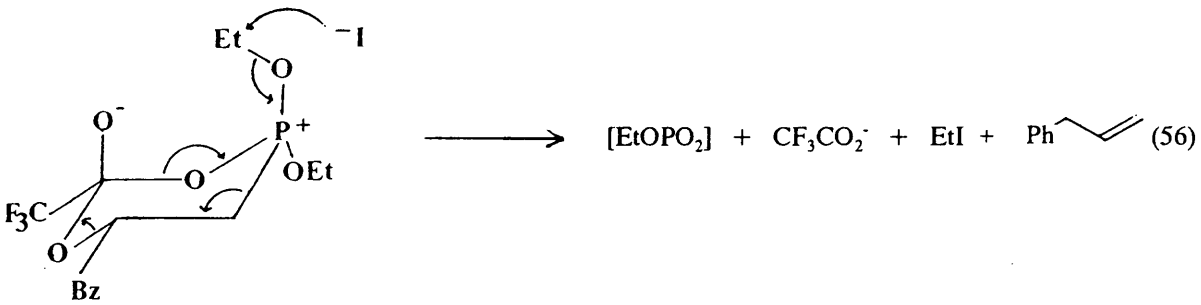
The second step cannot be rate determining as the dimethyl ester, 15d, does not react significantly faster than the diethyl ester, 15a. The intramolecular dealkylation should proceed more smoothly for the methyl ester. The first step is thus rate determining. For this mechanism we should expect a negative entropy of activation due to the rigid cyclic transition state. This is, indeed observed. Polar solvents should stabilize the developing charges in the transition state and thus enhance the rate. The aryl centre is not

involved in the bond-making and breaking sequences and changes here should not affect the rate. The phosphonic diamide, 15e, does not undergo this fragmentation, in accord with the fact that nucleophilic dealkylation of phosphoric amides does not normally take place. 15e can thus form the cyclic intermediate, but this cannot react further and returns to the uncharged open chain compound, (eq. 55).




(55)

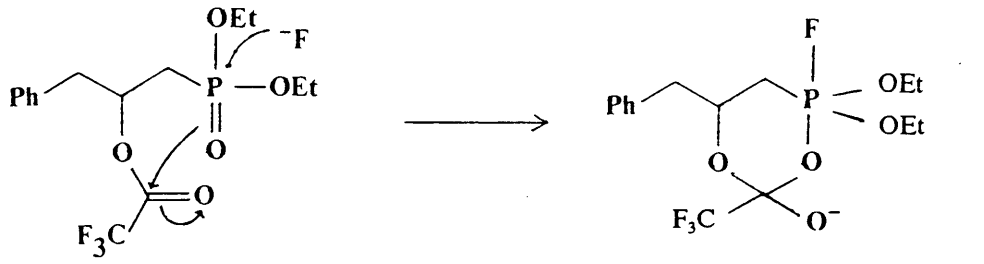
The most dramatic rate changes occur when the nature of the ß-acyloxy group is changed. The rate constant obtained for the fragmentation of 15f (OAc = OCOMe) represents an upper limit as some other decomposition reactions contribute to the decay of the substrate, while that obtained for 15g (OAc = $OSO_2Me$) is only approximate as the substrate fragments so fast that the applied experimental procedure is not too accurate. Nonetheless, the rate increases rapidly in going from the acetate to the trifluoroacetate and further to the mesylate. The increase in going from the acetate to the trifluoroacetate can be explained in terms of mechanism D. The carbonyl carbon of the trifluoroacetate should be more electrophilic than that of the acetate due to the greater electronwithdrawing ability of the trifluoromethyl group when compared to the methyl group. Intramolecular nucleophilic attack by phosphoryl oxygen should therefore occur faster in the trifluoroacetate and thus the observed rate increase. The electrophilicity of the sulfur centre in the mesylate is difficult to correlate with that of the carbonyl carbon in the acetates. Electrophilicity scale are limited and cannot be taken too rigorously. The observed rate increase may also be tied in to the relative softness of the sulfur centre in comparison to the carbonyl carbon of the acetates.[133] We expect iodide to accelerate the second step as indicated in equation 56.




(56)

That no significant rate increase is observed when 15a is decomposed in the presence of sodium iodide confirms that the second step is not rate-determining.

Due to the fluoride anion's known affinity for phosphorus we expected it to enhance the rate in the manner outlined in equation 57.




(57)

The small rate increase in the decomposition of 15a in the presence of lithium fluoride we ascribe to nucleophilic attack of the fluoride anion on phosphorus resulting in an increase of the nucleophilic character of the phosphoryl oxygen and thus enhancing the rate of the cyclization step.

The last remaining problem is the direct trapping of the metaphosphate ester, $[EtOPO_2]$. In the presence of alcohols transesterification of the substrate predominates over fragmentation, e.g. for 15a, (eq. 58).

$$PhCH_2CH(OTFA)CH_2P(O)(OEt)_2 \xrightarrow{ROH} PhCH_2CH(OH)CH_2P(O)(OEt)_2 + ROTFA \quad (58)$$

Among the alcohols used for this purpose was the poorly nucleophilic *tert*-butanol and isopropyl alcohol. The carbonyl centre must therefore be highly electrophilic and thus it should be difficult to trap the metaphosphate with nucleophiles. Fluoride was, however, succesfully used to trap the metaphosphate formed, (eq. 59).

$$F^- + [EtOPO_2] \longrightarrow (EtO)P(O)(F)O^- \quad (59)$$

That fluoride indeed traps ethyl metaphosphate was confirmed by decomposition of 15a in sulfolane at 210°C and in the presence of lithium fluoride. $^{31}P$, $^{19}F$ and $^{1}H$ n.m.r. spectra of the decomposition mixture was obtained. To the sample authentic N-methylanilinium ethylphosphorofluoridate [(EtO)P(O)-(F)O$^-$ $Me\overset{+}{N}H_2Ph$, 19) was added. The n.m.r. spectra were then used to confirm the presence of (EtO)P(O)(F)O$^-$ in the original sample. This represents the first example in which a metaphosphate has been trapped by the fluoride anion.

Ehtyl metaphosphate, [$EtOPO_2$], was also determined indirectly. The reaction mixture obtained after fragmentation of 15a was treated with NaOD/$D_2O$, and the aqueous extract was examined by n.m.r. ($^{31}P$ and $^{1}H$) spectroscopy. Addition of a sample of the authentic anilinium salt of ethyl phosphate resulted in no new signals, except in the aromatic region of the $^{1}H$ n.m.r. spectrum. There was, however, an increase in the intensity of a single signal at $\delta$ 1,2 ppm in the the $^{31}P$ n.m.r. spectrum and a multiplet at $\delta$ 3,86 ppm and a triplet at $\delta$ 1,19 ppm in the $^{1}H$ n.m.r. spectrum. It is clear that the phosphate monoester is formed from the ethyl metaphosphate derived polymeric product initially formed, (eq. 60).

$$\underline{15a} \longrightarrow [EtOPO_2] \longrightarrow (EtO\text{-}PO_2)_n \xrightarrow{D_2O/OD^-} EtOPO_3D^- \qquad (60)$$

We thus propose that the thermal fragmentation of the esters of ß-acyloxyalkylphosphonic acids proceeds via mechanism D. In the family of metaphosphate producing reactions, this is a novel mechanism in the sense that the alkyl group of the phosphonic ester has to be transferred intramolecularly to another nucleophilic centre in order that metaphosphate extrusion can take place.

# CONCLUSIONS AND SUGGESTIONS

We have succeeded in developing effective synthetic procedures for alkyl- and ß-hydroxyalkylphosphonic diamides. Anions of the type $(NR_2)_2PO^-$ have been found to be excellent nucleophiles in reactions with carbon electrophiles. In our work we studied the reactivity of such anions toward alkyl halides and epoxides, while Spilling *et al.*[95] has studied the reactivity towards aldehydes. These nucleophilic reagents make phosphonic diamides of various types more readily accessible and in so doing open up the chemistry of these compounds.

The $(Et_2N)_2PO^-$ ion reacts smoothly with primary bromides and iodides to give alkylphosphonic diamides. The reaction with primary chlorides and secondary halides appear to be less efficient. With a wide range of epoxides, ß-hydroxyalkylphosphonic diamides are obtained. Only with sterically hindered epoxides the reaction fails. Conformational analysis of the ß-hydroxyalkylphosphonic diamides revealed strong conformational preferences due to intramolecular hydrogen bonding and steric interactions.

Reaction of the $(R_2N)_2PO^-$ ion with a wide range of electrophiles can be envisaged. Some of the more interesting possibilities are listed in equations 1 to 3.

$$(R_2N)_2PO^- + R'COX \longrightarrow R'C(O)P(O)(NR_2)_2 \qquad (1)$$

$$(R_2N)_2PO^- + R'R''C{=}NR''' \longrightarrow R'R''C(NHR''')\text{-}P(O)(NR_2)_2 \qquad (2)$$

$$(R_2N)_2PO^- + \text{(N-heterocycle, R')} \longrightarrow R'CH(NH_2)\text{-}CH_2P(O)(NR_2)_2 \qquad (3)$$

The products derived from reactions 2 and 3 (α- and ß-aminophosphonic derivatives) should be

interesting from a biological point of view.

We have further shown that the thermal fragmentation of ß-acyloxyalkylphosphonates proceeds with a novel rearrangement. Metaphosphate extrusion from ß-acyloxyphosphonates is preceded by alkyl migration. This represents to our knowledge the first example of metaphosphate extrusion by a different type of mechanism compared to the previously known reactions yielding metaphosphates. What is further remarkable is that the only apparent driving force for this complex set of transformations is a net entropy gain coupled with the thermodynamic stability of the metaphosphate species.

The ethyl metaphosphate generated in this reaction was trapped by fluoride. It is the first time that the fluoride ion has been used for this purpose. Clarification of the steps subsequent to cyclization is still required. It may also be interesting to see if the reaction also takes place for the corresponding sulphonate esters, (eq. 4).

(4)

# EXPERIMENTAL

Solvents and commercially available reagents were purified and dried by conventional methods before use. Reactions involving organometallic reagents were carried out under an atmosphere of dry nitrogen. Bulb-to-bulb distillations were carried out using a Buchi GKR-50 apparatus. For column-chromatography, Merck Kieselgel 60 (0,063 - 0,200 mm) was used as a stationary phase. The following deuterated solvents were used:

1. Aldrich Chloroform-d; 99,8 atom % D.
2. Merck Uvasol $D_2O$; 99,8% deuteration.
3. Akademie der Wissenschaften der DDR - Dimethyl-sulfoxid-$d_6$; 99,7% D.

N.m.r. spectra were recorded on a Brucker AC300 spectrometer using $CDCl_3$, except where indicated otherwise, and the chemical shift values are reported relative to TMS ($^1H$; $^{13}C$) and 85% $H_3PO_4$ ($^{31}P$). Mass spectra were recorded on a Varian MAT-212 double focusing direct inlet spectrometer at an ionization potential of 70eV. IR spectra were recorded on a Bomem-Michelson 100 spectrometer as $CCl_4$ solutions. Only values of selected ion peaks and IR bands most relevant to structural determinations are reported. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Optical rotation was measured on a Atago Polax-D polarimeter and refractive indices on a Atago refractometer.

## Alkylphosphonic Diamides

### N,N,N',N'-tetraethyl phosphonic diamide (1)

To a well stirred solution of diethylamine (203 mℓ; 1,96 mol) in 250 mℓ benzene was added dropwise over a period of 2 hours phosphorus trichloride (34,1 g; 0,25 mol) with cooling in an ice-bath. After

addition was complete the mixture was allowed to return to room temperature and stirred for a further 2 hours before being left to stand overnight. The mixture was filtered and the precipitate washed thoroughly with benzene. Solvent evaporation and distillation at 81-82°C/0,25 mm Hg gave hexaethylphosphorus triamide as a colourless oil (48,4 g; 0,20 mol), which was dissolved in 70 mℓ dry THF and water (3,6 mℓ; 0,20 mol) added. The mixture was stirred at room temperature for 17 hours and solvent evaporated. The residue was taken up in petroleum ether (40-60) and left in a cold room overnight. Filtration and solvent evaporation gave the diamide as a colourless oil (38 g; 77%). $n_D^{17}$ 1,4574 (Lit.[96] $n_D^{20}$ 1,4551). $^{31}$P n.m.r.: δ 0,84 (12 H; t; $J_{HH}$ 7,1 Hz; 4 x $CH_3$ of $NEt_2$); 2,87 (8 H; m; 4 x $CH_2$ of $NEt_2$); 5,64; 7,54 (1H; d; $J_{HP}$ 570 Hz; P-H).

The following phosphonic diamides were synthesized using the same general procedure, which is illustrated by the synthesis of 2a.

**N,N,N',N'-tetraethyl-P-prop-2-enylphosphonic diamide (2a)**

A solution of 1 (10 g; 52 mmol) in 70 mℓ THF was cooled to -94°C and a *n*-butyllithium solution in *n*-hexane (33 mℓ; 53 mmol) was added. The mixture was stirred at -94°C for 15 minutes. 2-Bromopropene (4,4 mℓ; 51 mmol) was added dropwise; the temperature being kept below -40°C. The mixture was allowed to warm to room temperature for 2 hours. Volatile material was evaporated and 50 mℓ water added to the residue. Extraction with ether (4 x 30 mℓ) was followed by drying ($MgSO_4$). Filtration and solvent evaporation gave the diamide as a yellow oil (9,7 g; 82%). $n_D^{17}$ 1,4732. $^{31}$P n.m.r.: δ 32,8. $^1$H n.m.r.: δ 0,85 (12 H; t; $J_{HH}$ 7,1 Hz; 4 x $CH_3$ of $NEt_2$); 2,40 (2H; dd; $J_{HP}$ 17,3 Hz; $J_{HH}$ 7,3 Hz; $\underline{CH_2}$ P); 2,83 (8 H; m; 4 x $CH_2$ of $NEt_2$); 4,91 (2H; m; $\underline{CH_2}$ = CH); 5,63 (1H; m; $CH_2$ = $\underline{CH}$). $^{13}$C n.m.r.: δ 11,5 (s; 4 x $CH_3$ of $NEt_2$); 30,5 (d, $J_{CP}$ 112 Hz; $\underline{CH_2}$P); 35,8 (s; 4 x $CH_2$ of $NEt_2$); 115,4 (d; $J_{CP}$ 12,2 Hz; $\underline{CH_2}$ = CH); 127,3 (d; $J_{CP}$ 9,1 Hz; $CH_2$ = $\underline{CH}$). m/z 232 [$M^{+\cdot}$; 3%]; 191 [$(Et_2N)_2PO^+$; 100%]; 160 [$M^{+\cdot}$ - $NEt_2^{\cdot}$; 27%]; 120 [$Et_2NPOH^+$; 29%]; 72 [$Et_2N^+$; 65%].

**N,N,N'N'-tetraethyl-P-propylphosphonic diamide (2b)**

From 1-bromopropane as for 2a. Yellow oil. Yield 75%. $n_D^{17}$ 1,4655. (Lit.[60] $n_D^{30}$ 1,4580). $^{31}P$ n.m.r.: $\delta$ 36,9. $^{1}H$ n.m.r.: $\delta$ 0,88 (3H; t; $J_{HH}$ 7,1 Hz; $\underline{CH_3}CH_2CH_2P$); 0,96 (12H; t; $J_{HH}$ 7,1 Hz; 4 x $CH_3$ of $NEt_2$); 1,54 (4 H; overlapping m; $CH_3\underline{CH_2}\underline{CH_2}P$); 2,87 (8 H; m; 4 x $CH_2$ of $NEt_2$). $^{13}C$ n.m.r.: $\delta$ 13,4 (d; $J_{CP}$ 2,5 Hz; 4 x $CH_3$ of $NEt_2$); 14,9 (d; $J_{CP}$ 18,5 Hz; $\underline{CH_3}CH_2CH_2P$); 15,1 (d; $J_{CP}$ 3,6 Hz; $CH_3\underline{CH_2}CH_2P$); 27,8 (d; $J_{CP}$ 116 Hz; $\underline{CH_2}P$); 37,7 (d; $J_{CP}$ 4,2 Hz; 4 x $CH_2$ of $NEt_2$). m/z 234 [$M^{+\cdot}$; 9%]; 191 [$(Et_2N)_2PO^+$; 22%]; 162 [$M^{+\cdot}$ - $Et_2N^{\cdot}$; 100%]; 120 [$Et_2NPOH^+$; 85%]; 72 [$Et_2N^+$; 63%].

**N,N,N',N'-tetraethyl-P-(phenylmethyl)phosphonic diamide (2c)**

From benzyl bromide as for 2a. Pale yellow oil. Yield 85%. $n_D^{17}$ 1,5186. $^{31}P$ n.m.r.: $\delta$ 32,9. $^{1}H$ n.m.r.: $\delta$ 0,93 (12 H; t; $J_{HH}$ 7,1 Hz; 4 x $CH_3$ of $NEt_2$); 2,88 (8 H; m; 4 x $CH_2$ of $NEt_2$); 3,08 (2 H; d; $J_{HP}$ 16,6 Hz; $\underline{CH_2}$ P); 7,1 - 7,4 (5 H; m; Ph). $^{13}C$ n.m.r.: $\delta$ 12,9 (s; 4 x $CH_3$ of $NEt_2$); 32,5 (d; $J_{CP}$ 110 Hz; $\underline{CH_2}$ P); 37,5 (2 x s; 4 x $CH_2$ of $NEt_2$); 125,0; 126,8 (2 x s; meta and para carbons); 128,9 (d; $J_{CP}$ 6,2 Hz; ortho carbons); 131,9 (d; $J_{CP}$ 7,3 Hz; ipso carbon). m/z 282 [$M^{+\cdot}$; 7%]; 191 [$(Et_2N)_2PO^+$; 100%]; 120 [$Et_2NPOH^+$; 12%]; 91 [$C_7H_7^+$; 82%]; 72 [$Et_2N^+$; 23%].

**N,N,N',N'-tetraethyl-P-but-2-enylphosphonic diamide (2d)**

From crotyl bromide as for 2a. Crude 78%. Yield after bulb-to-bulb "distillation" at an oven temperature of 131-3°C / 0,08 mm Hg gave pure 2d as a colourless oil. Yield 54%. $n_D^{17}$ 1,4739. $^{31}P$ n.m.r.: $\delta$ 34,4. $^{1}H$ n.m.r.: $\delta$ 0,89 (12 H; t; $J_{HH}$ 6,9 Hz; 4 x $CH_3$ of $NEt_2$); 1,48 (3 H; m; $\underline{CH_3}CH=$); 2,41 (2 H; dd; $J_{HP}$ 16,6 Hz; $J_{HH}$ 5,5 Hz; $\underline{CH_2}P$); 2,81 (8 H; m; 4 x $CH_2$ of $NEt_2$); 5,30 (2 H; m; $CH_3\underline{CH}=\underline{CH}$). $^{13}C$ n.m.r.: $\delta$ 12,9 (s; 4 x $CH_3$ of $NEt_2$); 16,7 (s; $\underline{CH_3}$ CH=); 30,4 (d; $J_{CP}$ 113 Hz; $\underline{CH_2}P$); 37,3 (d; $J_{CP}$ 3,8 Hz; 4 x $CH_2$ of $NEt_2$); 127,8 (d; $J_{CP}$ 13,1 Hz; $CH_2\underline{CH}=$ ); 129,6 (d;

$J_{CP}$ 9,3 Hz; =CHCH$_2$P). m/z 246 [$M^+$; 4%]; 191 [$(Et_2N)_2PO^+$; 100%]; 120 [$Et_2NPOH^+$; 51%]; 72 [$Et_2N^+$; 68%]; 55 [$C_4H_7^+$; 38%].

**N,N,N',N'-tetraethyl-P-methylphosphonic diamide (2e)**

From iodomethane as for 2a. Pale yellow oil. Yield 100%. $n_D^{24}$ 1,4574. $^{31}$P n.m.r.: δ 34,7. $^1$H n.m.r.: δ 0,81 (12 H; t; $J_{HH}$ 7,1 Hz; 4 x $CH_3$ of $NEt_2$); 1,15 (3 H; d; $J_{HP}$ 14,6 Hz; $CH_3$ P); 2,75 (8 H; m; 4 x $CH_2$ of $NEt_2$). $^{13}$C n.m.r.: δ 12,8 (d; $J_{CP}$ 2,7 Hz; 4 x $CH_3$ of $NEt_2$); 28,5 (d; $J_{CP}$ 87,0 Hz; $CH_3$P); 37,1 (d; $J_{CP}$ 4,6 Hz; 4 x $CH_2$ of $NEt_2$). m/z 206 [$M^+$; 25%]; 191 [$(Et_2N)_2$ $PO^+$; 23%]; 134 [$M^{+\cdot}$ - $Et_2N^+$; 100%]; 120 [$Et_2NPOH^+$; 38%]; 72 [$Et_2N^+$; 65%].

**N,N,N',N'-tetraethyl-P-(3-phenylpropyl)phosphonic diamide (2f)**

From 1-bromo-3-phenylpropane as for 2a. After column-chromatography (Eluent: benzene followed by ethanol. $R_f^{EtOH}$ 0,87) and bulb-to-bulb "distillation" at an oven temperature of 248-250°C / 0,1 mm Hg. 2f was obtained as a pale yellow oil. Yield 30%, $n_D^{24}$ 1,5019. $^{31}$P n.m.r.: δ 37,5. $^1$H n.m.r.: δ 1,01 (12 H; t; $J_{HH}$ 7,1 Hz; 4 x $CH_3$ of $NEt_2$); 1,67 (2 H; m; $CH_2$P); 1,83 (2 H; m; PhCH$_2$CH$_2$); 2,64 (2 H; t; $J_{HH}$ 7,4 Hz; PhCH$_2$); 2,87 (8 H; m; 4 x $CH_2$ of $NEt_2$); 7,05 - 7,28 (5 H; m; Ph). $^{13}$C n.m.r.: δ 13,7 (2 x s; 4 x $CH_3$ of $NEt_2$); 23,7 (d; $J_{CP}$ 3,3 Hz; PhCH$_2$CH$_2$); 25,5 (d; $J_{CP}$ 116 Hz; $CH_2$P); 36,5 (d; $J_{CP}$ 17,4 Hz; PhCH$_2$); 38,0 (2 x s; 4 x $CH_2$ of $NEt_2$); 125,4; 127,8; 128,0; 140,9 (4 x s; Ph). m/z 310 [$M^+$; 26%]; 238 [$M^{+\cdot}$ - $Et_2N^\cdot$; 24%]; 191 [$(Et_2N)_2PO^+$; 39%]; 120 [$Et_2NPOH^+$; 23%]; 91 [$C_7H_7^+$; 20%]; 72 [$Et_2N^+$; 100%].

**N,N,N',N'-tetraethyl-P-pentylphosponic diamide (2g)**

From 1-chloropentane as for 2a. After bulb-to-bulb "distillation" at an oven temperature of 162-4°C / 0,2 mm Hg, 2g was obtained as a colourless oil. Yield 16%. $n_D^{24}$ 1,4570. $^{31}$P n.m.r.: δ 37,9. $^1$H

n.m.r.: $\delta$ 0,81 (3 H; t; $J_{HH}$ 7,1 Hz; ω-$CH_3$); 0,98 (12 H; t; $J_{HH}$ 7,0 Hz; 4 x $CH_3$ of $NEt_2$); 0,95 - 1,05 (2 H; m; $CH_3\underline{CH_2}CH_2CH_2CH_2P$); 1,25 (2 H; m; $CH_3CH_2\underline{CH_2}CH_2CH_2P$); 1,48 (2 H; m; $CH_3CH_2CH_2\underline{CH_2}CH_2P$); 1,61 (2 H; m; $\underline{CH_2}P$); 3,01 (8 H; m; 4 x $CH_2$ of $NEt_2$). $^{13}C$ n.m.r: $\delta$ 13,8 (s; ω-$CH_3$); 14,0 (d; $J_{CP}$ 2,8 Hz; $CH_3\underline{CH_2}CH_2CH_2CH_2P$); 14,2 (2 x s; 4 x $CH_3$ of $NEt_2$); 21,9 (d; $J_{CP}$ 3,7 Hz; $CH_3CH_2\underline{CH_2}CH_2CH_2P$); 22,3 (s; $CH_3CH_2CH_2\underline{CH_2}CH_2P$); 26,5 (d; $J_{CP}$ 116 Hz; $\underline{CH_2}P$); 38,4 (2 x s; 4 x $CH_2$ of $NEt_2$). m/z 262 [$M^{+\cdot}$; 10%]; 191 [$(Et_2N)_2PO^+$; 46%]; 190 [$M^{+\cdot}$ -$Et_2N^{\cdot}$; 32%]; 120 [$Et_2NPOH^+$; 54%]; 72 ($Et_2N^+$; 100%].

**N,N,N',N'-tetraethyl-P-hexylphosphonic diamide (2h)**

From 1-bromohexane as for 2a. Yield 75%. $n_D^{24}$ 1,4601. $^{31}P$ n.m.r.: $\delta$ 37,9. $^1H$ n.m.r.: $\delta$ 0,77 (3 H; t; $J_{HH}$ 6,7 Hz; ω-$CH_3$); 0,98 (12 H; t; $J_{HH}$ 7,1 Hz; 4 x $CH_3$ of $NEt_2$); 1,12 - 1,68 (8 H; m; $CH_3\underline{CH_2CH_2CH_2CH_2}CH_2P$); 1,74 (2 H; dt; $J_{HH}$ 7,3 Hz; $J_{HP}$ 14,7 Hz; $\underline{CH_2}P$); 2,93 (8 H; m; 4 x $CH_2$ of $NEt_2$). $^{13}C$ n.m.r.: $\delta$ 12,6 (s; $\underline{CH_3}CH_2CH_2CH_2CH_2CH_2P$); 12,7 (d; $J_{CP}$ 2,7 Hz; $CH_3CH_2\underline{CH_2}CH_2CH_2CH_2P$); 13,0 (2 x s; 4 x $CH_3$ of $NEt_2$); 21,0 (d; $J_{CP}$ 3,6 Hz; $CH_3CH_2CH_2\underline{CH_2}CH_2CH_2P$); 21,1 (s; $CH_3CH_2CH_2CH_2\underline{CH_2}CH_2P$); 25,2 (d; $J_{CP}$ 115 Hz; $\underline{CH_2}P$); 37,2 (2 x s; 4 x $CH_2$ of $NEt_2$). m/z 276 [$M^{+\cdot}$; 19%]; 261 [$M^{+\cdot}$ - $Me^{\cdot}$; 10%]; 204 [$M^{+\cdot}$ - $Et_2N^{\cdot}$; 58%]; 191 [$(Et_2N)_2PO^+$; 26%]; 120 [$Et_2NPOH^+$; 42%]; 72 [$Et_2N^+$; 100%].

**2-Hydroxyalkylphosphonic diamides**

**1,2-Epoxy-3-phenylpropane (3)**

A mixture of allylbenzene, 16a, (5 g; 0,04 mol); MCPBA (16 g; 0,08 mol) and 50 mℓ benzene was stirred at room temperature for 5 hours. Benzene was evaporated and 20 mℓ aq. sodium bicarbonate added. After extraction with ether (2 x 20 mℓ), the ether solution was washed with 20 mℓ aq. sodium bicarbonate and 20 mℓ water and then dried ($MgSO_4$). Filtration and evaporation gave a yellow powder

which was washed several times with small portions of chloroform. After evaporation of the chloroform, distillation gave 3 as a pale yellow oil at 50-4°C / 0,6 mm Hg (3,7 g; 64%). $n_D^{22}$ 1,5257 (Lit.[134] $n_D^{20}$ 1,5262). $^1$H n.m.r.: δ 2,5 - 3,3 (5 H; complex multiplets; PhCH$_2$CHCH$_2$O); 7,15 - 7,38 (5 H; m; Ph).

**N,N,N',N'-tetraethyl-P-(2-hydroxy-3-phenylpropyl)phosphonic diamide (4a)**

A solution of 1, (4,0 g; 21 mmol) in 10 mℓ THF was cooled to -94°C and a *n*-butyllithium solution (13 mℓ; 21 mmol) was added dropwise. Stirring at -94°C was continued for 20 minutes. 3 (2,5 g; 19 mmol) was added and the mixture returned to room temperature over 2 hours. 20 mℓ aq. ammonium chloride was added and extracted with ether (3 x 20 mℓ). Drying ($MgSO_4$), filtration and evaporation of volatiles gave 4a as a pale yellow oil (4,8 g; 79%). $n_D^{25}$ 1,5072. $^{31}$P n.m.r.: δ 38,3. $^1$H n.m.r.: δ 0,78 (6 H; t, $J_{HH}$ 7,1 Hz; 2 x Me of NEt$_2$); 0,94 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of NEt$_2$); 1,68 (1 H; ddd; $J_{HH}$ (gem) 14,9 Hz; $J_{HP}$ 12,9 Hz; $J_{HH}$ (vic) 2,0 Hz; 1 H of CH$_2$P); 1,78 (1 H; ddd; $J_{HH}$ (gem) 14,8 Hz; $J_{HP}$ 12,0 Hz; $J_{HH}$ (vic) 10,0 Hz; 1 H of CH$_2$P); 2,48 - 2,97 (10 H; 2 x m; PhCH$_2$ and 4 x CH$_2$ of NEt$_2$); 3,93 - 4,06 (1 H; m; CHOH); 5,31 (1 H; br; OH); 7,01 - 7,25 (5 H; m; Ph). $^{13}$C n.m.r.: δ 13,5; 13,9 (2 x s; 4 x Me of NEt$_2$); 31,5 (d; $J_{CP}$ 114 Hz; CH$_2$P); 38,1 (2 x d; $J_{CP}$ 4,6 Hz; 4 x CH$_2$ of NEt$_2$); 44,2 (d; $J_{CP}$ 17,1 Hz; PhCH$_2$); 67,7 (d; $J_{CP}$ 3,7 Hz; CHOH); 126,0; 127,9; 129,0; 137,6 (4 x s; Ph). IR: 1208 ($\upsilon_{P=O}$); 2927 ($\upsilon_{C-H}$ (arom)); 3364 ($\upsilon_{O-H}$). m/z 326 [$M^+$; 4%]; 254 [$M^+$ - NEt$_2^+$; 20%]; 235 [(Et$_2$N)$_2$P(O)CH$_2$CH=OH$^+$; 49%]; 191 [(Et$_2$N)$_2$PO$^+$; 100%]; 120 [Et$_2$NPOH$^+$; 14%]; 91 [C$_7$H$_7^+$; 13%]; 72 [NEt$_2^+$; 23%].

**N,N,N',N'-tetraethyl-P-(2-hydroxy-2-phenylethyl)phosphonic diamide (4b)**

From styrene oxide as for 4a. Yellow oil. Yield 99%. $n_D^{22}$ 1,5133. $^{31}$P n.m.r.: δ 37,5. $^1$H n.m.r.: δ 1,05 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of NEt$_2$); 1,14 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of NEt$_2$); 1,85 - 1,97 (1 H; ddd; $J_{HH}$ (vic) 1,8 Hz; $J_{HH}$ (gem) 14,5 Hz; $J_{HP}$ 12,3 Hz; 1 H of CH$_2$P); 2,06 - 2,20 (1 H; ddd; $J_{HH}$

(vic) 11,1 Hz; $J_{HH}$ (gem) 14,9 Hz; $J_{HP}$ 11,1 Hz; 1 H of $\underline{CH_2}P$): 2,90 - 3,17 (8 H; 2 x m; 4 x $CH_2$ of $NEt_2$); 4,98 (1 H; m; $\underline{CH}OH$); 5,68 (1 H; br; OH); 7,20 - 7,37 (5 H; m; Ph). $^{13}C$ n.m.r.: $\delta$ 14,2 (s; 4 x Me of $NEt_2$); 36,0 (d; $J_{CP}$ 111 Hz; $\underline{CH_2}P$); 38,4 (d; $J_{CP}$ 3,7 Hz; 2 x $CH_2$ of $NEt_2$); 38,6 (d; $J_{CP}$ 4,4 Hz; 2 x $CH_2$ of $NEt_2$); 68,8 (d; $J_{CP}$ 3,5 Hz; $\underline{CH}OH$); 125,3; 127,2; 128,3 (o, m, p carbons of Ph); 144,4 (d; $J_{CP}$ 16,7 Hz; ipso carbon of Ph). m/z 240 [$M^{+\cdot}$ - $NEt_2^{\cdot}$; 5%]; 191 [$(Et_2N)_2PO^+$; 15%]; 136 [$(Et_2N)(HO)PO^+$; 34%]; 120 [$Et_2NPOH^+$; 28%]; 105 [$PhC\equiv O^+$; 53%]; 72 [$NEt_2^+$; 100%].

**N,N,N',N'-tetraethyl-P-(2-hydroxybutyl)phosphonic diamide (4c)**

From 1,2-epoxybutane as for 4a. Pale yellow oil. Yield 65%. $n_D^{27}$ 1,4658. $^{31}P$ n.m.r.: $\delta$ 38,6. $^1H$ n.m.r.: $\delta$ 0,83 (3 H; t; $J_{HH}$ 7,4 Hz; $\omega$-$CH_3$); 0,988 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of $NEt_2$); 0,994 (6 H; t; $J_{HH}$ 7,0 Hz; 2 x Me of $NEt_2$); 1,25 - 1,80 (4 H; m; $\underline{CH_2}CH(OH)\underline{CH_2}P$); 2,75 - 3,10 (8 H; m; 4 x $CH_2$ of $NEt_2$); 3,73 (1 H; m; $\underline{CH}OH$); 5,03 (1 H; br; OH). $^{13}C$ n.m.r.: $\delta$ 9,6 (s; $\omega$-$CH_3$); 14,1 (2 x s; 4 x Me of $NEt_2$); 31,1 (d; $J_{CP}$ 17,4 Hz; $\underline{CH_2}CH(OH)CH_2P$); 32,2 (d; $J_{CP}$ 114 Hz; $\underline{CH_2}P$); 38,4; (s; 4 x $CH_2$ of $NEt_2$); 67,6 (d, $J_{CP}$ 4,6 Hz; $\underline{CH}OH$). IR 1193 ($\upsilon_{P=O}$); 3386 ($\upsilon_{O-H}$). m/z 264 [$M^{+\cdot}$; 5%]; 235 [$M^{+\cdot}$ - $Et^{\cdot}$; 21%]; 192 [$M^{+\cdot}$ - $NEt_2^{\cdot}$; 86%]; 191 [$(Et_2N)_2PO^+$; 88%]; 136 [$(Et_2N)(HO)PO^+$; 100%]; 120 [$Et_2NPOH^+$; 55%]; 72 [$NEt_2^+$; 95%].

**N,N,N',N'-tetraethyl-P-(2-hydroxycyclohexyl)phosphonic diamide (4d)**

A solution of 1 (0,98 g; 5,1 mmol) in 5 m$\ell$ THF was cooled to -94°C and a *n*-butyllithium solution (3,2 m$\ell$; 5,1 mmol) added. The mixture was stirred for 15 minutes and cyclohexene oxide (0,50 m$\ell$; 4,9 mmol) added. Cooling was removed after 10 minutes and after a further 20 minutes the mixture was refluxed in an oilbath at 80°C for 2 hours. After cooling aq. ammonium chloride (20 m$\ell$) was added and extracted with ether (3 x 20 m$\ell$). Drying ($MgSO_4$), filtration and evaporation gave a yellow oil which was bulb-to-bulb "distilled" to give 4d at 232-3°C / 0,5 mm Hg (1,09 g; 76%). $n_D^{17}$ 1,4923. $^{31}P$ n.m.r.: $\delta$ 42,6. $^1H$ n.m.r.: $\delta$ 1,07 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of $NEt_2$); 1,09 (6 H; t; $J_{HH}$ 7,1 Hz;

2 x Me of $NEt_2$); 1,0 - 2,1 (9 H; overlapping m; HOCHCH$_2$CH$_2$CH$_2$CH$_2$CHP); 2,9 - 3,1 ( 8 H; m; 4 x $CH_2$ of $NEt_2$); 3,65 (1 H; m; CHOH); 6,19 (1 H; br; OH). $^{13}$C n.m.r.: $\delta$ 13,3 (d; $J_{CP}$ 3,6 Hz; 2 x Me of $NEt_2$); 13,8 (d; $J_{CP}$ 1,1 Hz; 2 x $CH_3$ of $NEt_2$); 24,1 (s; HOCHCH$_2$CH$_2$CH$_2$CH$_2$CHP); 25,1 (d; $J_{CP}$ 4,0 Hz; HOCHCH$_2$CH$_2$CH$_2$CH$_2$CHP); 25,5 (d; $J_{CP}$ 13,8 Hz; HOCHCH$_2$CH$_2$CH$_2$CH$_2$CHP); 34,9 (d; $J_{CP}$ 14,0 Hz; HOCHCH$_2$CH$_2$CH$_2$CH$_2$CHP); 37,5 (d; $J_{CP}$ 1,7 Hz; 2 x $CH_2$ of $NEt_2$); 38,7 (d; $J_{CP}$ 3,3 Hz; 2 x $CH_2$ of $NEt_2$); 43,6 (d; $J_{CP}$ 114 Hz; CHP); 68,7 (d; $J_{CP}$ 4,7 Hz; CHOH). IR 1182 ($\upsilon_{P=O}$); 3320 ($\upsilon_{O-H}$). m/z 218 [$M^{+\cdot}$ - $NEt_2$; 26%]; 191 [$(Et_2N)_2PO^+$; 70%]; 136 [$(Et_2N)(HO)PO^+$; 67%]; 120 [$Et_2NPOH^+$; 100%]; 72 [$Et_2N^+$; 70%].

**N,N,N',N'-tetraethyl-P-(2-hydroxycyclopentyl)phosphonic diamide (4e)**

From cyclopentene oxide as for 4d using 6 hours of reflux. Yield 62%. $n_D^{17}$ 1,4901. $^{31}$P n.m.r.: $\delta$ 40,6. $^1$H n.m.r.: $\delta$ 1,04 (6 H; t; $J_{HH}$ 7,0 Hz; 2 x $CH_3$ of $NEt_2$); 1,07 (6 H; t; $J_{HH}$ 7,0 Hz; 2 x $CH_3$ of $NEt_2$); 1,5 - 2,20 (7 H; m; HOCHCH$_2$CH$_2$CH$_2$CHP); 2,90 - 3,20 ( 8 H; m; 4 x $CH_2$ of $NEt_2$); 4,20 (1 H; m; HOCH); 5,41 (1 H; br; OH). $^{13}$C n.m.r.: $\delta$ 13,9 (d; 2,7 Hz; 2 x $CH_3$ of $NEt_2$); 14,1 (s; 2 x $CH_3$ of $NEt_2$); 22,2 (d; $J_{CP}$ 10,6 Hz; HOCHCH$_2$CH$_2$CH$_2$CHP); 25,2 (s; HOCHCH$_2$CH$_2$CH$_2$CHP); 34,4 (d; $J_{CP}$ 12,8 Hz; HOCHCH$_2$CH$_2$CH$_2$CHP(O)(NEt$_2$)$_2$); 38,0 (d; $J_{CP}$ 3,9 Hz; 2 x $CH_2$ of $NEt_2$); 38,6 (d; $J_{CP}$ 3,7 Hz; 2 x $CH_2$ of $NEt_2$); 44,9 (d; $J_{CP}$ 119 Hz; CHP); 74,1 (s; HOCH). IR 1189 ($\upsilon_{P=O}$); 3300 ($\upsilon_{O-H}$). m/z 204 [$M^{+\cdot}$ - $NEt_2$; 10%]; 191 [$(Et_2N)_2PO^+$; 28%]; 136 [$(Et_2N)(HO)PO^+$; 25%]; 120 [$Et_2NPOH^+$; 51%]; 72 [$Et_2N^+$; 100%].

**N,N,N',N'-tetraethyl-P-(2-hydroxy-1-methylpropyl)phosphonic diamide (RR,SS) (4f)**

From cis-2,3-epoxybutane as for 4e. Yellow solid. Yield 50%. Several washes with petroleum ether 40-60 gave a white powder in 17% yield. mp 74-77°C. $^{31}$P n.m.r.: $\delta$ 44,2. $^1$H n.m.r.: $\delta$ 1,00 (3 H; dd; $J_{HP}$ 16,6 Hz; $J_{HH}$ 7,4 Hz; CH$_3$CHP); 1,10 (6 H; t; $J_{HH}$ 7,8 Hz; 2 x $CH_3$ of $NEt_2$); 1,13 (6 H; t; $J_{HH}$ 7,8 Hz; 2 x $CH_3$ of $NEt_2$); 1,21 (3 H; d; $J_{HH}$ 6,1 Hz; CH$_3$CHOH); 2,03 (1 H; ddq; $J_{HH}$ 7,4 Hz; $J_{HH}$ 9,1

Hz; $J_{HP}$ 12,1 Hz; CHP); 2,96 - 3,20 (8 H; m; 4 x $CH_2$ of $NEt_2$); 3,87 (1 H; m; CHOH); 6,00 (1 H; br; OH). $^{13}C$ n.m.r.: $\delta$ 11,7 (d; $J_{CP}$ 4,7 Hz; $CH_3$CHP); 13,6 (d; $J_{CP}$ 4,1 Hz; 2 x $CH_3$ of $NEt_2$); 14,2 (d; $J_{CP}$ 1,9 Hz; 2 x $CH_3$ of $NEt_2$); 21,4 (d; $J_{CP}$ 15,2 Hz; $CH_3$CHOH); 37,9 (d; $J_{CP}$ 2,8 Hz; 2 x $CH_2$ of $NEt_2$); 39,1 (d; $J_{CP}$ 4,1 Hz; 2 x $CH_2$ of $NEt_2$); 39,3 (d; $J_{CP}$ 114 Hz; CHP); 67,7 (d; $J_{CP}$ 4,0 Hz; CHOH). IR 1207 ($\upsilon_{P=O}$); 3332 ($\upsilon_{O-H}$). m/z 192 [$M^{+\cdot}$ - $NEt_2$; 12%]; 191 [$(Et_2N)_2PO^+$; 35%]; 136 [$(Et_2N)(HO)PO^+$; 30%]; 120 [$Et_2NPOH^+$; 42%]; 72 [$NEt_2^+$; 100%].

**N,N,N',N'-tetraethyl-P-(2-hydroxy-1-methylpropyl)phosphonic diamide (RS,SR) (4g)**

From trans-2,3-epoxybutane as for 4d using 22 hours of reflux. Yield 56% of a yellow oil. $n_D^{14}$ 1,4769. $^{31}P$ n.m.r.: $\delta$ 42,2. $^1H$ n.m.r.: $\delta$ 1,00 - 1,08 (15 H; m; 4 x $CH_3$ of $NEt_2$ and $CH_3$CHP); 1,12 (d; $J_{HH}$ 6,3 Hz; $CH_3$CHOH); 1,82 (1 H; ddq; $J_{HH}$ (vic) 1,0 Hz; $J_{HH}$ (vic) 7,2 Hz; $J_{HP}$ 12,4 Hz; CHP); 2,84 - 3,08 (8 H; m; 4 x $CH_2$ of $NEt_2$); 4,18 (1 H; m; CHOH); 4,63 (1 H; br; OH). $^{13}C$ n.m.r.: $\delta$ 5,6 (d; $J_{CP}$ 1,4 Hz; $CH_3$CHP); 14,0; 14,2 (2 x s; 4 x $CH_3$ of $NEt_2$); 20,2 (d; $J_{CP}$ 15,4 Hz; $CH_3$CHOH); 34,5 (d; $J_{CP}$ 112 Hz; CHP); 38,6 (d; $J_{CP}$ 3,3 Hz; 2 x $CH_2$ of $NEt_2$); 38,8 (d; $J_{CP}$ 4,0 Hz; 2 x $CH_2$ of $NEt_2$); 64,9 (d; $J_{CP}$ 3,4 Hz; CHOH). IR 1192 ($\upsilon_{P=O}$); 3378 ($\upsilon_{O-H}$). m/z 192 [$M^{+\cdot}$ - $NEt_2$; 44%]; 191 [$(Et_2N)_2PO^+$; 65%]; 136 [$(Et_2N)(HO)PO^+$; 100%]; 120 [$Et_2NPOH^+$; 91%]; 72 [$Et_2N^+$; 100%].

**Resolution of RR and SS trans-1,2-diaminocyclohexane**

The enantiomers were resolved using a method of Sørensen.[117] 10 m$\ell$ of trans-1,2-diaminocyclohexane was dissolved in 17 m$\ell$ of water in a 400 m$\ell$ beaker. The solution was heated to 90°C and 6,25 g of L-tartaric acid (i.e. (+)-tartaric acid) was added in small portions, followed by 4,2 m$\ell$ of glacial acetic acid also in small portions. The solution was cooled in ice with stirring for an hour. The mixture was filtered and the precipitate washed with a small portion of ice cold water and 8 m$\ell$ of ethanol. The mother liquid is used to obtain the SS isomer. The crude (1R,2R)-trans-1,2-cyclohexanediammonium tartrate, {(-)chxn(+)tart}, was recrystallized from water giving, after drying in vacuo, 3,4 g of a white

powder. A further 2,9 g could be obtained by treating the liquor with ethanol. The original mother liquor was heated to 80°C and 15,6 g of L-tartaric acid added in small portions. The solution was left to stand overnight at room temperature. Filtration afforded a paste which was recrystallized from water to give 5,4 g of (1S,2S)-trans-1,2-cyclohexanediammonium tartrate, {(+)chxn(+)tart}, as a white powder after drying in vacuo. A further 4,2 g could be obtained as for the RR isomer.

{(-)chxn(+)tart}: Dec >230°C: $[\alpha]_D^{21}$ = +11 (1% aq. solution). Lit.[117] $[\alpha]_D^{20}$ = +12,2° (1% aq. solution). $^1$H n.m.r. ($D_2O$): δ 1,24 - 1,32 (2 H; br; $H_e$); 1,39 - 1,52 (2 H; br; $H_d$); 1,65 - 1,79 (2 H; br; $H_c$); 2,04 - 2,13 (2 H; br; $H_b$); 3,27 - 3,31 (2 H; br; $H_a$); 4,25 (2 H; s; H of $[C\underline{H}(OH)CO_2^-]_2$).

{(+)chxn(+)tart}: 5: mp 150-2°C. $[\alpha]_D^{18}$ = +30 (1% aq. solution). Lit.[117] $[\alpha]_D^{20}$ = +26° (1% aq. solution).$^1$H n.m.r. ($D_2O$): δ 1,24 - 1,33 (2 H; br; $H_e$); 1,40 - 1,55 (2 H; br; $H_d$); 1,70 - 1,81 (2 H; br; $H_c$); 2,03 - 2,13 (2 H; br; $H_b$); 3,27 - 3,35 (2 H; br; $H_a$); 4,45 (2 H; s; H of $[C\underline{H}(OH)CO_2^-]_2$).

**(1S,2S)-N,N'-dibenzylcyclohexyl-1,2-diammonium chloride (6)**

To a solution of 5 (8,0 g; 30 mmol) in 80 mℓ methanol was added dropwise a solution of potassium hydroxide (4,8 g; 84 mmol) in 40 mℓ methanol over a period of 1 hour. The solution was stirred for a further 30 minutes, filtered and concentrated to 40 mℓ. After cooling to 5°C, benzaldehyde (8,4 mℓ; 84 mmol) was added. The mixture was then heated under reflux for 1 hour and again cooled to 5°C. Sodium borohydride (4,4 g; 120 mmol) was added in small portion and the mixture stirred overnight. The mixture was poured into ice water and extracted with dichloromethane (5 x 40 mℓ). After drying ($MgSO_4$), filtration and evaporation the residue was dissolved in 20 mℓ of methanol and 6,4 mℓ of conc. hydrochloric acid in 20 mℓ of water was added. After evaporation the crude product was recrystallised from ether/methanol (1/1) giving 6 as white crystals (5,2 g; 48%). $[\alpha]_D^{25}$ = +48 (1% aq. solution). mp 209-212°C. $^1$H n.m.r. ($D_2O$): 1,32 - 1,48 (2 H; br; $H_e$); 1,55 - 1,88 (4 H; 2 x br; $H_d$ and $H_c$); 2,25 - 2,40 (2 H; br; $H_b$); 3,40 - 3,52 (2 H; br; $H_a$); 4,13 (2 H; d; $J_{HH}$ 13 Hz; $CH_2$ of $B_z$); 4,35 (2 H; d; $J_{HH}$ 13 Hz; $CH_2$ of Bz); 7,36 - 7,53 (10 H; m; 2 x Ph).

**(1S,6S)-7,9-dibenzyl-7,9-diaza-8-phosphabicyclo[4.3.0]nonane 8-oxide (7)**

The free base was released from the hydrochloride, 6, by aqueous potassium hydroxide and extracted with ether followed by benzene. The organic solution was dried ($MgSO_4$), filtered and evaporated. The residual oil was further subjected to a vacuum of 1 mm Hg to ensure removal of all water. To 3,6 g (12 mmol) of the free amine was added 3 g of dried molecular sieves and left overnight. Triethylamine (3,6 mℓ; 25 mmol) and 50 mℓ dry toluene was added. The solution was cooled to -94°C and phosphorus trichloride (1,1 mℓ; 13 mmol) was added dropwise. The mixture was allowed to return to room temperature and then stirred for a further three hours before being recooled to -94°C. Water (0,2 mℓ; 12 mmol) in triethylamine (1,8 mℓ; 13 mmol) was added. After returning to room temperature stirring was continued for 1 hour. The solution was filtered through anhydrous magnesium sulphate, which was washed with dry toluene. Evaporation gave 7 as a yellow powder (3,0 g; 72%). $^{31}P$ n.m.r.: δ 20,8. $^{1}H$ n.m.r.: δ 1,04 - 1,24 (4 H; br; $H_e$ and $H_d$); 1,59 - 1,91 (4 H; 2 x br; $H_c$ and $H_b$); 2,91 - 3,09 (2 H; m; $H_a$); 4,01 - 4,23 (4 H; m; 2 x $CH_2$ of $B_z$); 6,49; 8,50 (1 H; d; $J_{HP}$ 600 Hz; PH)); 7,20 - 7,46 (10 H; m; 2 x Ph).

**(1S,6S)-7,9-dibenzyl-8-(2'-hydroxybutyl)-7,9-diaza-8-phosphabicyclo[4.3.0]nonane 8-oxide (8)**

A solution of 7 (1,0 g; 2,9 mmol) in 10 mℓ THF was cooled to -94°C. *n*-butyllithium (1,9 mℓ; 3,0 mmol) was added and stirring was continued at -94°C for 20 minutes. 1,2-epoxybutane (0,76 mℓ; 8,8 mmol) was added. After 10 minutes cooling was removed and after a further 20 minutes the mixture was refluxed for 1 hour. 10 mℓ aqueous ammonium chloride was added and extracted with ether (3 x 20 mℓ). Drying ($MgSO_4$), filtration and evaporation gave 8 as a yellow oil (0,81 g; 71%). $^{31}P$ n.m.r.: δ 43,2 and 44,1. $^{1}H$ n.m.r.: δ 0,80 (3 H; m; ω-$CH_3$); 1,05 - 1,25 (4 H; m; $H_e$ and $H_d$); 1,30 - 1,90 (6 H; m; $H_c$, $H_b$ and $CH_3\underline{CH_2}CH(OH)$); 2,13 (1 H; m) and 2,33 (1 H; m) ($\underline{CH_2}P$); 2,86 (1 H; br; s; OH); 2,95 - 3-12 (2 H; m; $H_a$); 3,60 - 4,05 (4 H; m; 2 x $CH_2$ of $CH_2Ph$); 4,40 (1 H; m; $\underline{CH}OH$); 7,10 - 7,30 (10 H; m; 2 x Ph).

**Sodium salt of 2-hydroxybutylphosphonic acid (9)**

4c (0,5 g; 1,9 mmol) was dissolved in 10 mℓ of water and 2 mℓ conc. hydrochloric acid was added. The solution was stirred overnight and then the pH was adjusted to 9 with solid sodium carbonate. Water was removed in vacuo. Ethanol was added and the mixture was refluxed. The hot solution was filtered. Upon addition of ether a white solid precipitated. Filtration gave 9 as a white powder (0,03 g; 9%). $^{31}$P n.m.r. ($D_2O$): δ 22,7. $^{1}$H n.m.r. ($D_2O$): δ 0,88 (3 H; t; $J_{HH}$ 7,4 Hz; ω-$CH_3$); 1,38 - 1,90 (4 H; overlapping m; $CH_2CH(OH)CH_2P$); 3,76 - 3,91 (1 H; m; CHOH).

**Hydrolysis of 8**

8 (0,81 g) was dissolved in 10 mℓ of water and 2 mℓ conc. hydrochloric acid was added. The solution was stirred overnight and then the pH was adjusted to 6 with solid sodium hydrogen carbonate. After evaporation the residue was washed with ethanol and the ethanol removed. The residue was dissolved in water and solid sodium carbonate used to adjust the pH to 10. Ether was added and the aqueous layer was removed. The ether solution was washed once with water. The aqueous solution was evaporated in vacuo to dryness. The residual powder gave a $^{31}$P n.m.r. spectrum identical to that of 9 and the signals in the $^{1}$H n.m.r. spectrum corresponded to those observed for 9.

**Substrates for fragmentation studies**

**O,O-diethyl methylphosphonate (10)**

A mixture of iodomethane (32 mℓ; 0,51 mol), triethyl phosphite (79 mℓ; 0,46 mol) and 130 mℓ benzene was refluxed in an oilbath at 80°C for 3 hours. After 1 hour a further quantity of iodomethane (16 mℓ; 0,26 mol) had been added. Solvent evaporation and distillation gave 10 as a colourless oil at 183-5°C / water pump vacuum (63 g; 90%). $n_D^{16}$ 1,4183 (Lit.[135] $n_D^{16}$ 1,4120). $^{31}$P n.m.r.: δ 30,8. $^{1}$H n.m.r.:

δ 1,16 (6 H; t; $J_{HH}$ 6,3 Hz; 2 x $CH_3$ of OEt); 1,30 (3 H; d; $J_{HP}$ 17,3 Hz; $CH_3P$); 3,92 (4 H; m; 2 x $CH_2$ of OEt).

**O,O-diethyl 2,3-epoxypropylphosphonate (11)**

A mixture of epiiodohydrin (27 g; 0,15 mol) and triethyl phosphite (24 mℓ; 0,14 mol) was refluxed at 140°C in an oil bath for 3 hours. Low boiling material was removed by distilling using a water pump. Distillation gave 11 as a colourless oil at 89-95°C / 0,45 mm Hg. (10,6 g; 37%). $n_D^{16}$ 1,4419 (Lit.[136] $n_D^{20}$ 1,4405). $^{31}P$ n.m.r.: δ 26,7. $^1H$ n.m.r.: δ 1,20 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x $CH_3$ of OEt); 1,72 (1 H; ddd; $J_{HP}$ 19,9 Hz; $J_{HH}$ (gem) 15,1 Hz; $J_{HH}$ (vic) 6,4 Hz; 1 H of $CH_2P$); 2,05 (1 H; ddd; $J_{HP}$ 18,3 Hz; $J_{HH}$ (gem) 15,0 Hz; $J_{HH}$ (vic) 5,6 Hz; 1 H of $CH_2P$); 2,44 (1 H; dd; $J_{HH}$ (gem) 5,0 Hz; $J_{HH}$ (vic) 2,5 Hz; 1 H of C$\underline{CH_2}$O); 2,69 (1 H; ddd; $J_{HH}$ (gem) 5,1 Hz; $J_{HH}$ (vic) 1,4 Hz; $J_{HP}$ 3,8 Hz; 1 H of C$\underline{CH_2}$O); 3,03 (1 H; m; $\underline{CH}CH_2O$); 3,99 (4 H; m; 2 x $CH_2$ of OEt).

**Phenylacetylchloride (12a)**

Solid phenylacetic acid (30 g; 0,22 mol) was added over a period of an hour to thionylchloride (30 mℓ; 0,41 mol) heated to 40°C. The mixture was then refluxed at 80°C for 2 hours and volatiles evaporated. Distillation gave 12a as a colourless oil at 58-60°C / 1 mm Hg (30 g; 87%). $n_D^{16}$ 1,5369 (Lit.[137] $n_D^{20}$ 1,5333). $^1H$ n.m.r.: δ 4,17 (2 H; s; Ar$\underline{CH_2}$COCl); 7,39 (5 H; m; Ph).

**p-Methoxyphenylacetylchloride (12b)**

Prepared as 12a from p-methoxyphenylacetic acid and thionyl chloride. Distillation gave 12b as a colourless oil at 154-6°C / < 1 mm Hg. Yield 88%. $n_D^{16}$ 1,5432 (Lit.[138] $n_D^{20}$ 1,5422). $^1H$ n.m.r.: δ 3,79 (3 H; s; OMe); 4,07 (2 H; s; Ar$\underline{CH_2}$); 6,91 (2 H; d; $J_{HH}$ 8,6 Hz; H meta to OMe); 7,19 (2 H; d; $J_{HH}$ 8,6 Hz; H ortho to OMe).

**3-Phenylpropionylchloride (12c)**

Prepared as 12a from hydrocinnamic acid. Distillation at 60-68°C / 0,3 mm Hg gave the chloride as a colourless oil. Yield 86%. $n_D^{15}$ 1,5327. (Lit.[139] $n_D^{20}$ 1,5265). $^1$H n.m.r.: δ 3,03 (2 H; t; $J_{HH}$ 7,4 Hz; Ph$\underline{CH_2}$); 3,22 (2 H; t; $J_{HH}$ 7,4 Hz; $\underline{CH_2}$COCl); 7,15 - 7,40 (5 H; m; Ph).

ß-hydroxyalkylphosphonates were synthesized by either of two methods given below. Both are illustrated by the synthesis of O,O-diethyl 2-hydroxy-3-phenylpropylphosphonate.

**Method 1**[124]

**O,O-diethyl 2-oxo-3-phenylpropylphosphonate (13a)**

To a solution of 10 (15 g; 0,099 mol) in 30 mℓ THF cooled to -60°C was added dropwise a *n*-butyllithium solution (68 mℓ; 0,11 mol). The mixture was stirred at -60°C for 10 minutes and a suspension of copper(I)iodide (21 g; 0,11 mol) in 20 mℓ THF was introduced. After warming to -40°C the mixture was stirred at this temperature for 1 hour. A solution of 12a (17 g; 0,11 mol) in 10 mℓ THF was added dropwise to the mixture - the temperature being maintained below -40°C. The mixture was then allowed to warm to room temperature over a 4 hour period. 100 mℓ of a saturated aq. ammonium chloride solution was added and the mixture stirred overnight. After filtration through "Celite" 545 with ether washing, the ethereal solution was separated and the aqueous phase extracted with chloroform. The combined organic phases were dried ($MgSO_4$) and filtered. Solvent evaporation gave the ketone 13a as a yellow oil (30 g; 89%). $n_D^{16}$ 1,5079. $^{31}$P n.m.r.: δ 20,3. $^1$H n.m.r.: δ 1,28 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of OEt); 3,04 (2 H; d; $J_{HP}$ 22,7 Hz; $\underline{CH_2}$P); 3,85 (2 H; s; Ph$\underline{CH_2}$); 4,09 (4 H; m; 2 x $CH_2$ of OEt); 7,12 - 7,32 (5 H; m; Ph). $^{13}$C n.m.r.: δ 16,1 (d; $J_{CP}$ 6,7 Hz; 2 x Me of OEt); 41,2 (d; $J_{CP}$ 128 Hz; $\underline{CH_2}$P); 50,6 (s; Ph$\underline{CH_2}$); 62,5 (d; $J_{CP}$ 7,0 Hz; 2 x $CH_2$ of OEt); 126,8; 128,6; 129,8; 133,3 (4 x s; Ph); 199,4 (d; $J_{CP}$ 6,1 Hz; C=O). IR: 1254 ($\upsilon_{P=O}$); 1719 ($\upsilon_{C=O}$); 2985

($\upsilon_{C-H}$ (arom)). m/z 270 ($M^{+\cdot}$; 97%); 179 [$(EtO)_2P(O)CH_2C\equiv O^+$; 90%]; 151 [$(EtO)(HO)P(O)$-$CH_2C\equiv O^{+\cdot}$; 69%]; 137 [$(EtO)_2P=O^+$; 23%]; 123 [$(HO)_2P(O)CH_2C\equiv O^+$; 67%]; 91 [$C_7H_7^+$; 100%]; 109 [$(EtO)(HO)P=O^+$; 57%].

**O,O-diethyl 2-hydroxy-3-phenylpropylphosphonate (14a)**

To a suspension of sodium borohydride (13 g; 0,33 mol) in 100 mℓ ethanol cooled to 0°C in an ice-bath was added dropwise a solution of 13a (30 g; 0,11 mol)in 30 mℓ ethanol. After addition was complete the ice-bath was removed and the mixture stirred at room temperature for 2 hours. The mixture was poured into 100 mℓ of a dilute hydrochloric acid solution and then neutralized with solid sodium bicarbonate. Extraction with chloroform (3 x 50 mℓ) was followed by drying ($MgSO_4$). Filtration and solvent evaporation gave 14a as a yellow oil (24 g; 80%). $n_D^{15}$ 1,5137. $^{31}P$ n.m.r.: δ 30,3. $^1H$ n.m.r.: δ 1,25; 1,26 (6 H; 2 x t; $J_{HH}$ 7,1 Hz; 2 x $CH_3$ of OEt); 1,87 (2 H; m; $\underline{CH_2}P$); 2,81 (2 H; m; $Ph\underline{CH_2}$); 4,04 (4 H; m; 2 x $CH_2$ of OEt); 4,19 (1 H; m; $\underline{CH}OH$); 7,12 - 7,29 (5 H; m; Ph). $^{13}C$ n.m.r.: δ 16,3 (d; $J_{CP}$ 5,8 Hz; 2 x $CH_3$ of OEt); 32,6 (d; $J_{CP}$ 139 Hz; $\underline{CH_2}P$); 44,4 (d; $J_{CP}$ 16,7 Hz; $Ph\underline{CH_2}$); 61,8 (d; $J_{CP}$ 7,8 Hz; 2 x $CH_2$ of OEt); 67,5 (d; $J_{CP}$ 4,1 Hz; $\underline{CH}OH$); 126,5; 128,4; 129,5; 137,6 (4 x s; Ph). IR: 1240 ($\upsilon_{P=O}$); 2928 ($\upsilon_{C-H}$ (arom)); 3363 ($\upsilon_{O-H}$). m/z 254 [$M^{+\cdot}$ - $H_2O$; 11%); 181 [$(EtO)_2P(O)CH_2CH=OH^+$; 86%]; 153 [$(EtO)(HO)P(O)CH_2CH=OH^+$; 39%]; 125 [$(HO)_2P(O)CH_2$-$CH=OH^+$; 100%]; 91 [$C_7H_7^+$; 40%].

**Method 2**

**O,O-diethyl 2-hydroxy-3-phenylpropylphosphonate (14a)**

According to the procedure given by Linstrumelle.[125] To magnesium turnings (0,94 g; 39 mmol) in 10 mℓ THF was added dropwise a solution of bromobenzene (4,0 mℓ; 38 mmol) in 20 mℓ THF while refluxing. After addition was complete and all magnesium had reacted, reflux was continued for 15

minutes. The Grignard solution was cooled and transferred via syringe to a suspension of copper(I)iodide (0,74 g; 39 mmol) in 10 mℓ THF at -30°C. The mixture was allowed to warm to -5°C and 11 (5,1 g; 26 mmol) was added dropwise as a solution in 5 mℓ THF. The mixture was stirred at 0°C for 2 hours and then quenched with 100 mℓ of a satd. ammonium chloride solution. The resulting mixture was stirred at room temperature for 1 hour. After extraction with ether (4 x 100 mℓ); drying ($MgSO_4$); filtration and evaporation, column chromatography (Eluent: Benzene/Acetone 4:1 followed by ethanol) gave 14a ($R_f^{EtOH}$ 0,85) as a yellow oil (5,9 g; 82%). The physical data were the same as for the compound prepared by method 1.

**O,O-diethyl 3-(4'-methoxyphenyl)-2-oxopropylphosphonate (13b)**

As 13a. Bulb-to-bulb "distillation" gave 13b in 68% yield at an oven temperature of 231-3°C / 0,45 mm Hg. $n_D^{16}$ 1,5029. $^{31}P$ n.m.r.: δ 20,3. $^{1}H$ n.m.r.: δ 1,28 (6 H; t; $J_{HH}$ 7,0 Hz; 2 x $CH_3$ of OEt); 3,03 (2 H; d; $J_{HP}$ 22,7 Hz; $\underline{CH_2}P$); 3,73 (3 H; s; OMe); 3,78 (2 H; s; $Ph\underline{CH_2}$); 4,07 (4 H; m; 2 x $CH_2$ of OEt); 6,81 (2 H; d; $J_{HH}$ 8,7 Hz; H meta to OMe); 7,07 (2 H; d; $J_{HH}$ 8,6 Hz; H ortho to OMe). $^{13}C$ n.m.r.: δ 16,2 (d; $J_{CP}$ 6,6 Hz; 2 x Me of OEt); 41,0 (d; $J_{CP}$ 128 Hz; $\underline{CH_2}P$); 49,8 (s; $Ar\underline{CH_2}$); 55,1 (s; OMe); 62,6 (d; $J_{CP}$ 7,0 Hz; 2 x $CH_2$ of OEt); 114,0; 130,1; 130,5; 158,7 (4 x s; Ar); 199,8 (d; $J_{CP}$ 6,1 Hz; C=O). IR: 1250 ($\upsilon_{P=O}$); 1718 ($\upsilon_{C=O}$); 2956 ($\upsilon_{C-H}$ (arom)). m/z 300 [$M^{+\cdot}$; 5%]; 121 [$MeOC_7H_6^+$; 100%]; 152 [$CH_3P(O)(OEt_2^{+\cdot}$; 37%]; 135 [$MeOC_6H_4CH_2CH_2^+$; 71%].

**O,O-diethyl 2-hydroxy-3-(4'-methoxyphenyl)propylphosphonate (14b)**

Method 1: Yield 79%. $n_D^{16}$ 1,5072. $^{31}P$ n.m.r.: δ 30,9. $^{1}H$ n.m.r.: δ 1,27 (6 H; t; $J_{HH}$ 7,0 Hz; 2 x Me of OEt); 1,89 (2 H; m; $\underline{CH_2}P$); 2,75 (2 H; m; $Ar\underline{CH_2}$); 3,75 (3 H; s; OMe); 3,99 - 4,15 (5 H; 2 x m; $\underline{CH}OH$ and 2 x $CH_2$ of OEt); 6,81 (2 H; d; $J_{HH}$ 8,6 Hz; H meta to OMe); 7,10 (2 H; d; $J_{HH}$ 8,6 Hz; H ortho to OMe). $^{13}C$ n.m.r.: δ 16,1 (d; $J_{CP}$ 5,8 Hz; 2 x Me of OEt); 32,4 (d; $J_{CP}$ 139 Hz;

$\underline{CH_2}P$); 43,2 (d; $J_{CP}$ 16,4 Hz; Ar$\underline{CH_2}$); 54,9 (s; OMe); 61,5 (2 x d; $J_{CP}$ 4,3 Hz; 2 x $CH_2$ of OEt); 67,5 (d; $J_{CP}$ 4,8 Hz; $\underline{CH}$OH); 113,6; 129,5; 130,2; 158,1 (4 x s; Ar). IR: 1236 ($\upsilon_{P=O}$); 2951 ($\upsilon_{C-H}$ (arom)); 3384 ($\upsilon_{O-H}$). m/z 302 [$M^{+\cdot}$; 2%]; 284 [$M^{+\cdot}$ - $H_2O$; 40%]; 181 [$(EtO)_2P(O)CH_2CH{=}OH^+$; 21%]; 147 [$MeOC_9H_8^+$; 63%]; 125 [$(HO)_2P(O)CH_2CH{=}OH^+$; 47%]; 121 [$MeOC_7H_6^+$; 100%].

**O,O-diethyl 2-oxo-4-phenylbutylphosphonate (13c)**

As for 13a. Yield 99%. $n_D^{15}$ 1,5060. $^{31}P$ n.m.r.: $\delta$ 20,4. $^1H$ n.m.r.: $\delta$ 1,25 (6 H; t; $J_{HH}$ 7,0 Hz; 2 x Me of OEt); 2,88 (4 H; m; Ph$\underline{CH_2}\underline{CH_2}$); 3,01 (2 H; d; $J_{HP}$ 22,8 Hz; $\underline{CH_2}P$); 4,05 (4 H; m; 2 x $CH_2$ of OEt); 7,16 (5 H; m; Ph). $^{13}C$ n.m.r.: $\delta$ 16,0 (d; $J_{CP}$ 6,4 Hz; 2 x Me of OEt); 29,2 (s; Ph$CH_2\underline{CH_2}$); 42,2 (d; $J_{CP}$ 127 Hz; $\underline{CH_2}P$); 45,1 (s; Ph$\underline{CH_2}$); 62,3 (d; $J_{CP}$ 6,5 Hz; 2 x $CH_2$ of OEt); 125,8; 128,1; 128,2; 140,4 (4 x s; Ph); 200,8 (d; $J_{CP}$ 6,0 Hz; C=O). IR: 1254 ($\upsilon_{P=O}$); 1720 ($\upsilon_{C=O}$); 2963 ($\upsilon_{C-H}$ (arom)). m/z 284 [$M^{+\cdot}$; 11%]; 91 [$C_7H_7^+$; 100%]; 257 [$M^{+\cdot}$-$C_2H_4$; 11%]; 229 [$Me^{+\cdot}$ - 2 x $C_2H_4$; 19%]; 152 [$CH_3P(O)(OEt)_2^{+\cdot}$; 35%].

**O,O-diethyl 2-hydroxy-4-phenylbutylphosphonate (14c)**

Method 1. Yield 78%. $n_D^{15}$ 1,5069. $^{31}P$ n.m.r.: $\delta$ 30,9. $^1H$ n.m.r.: $\delta$ 1,30 (6 H; 2 x t; $J_{HH}$ 7,1 Hz; 2 x Me of OEt); 1,71 - 1,98 (4 H; m; Ph$CH_2\underline{CH_2}$ and $\underline{CH_2}P$); 2,70 (2 H; m; Ph$\underline{CH_2}$); 3,63 (1 H; br; OH); 4,07 (5 H; 2 x m; $\underline{CH}$OH and 2 x $CH_2$ of OEt); 7,13 - 7,30 (5 H; m;.Ph). $^{13}C$ n.m.r.: $\delta$ 16,4 (d; $J_{CP}$ 6,7 Hz; 2 x Me of OEt); 31,7 (s; Ph$\underline{CH_2}$); 33,6 (d; $J_{CP}$ 138 Hz; $\underline{CH_2}P$); 39,7 (d; $J_{CP}$ 17,1 Hz; Ph$CH_2\underline{CH_2}$); 61,9 (d; $J_{CP}$ 8,0 Hz; 2 x $CH_2$ of OEt); 65,8 (d; $J_{CP}$ 6,3 Hz; $\underline{CH}$OH); 125,8; 128,3; 128,4; 141,7 (4 x s; Ph). IR: 1230 ($\upsilon_{P=O}$); 2948 ($\upsilon_{C-H}$(arom)); 3357 ($\upsilon_{O-H}$). m/z 268 [$M^{+\cdot}$-$H_2O$; 34%]; 181 [$(EtO)_2P(O)CH_2CH{=}OH^+$; 30%]; 125 [$(HO)_2P(O)CH_2CH = OH^+$; 52%]; 117 [$C_9H_9^+$; 81%]; 104 [$C_8H_8^{+\cdot}$; 81%]; 91 [$C_7H_7^+$; 100%].

**O,O-dimethyl 2-oxo-3-phenylpropylphosphonate (13d)**

From 12a and commercially available O,O-dimethyl methylphosphonate as for 13a. Bulb-to-bulb "distillation" gave 13d in 53% yield at an oven temperature of 203-5°C / 0,5 mm Hg. $n_D^{23}$ 1,5146. $^{31}$P n.m.r.: δ 23,5. $^1$H n.m.r.: δ 3,09 (2 H; d; $J_{HP}$ 22,6 Hz; $\underline{CH_2}$P); 3,74 (6 H; d; $J_{HP}$ 11,3 Hz; 2 x Me of OMe); 3,85 (2 H; s; Ph$\underline{CH_2}$); 7,15 - 7,40 (5 H; m; Ph). $^{13}$C n.m.r.: δ 39,8 (d; $J_{CP}$ 130 Hz; $\underline{CH_2}$P); 40,9 (s; Ph$\underline{CH_2}$); 53,0 (d; $J_{CP}$ 6,4 Hz; 2 x OMe); 127,0; 128,5; 129,4; 133,0 (4 x s; Ph); 200,3 (s; C=O). IR: 1219 ($\upsilon_{P=O}$); 1720 ($\upsilon_{C=O}$); 2998 ($\upsilon_{C-H}$ (arom)). m/z 242 [$M^{+\cdot}$; 63%]; 151 [$(MeO)_2P(O)CH_2C\equiv O^+$; 100%]; 124 [$CH_3P(O)(OMe)_2^{+\cdot}$; 62%]; 109 [$(MeO)_2PO^+$; 88%]; 105 [$PhCH_2CH_2^+$; 44%]; 91 [$C_7H_7^+$; 91%].

**O,O-dimethyl 2-hydroxy-3-phenylpropylphosphonate (14d)**

Method 1. Yield 76%. $n_D^{23}$ 1,5009. $^{31}$P n.m.r.: δ 33,4. $^1$H n.m.r.: δ 1,91 (2 H; m; P$\underline{CH_2}$); 3,68 (2 x d; $J_{HP}$ 2,9 Hz; 2 x Me of OMe); 4,20 (1 H; m; $\underline{CH}$CH); 7,10 - 7,40 (5 H; m; Ph). $^{13}$C n.m.r.: δ 31,7 (d; $J_{CP}$ 139 Hz; $\underline{CH_2}$P); 44,4 (d; $J_{CP}$ 16,1 Hz; Ph$\underline{CH_2}$); 52,2; 52,3 (2 x d; $J_{CP}$ 6,3 Hz; 6,7 Hz, 2 x OMe); 67,3 (d; $J_{CP}$ 4,7 Hz; $\underline{CH}$CH); 126,4; 128,3; 129,3; 137,5 (4 x s; Ph). IR: 1227 ($\upsilon_{P=O}$); 2949 ($\upsilon_{C-H}$ (arom)); 3381 ($\upsilon_{O-H}$). m/z 226 [$M^{+\cdot}$-$H_2O$; 100%]; 153 [$(MeO)_2P(O)CH_2CH=OH^+$; 94%]; 117 [$C_9H_9^+$; 79%]; 91 ($C_7H_7^+$; 78%].

**O,O-diethyl 3-phenyl-2-trifluoroacetoxypropylphosphonate (15a)**

Trifluoroacetic anhydride (1,6 mℓ; 12 mmol) was added with stirring to a solution of 14a (2,0 g; 7,3 mmol) in 10 mℓ THF. The mixture was stirred at room temperature for 15 minutes and volatiles were evaporated. Bulb-to-bulb "distillation" at an oven temperature of 160-170°C / 0,08 mm Hg gave 15a as a pale yellow oil (2,3 g; 84%). $n_D^{15}$ 1,4425. $^{31}$P n.m.r.: δ 25,6. $^1$H n.m.r.: δ 1,25 (3 H; t; $J_{HH}$ 7,1 Hz; $CH_3$ of OEt); 1,26 (3 H; t; $J_{HH}$ 7,1 Hz; $CH_3$ of OEt); 2,11 (1 H; ddd; $J_{HP}$ 19,1 Hz; $J_{HH}$ (vic)

5,6 Hz; $J_{HH}$ (gem) 15,6 Hz; 1 H of $\underline{CH_2}P$); 2,19 (1 H; ddd; $J_{HP}$ 18,2 Hz; $J_{HH}$ (gem) 15,6 Hz; $J_{HH}$ (vic) 7,1 Hz; 1 H of $\underline{CH_2}P$); 3,02 (2 H; m; $Ph\underline{CH_2}$); 4,06 (4 H; m; 2 x $CH_2$ of OEt); 5,46 (1 H; m; $\underline{CH}$OTFA); 7,12 - 7,20 (5 H; m; Ph). $^{13}C$ n.m.r.: $\delta$ 16,0 (2 x s; 2 x $CH_3$ of OEt); 29,8 (d; $J_{CP}$ 143 Hz; $\underline{CH_2}P$); 40,8 (d; $J_{CP}$ 10,7 Hz; $Ph\underline{CH_2}$); 62,2 (2 x d; $J_{CP}$ 7,8 Hz; 2 x $CH_2$ of OEt); 74,0 (d; $J_{CP}$ 3,2 Hz; $\underline{CH}$OTFA); 114,9 (q; $J_{CF}$ 299 Hz; $CF_3$); 127,2; 128,6; 129,3; 134,9 (4 x s; Ph); 158,7 (q; $J_{CF}$ 40,5 Hz; C=O). IR: 1228 ($\upsilon_{P=O}$); 1773 ($\upsilon_{C=O}$); 2985 ($\upsilon_{C-H}$ (arom)). m/z 254 [$M^{+}$-$CF_3CO_2H$; 56%]; 117 [$C_9H_9^{+}$; 56%]; 91 [$C_7H_7^{+}$; 33%]; 69 [$CF_3^{+}$; 97%]; 45 [$HOC\equiv O^{+}$; 100%].

**O,O-diethyl 3-(4'-methoxyphenyl)-2-trifluoroacetoxypropylphosphonate (15b)**

From 14b as for 15a. Yield 88% after bulb-to-bulb "distillation" at an oven temperature of 234-5°C / 0,6 mm Hg. $n_D^{16}$ 1,4643. $^{31}P$ n.m.r.: $\delta$ 25,6. $^{1}H$ n.m.r.: $\delta$ 1,27; 1,28 (6 H; 2 x t; $J_{HH}$ 7,0 Hz; 2 x Me of OEt); 2,07 (2 H; m; $\underline{CH_2}P$); 2,98 (2 H; m; $Ar\underline{CH_2}$); 3,76 (3 H; s; OMe); 4,07 (4 H; m; 2 x $CH_2$ of OEt); 5,45 (1 H; m; $\underline{CH}$OTFA); 6,81 (2 H; d; $J_{HH}$ 8,6 Hz; H meta to OMe); 7,09 (2 H; d; $J_{HH}$ 8,6 Hz; H ortho to OMe). $^{13}C$ n.m.r.: $\delta$ 16,0 (2 x s; 2 x Me of OEt); 29,7 (d; $J_{CP}$ 142 Hz; $\underline{CH_2}P$); 39,9 (d; $J_{CP}$ 10,7 Hz; $Ar\underline{CH_2}$); 54,9 (s; OMe); 61,9 (2 x d; $J_{CP}$ 6,7 Hz; 2 x $CH_2$ of OEt); 74,2 (d; $J_{CP}$ 3,0 Hz; $\underline{CH}$OTFA); 113,9; 126,8; 130,4; 158,7 (4 x s; Ar); 114,3 (q; $J_{CF}$ 286 Hz; $CF_3$); 156,2 (q; $J_{CF}$ 42,3 Hz; C=O). IR: 1236 ($\upsilon_{P=O}$); 1785 ($\upsilon_{C=O}$); 2985 ($\upsilon_{C-H}$ (arom)). m/z 284 [$M^{+}$-$CF_3CO_2H$; 68%]; 147 [$MeOC_9H_8^{+}$; 100%]; 121 [$MeOC_7H_6^{+}$; 45%].

**O,O-diethyl 4-phenyl-2-trifluoroacetoxybutylphosphonate (15c)**

From 14c as for 15a. Yield 56% after bulb-to-bulb "distillation" at an oven temperature of 207-9°C / 0,2 mm Hg. $n_D^{15}$ 1,4608. $^{31}P$ n.m.r.: $\delta$ 25,1. $^{1}H$ n.m.r.: $\delta$ 1,27; 1,28 (6 H; 2 x t; $J_{HH}$ 7,0 Hz; 2 x Me of OEt); 2,13 (4 H; 2 x m; $\underline{CH_2}P$ and $PhCH_2\underline{CH_2}$); 2,65 (2 H; m; $Ph\underline{CH_2}$); 4,08 (4 H; m; 2 x $CH_2$ of OEt); 5,32 (1 H; m; $\underline{CH}$OTFA); 7,10 - 7,30 (5 H; m; Ph). $^{13}C$ n.m.r.: $\delta$ 15,4 (d; $J_{CP}$ 5,4 Hz; 2 x Me of OEt); 29,9 (d; $J_{CP}$ 142 Hz; $\underline{CH_2}P$); 30,4 (s; $Ph\underline{CH_2}$); 35,6 (d; $J_{CP}$ 8,8 Hz; $PhCH_2\underline{CH_2}$); 61,6

(2 x d; $J_{CP}$ 6,9 Hz; 2 x $CH_2$ of OEt); 73,0 (s; CHOTFA); 114,0 (q; $J_{CF}$ 286 Hz; $CF_3$); 125,7; 127,7; 128,0; 139,5 (4 x s; Ph); 156,0 (q; $J_{CF}$ 42,2 Hz; C=O). IR: 1208 ($\upsilon_{P=O}$); 1776 ($\upsilon_{C=O}$); 2958 ($\upsilon_{C-H}$ (arom)). m/z 268 [$M^{+\cdot}$-$CF_3CO_2H$; 40%]; 91 [$C_7H_7^+$; 100%].

**O,O-dimethyl 3-phenyl-2-trifluoroacetoxypropylphosphonate (15d)**

From 14d as for 15a. Yield 57% after bulb-to-bulb "distillation" at an oven temperature of 192-4°C / 0,4 mm Hg. $n_D^{24}$ 1,4534. $^{31}P$ n.m.r.: δ 28,1. $^1H$ n.m.r.: δ 2,15; (2 H; m; $CH_2P$); 3,05 (2 H; m; $PhCH_2$); 3,71 (2 x d; 6 H; $J_{HP}$ 4,4 Hz; 2 x $CH_3$ of OMe); 5,49 (1 H; m; CHOTFA); 7,15 - 7,40 (5 H; m: Ph). $^{13}C$ n.m.r.: δ 28,8 (d; $J_{CP}$ 152 Hz; $CH_2P$); 40,7 (d; $J_{CP}$ 11,2 Hz; $PhCH_2$); 52,4 (2 x d; $J_{CP}$ 6,7 Hz; 2 x $CH_3$ of OMe); 73,8 (d; $J_{CP}$ 3,5 Hz; CHOTFA); 114,2 (q; $J_{CF}$ 286 Hz; $CF_3$); 127,2; 128,5; 129,3; 134,8 (4 x s; Ph); 156,1 (q; $J_{CF}$ 42,3 Hz; C=O). IR: 1226 ($\upsilon_{P=O}$); 1785 ($\upsilon_{C=O}$); 2955 ($\upsilon_{C-H}$ (arom)). m/z [$M^{+\cdot}$-$CF_3CO_2H$; 71%]; 117 [$C_9H_9^+$; 72%]; 91 [$C_7H_7^+$; 65%]; 69 [$CF_3^+$; 100%]; 45 [$HOC\equiv O^+$; 99%].

**N,N,N',N'-tetraethyl-P-(3-phenyl-2-trifluoroacetoxypropyl)phosphonic diamide (15e)**

From 4a as for 15a. Yield 100%. $n_D^{24}$ 1,4270. $^{31}P$ n.m.r.: δ 34,2. $^1H$ n.m.r.: δ 1,02 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of $NEt_2$); 1,09 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of $NEt_2$); 2,30 - 2,40 (2 H; m; $CH_2P$); 2,88 - 3,22 (10 H; m; $PhCH_2$ and 4 x $CH_2$ of $NEt_2$); 5,45 - 5,56 (1 H; m; CHOTFA); 7,25 - 7,40 (5 H; m; Ph). $^{13}C$ n.m.r.: δ 13,67; 13,75 (2 x s; 4 x Me of $NEt_2$); 29,4 (d; $J_{CP}$ 118 Hz; $CH_2P$); 38,6; 38,7 (2 x d; $J_{CP}$ 3,9 Hz; 4,3 Hz; 4 x $CH_2$ of $NEt_2$); 41,1 (d; $J_{CP}$ 8,8 Hz; $PhCH_2$); 74,8 (s; CHOTFA); 114,4 (q; $J_{CF}$ 286 Hz; $CF_3$); 127,5; 128,6; 129,5; 135,3 (4 x s; Ph); 159,5 (q; $J_{CF}$ 39,8 Hz; C=O). IR: 1183 ($\upsilon_{P=O}$); 1783 ($\upsilon_{C=O}$); 2942 ($\upsilon_{C-H}$ (arom)). m/z 308 [$M^{+\cdot}$-$CF_3CO_2H$; 1%]; 191 [$(NEt_2)_2PO^+$; 10%]; 117 [$C_9H_9^+$; 100%]; 91 [$C_7H_7^+$; 33%]; 72 [$NEt_2^+$; 29%].

**O,O-diethyl 2-acetoxy-3-phenylpropylphosphonate (15f)**

A mixture of 14a (4,0 g; 15 mmol) and acetic anhydride (50 mℓ; 530 mmol) was refluxed for 2 hours. 50 mℓ water was added. After extraction with chloroform (3 x 50 mℓ), drying ($MgSO_4$), filtration and solvent evaporation, bulb-to-bulb "distillation" at an oven temperature of 232-4°C / 0,4 mm Hg gave 15f as a yellow oil (1,9 g; 40%). $n_D^{15}$ 1,4922. $^{31}P$ n.m.r.: δ 27,2. $^{1}H$ n.m.r.: δ 1,26 (6 H; 2 x t; $J_{HH}$ 7,0 Hz; 2 x $CH_3$ of OEt); 1,91 - 2,09 (2 H; m; $CH_2P$); 1,97 (3 H; s; $COCH_3$), 2,96 (2 H; d; $J_{HH}$ 6,0 Hz; $PhCH_2$); 4,05 (4 H; m; 2 x $CH_2$ of OEt); 5,29 (1 H; m; CHOAc); 7,25 - 7,30 (5 H; m; Ph). $^{13}C$ n.m.r.: δ 16,3 (d; $J_{CP}$ 6,9 Hz; 2 x Me of OEt); 21,0 (s; $COCH_3$); 30,0 (d; $J_{CP}$ 141 Hz; $CH_2P$); 40,9 (d; $J_{CP}$ 9,6 Hz; $PhCH_2$); 61,7 (2 x d; $J_{CP}$ 6,0 Hz; 6,5 Hz; 2 x $CH_2$ of OEt); 69,6 (s; CHOAc); 126,7; 128,4; 129,5; 136,6 (4 x s; Ph); 169,9 (s; C=O). IR: 1241 ($\upsilon_{P=O}$); 1738 ($\upsilon_{C=O}$); 2962 ($\upsilon_{C-H}$ (arom)). m/z 254 [$M^{+\cdot}$-$CH_3CO_2H$; 88%]; 117 [$C_9H_9^+$; 84%]; 91 [$C_7H_7^+$; 60%]; 43 [$CH_3C{\equiv}O^+$; 100%].

**2-(1-diethylphosphonyl-3-phenyl)propyl methanesulphonate (15g)**

A mixture of 14a (1,5 g; 5,5 mmol) and pyridine (1,8 mℓ; 22 mmol) was cooled to 0°C. Mesyl chloride (0,47 mℓ; 6 mmol) was added dropwise and stirring was continued at 0°C for 3 hours. A solution of 3,3 mℓ conc. hydrochloric acid in 11 mℓ ice-water was added and extracted with cold ether. Drying ($MgSO_4$), filtration and evaporation at reduced pressure gave 15g as a yellow oil (1,6 g; 83%). No attempts at further purification were undertaken due to the thermal instability of the compound. $^{31}P$ n.m.r. shows only one peak for the crude. $n_D^{25}$ 1,4952. $^{31}P$ n.m.r.: δ 25,5. $^{1}H$ n.m.r.: δ 1,262 (3 H; t; $J_{HH}$ 7,1 Hz; $CH_3$ of OEt); 1,268 (3 H; t; $J_{HH}$ 7,1 Hz; $CH_3$ of OEt); 2,07 - 2,39 (2 H; m; $CH_2P$); 2,51 (3 H; s; $CH_3SO_2$); 2,94 - 3,22 (2 H; m; $PhCH_2$); 3,95 - 4,11 (4 H; 2 x $CH_2$ of OEt); 4,87 - 5,00 (1 H; m; CHOMs); 7,10 - 7,27 (5 H; m; Ph). $^{13}C$ n.m.r.: δ 16,0 (d; $J_{CP}$ 5,9 Hz; 2 x $CH_3$ of OEt); 31,3 (d; $J_{CP}$ 139 Hz; $CH_2P$); 37,3 (s; $CH_3SO_2$); 41,4 (d; $J_{CP}$ 6,2 Hz; $PhCH_2$); 62,0; 62,1 (2 x s; 2 x $CH_2$ of OEt); 79,0 (s; CHOMs); 127,0; 128,5; 129,6; 135,8 (4 x s; Ph). IR: 1208 ($\upsilon_{P=O}$); 1360 ($\upsilon_{S=O}$); 2985

($\upsilon_{C-H}$ (arom)). m/z 255 [$M^{+\cdot}$ - $CH_3SO_3$; 100%]; 117 [$C_9H_9^+$; 22%]; 91 [$C_7H_7^+$; 36%]; 79 [$CH_3SO_2^+$; 46%].

**Allylbenzene (16)**

To magnesium turnings (1,2 g; 49 mmol) and 10 mℓ THF was added dropwise a solution of bromobenzene (5,0 mℓ; 48 mmol) in 20 mℓ THF while refluxing. After all magnesium had disappeared refluxing was continued for 15 minutes before a solution of allyl bromide(4,1 mℓ; 47 mmol) in 10 mℓ THF was added. Reflux was continued for 1 hour. The mixture was allowed to cool overnight and 20 mℓ water added. The ether layer was removed and the aqueous residue extracted with ether (30 mℓ). The ether extracts were dried ($MgSO_4$), filtered and the solvent evaporated. Distillation at 152-7°C gave 16a as a colourless oil (4,7 g; 84%). $n_D^{16}$ 1,5183 (Lit.[140] $n_D^{15}$ 1,5145). $^1$H n.m.r.: δ 3,42 (2 H; d; $J_{HH}$ 6,7 Hz; Ph$\underline{CH_2}$); 5,12 (2 H; m; CH=$\underline{CH_2}$); 6,00 (1 H; m; $\underline{CH}$=$CH_2$); 7,30 (5 H; m; Ph).

**Estragole (16b)**

From 4-bromoanisole and allyl bromide as for 16a. Distillation at 198-201°C gave 16b as a colourless oil. Yield 74%. $n_D^{16}$ 1,5268. (Lit.[141] $n_D^{18}$ 1,5230). $^1$H n.m.r.: δ 3,38 (2 H; d; $J_{HH}$ 6,7 Hz; Ar$\underline{CH_2}$); 3,82 (3 H; s; OMe); 5,11 (2 H; m; CH=$\underline{CH_2}$); 6,00 (1 H; m; $\underline{CH}$ = $CH_2$); 6,90 (2 H; d; $J_{HH}$ 8,6 Hz; H meta to OMe); 7,15 (2 H; d; $J_{HH}$ 8,6 Hz; H ortho to OMe).

**4-phenyl-1-butene (16c)**

From benzylchloride and allyl bromide as for 16a. Distillation 91-3°C/water vacuum gave 16c as a colourless oil. Yield 73%. $n_D^{22}$ 1,5098. $^1$H n.m.r.: δ 2,44 (2 H; m; Ph$CH_2\underline{CH_2}$); 2,78 (2 H; t; $J_{HH}$ 7,8 Hz; Ph$\underline{CH_2}$); 5,07 (2 H; m; CH=$\underline{CH_2}$); 5,92 (1 H; ddt; $J_{HH}$ 6,7 Hz; $J_{HH}$ (cis) 10,3 Hz; $J_{HH}$ (trans) 17,0 Hz; $\underline{CH}$=$CH_2$); 7,2 - 7,4 (5 H; m; Ph).

**Ethyl trifluoroacetate (17a)**

To a mixture of ethanol (0,87 mℓ; 15 mmol) and pyridine (1,2 mℓ; 15 mmol) was added trifluoroacetic anhydride (2,0 mℓ; 15 mmol). After stirring at room temperature for 15 minutes, ethyl trifluoroacetate was distilled off at 58-9°C as a colourless oil (1,3 g; 62%). $^1$H n.m.r.: δ 1,33 (3 H; t; $J_{HH}$ 7,2 Hz; $CH_3$ of OEt); 4,35 (2 H; q; $J_{HH}$ 7,1 Hz; $CH_2$ of OEt).

**Methyl trifluoroacetate (17b)**

As 17a from methanol. Distillation gave 17b as colourless oil at 39-40°C. Yield 65%. $^1$H n.m.r.: δ 3,91 (s; OMe).

**Ethyl methanesulphonate (17c)**

A mixture of ethanol (5,0 mℓ; 85 mmol) and pyridine (28 mℓ; 340 mmol) was cooled to 0°C. Mesyl chloride (6,6 mℓ; 85 mmol) was added and the mixture was stirred at 0°C for 3 hours. A solution of 51 mℓ conc. hydrochloric acid in 100 mℓ ice-water was added. After extraction with ether (4 x 50 mℓ), drying ($MgSO_4$) and filtration, solvent was evaporated in vacuo without heating to give 17c as a colourless oil (7,5 g; 70%). $n_D^{24}$ 1,4170. (Lit.[142] $n_D^{15}$ 1,4194). $^1$H n.m.r.: δ 1,28 (3 H; t; $J_{HH}$ 7,0 Hz; $CH_3$ of OEt); 2,88 (3 H; s; $CH_3S$); 4,16 (2 H; q; $J_{HH}$ 7,0 Hz; $CH_2$ of OEt).

**O,O-diethyl 3-phenylprop-2-enylphosphonate (18)**

A mixture of cinnamyl bromide (1,5 g; 7,6 mmol) and triethyl phosphite (1,3 mℓ; 7,7 mmol) was refluxed at 140°C for 4 hours. After bulb-to-bulb "distillation" at an oven temperature of 187-9°C /0,4 mm Hg, 18 was obtained as a colourless oil (1,7 g; 87%). $n_D^{22}$ 1,5278. $^{31}$P n.m.r.: δ 27,4. $^1$H n.m.r.: δ 1,28 (6 H; t; $J_{HH}$ 7,1 Hz; 2 x Me of OEt); 2,72 (2 H; ddd; $J_{HP}$ 22,2 Hz; $J_{HH}$ 7,5 Hz; $J_{HH}$ 1,2 Hz;

$\underline{CH_2}P$); 4,08 (4 H; m; 2 x $CH_2$ of OEt); 6,13 (1 H; m; PhCH=$\underline{CH}$); 6,49 (1 H; m; Ph$\underline{CH}$); 7,15 - 7,35 (5 H; m; Ph). $^{13}C$ n.m.r.: $\delta$ 16,1 (d; $J_{CP}$ 5,7 Hz; 2 x Me of OEt); 30,7 (d; $J_{CP}$ 139 Hz; $\underline{CH_2}P$); 61,6 (d; $J_{CP}$ 6,6 Hz; 2 x $CH_2$ of OEt); 118,4 (d; $J_{CP}$ 11,9 Hz; PhCH=$\underline{CH}$); 125,8; 127,1; 128,1; 136,4 (4 x s; Ph); 134,3 (d; $J_{CP}$ 16,5 Hz; Ph$\underline{CH}$). IR: 1245 ($\upsilon_{P=O}$); 2983 ($\upsilon_{C-H}$ (arom)). m/z 254 [$M^{+\cdot}$; 69%]; 226 [$M^{+\cdot}$ - $C_2H_4$; 18%]; 198 [$PhCH=CHCH_2P(O)(OH)_2^{+\cdot}$; 27%]; 117 [$C_9H_9^+$; 100%]; 91 [$C_7H_7^+$; 48%].

**Experiment carried out to determine if the fragmentation reaction is acid catalyzed**

0,06 g of $\underline{14a}$ in 400 $\mu\ell$ $CF_3CO_2D$ was sealed in an n.m.r. tube. After 68 hours at room temperature $^{31}P$ and $^1H$ n.m.r. spectroscopy showed only the presence of $\underline{15a}$. Heating the sample in a waterbath at 70°C for 44 hours showed no further change.

**Attempt to trap ethyl metaphosphate with isoamylalcohol**

$\underline{15a}$ (0,5 g; 1,4 mmol) was dissolved in 0,5 m$\ell$ isoamylalcohol. The solution was heated under reflux at 140°C for 23 hours. $^{31}P$ n.m.r. spectroscopy showed only the formation of $\underline{14a}$.

**Attempts to trap ethyl metaphosphate with either *tert*-butanol or isopropyl alcohol**

A solution of $\underline{15a}$ in a mixture of sulfolane and either *tert*-butanol or isopropyl alcohol was refluxed at 190°C for 5 hours. After cooling the solution was transferred to a separatory funnel using ca. 10 m$\ell$ benzene. The benzene solution was extracted with $D_2O$ containing sodium carbonate. The $D_2O$ solution was subjected to $^{31}P$ n.m.r. and $^1H$ n.m.r. spectroscopy showing $\underline{14a}$. The benzene solution after drying ($MgSO_4$) and solvent evaporation also showed $\underline{14a}$ by $^{31}P$ and $^1H$ n.m.r. spectroscopy.

**Identification of ethyl phosphate in the hydrolysate of the fragmentation of 15a**

15a (0,76 g) was dissolved in 0,5 mℓ sulfolane and heated at 210°C for 23 hours. After cooling 1 mℓ of a NaOD solution in $D_2O$ was added and the mixture stirred for 10 minutes. 1 mℓ $CDCl_3$ was added and the $D_2O$ solution after separation subjected to n.m.r. spectroscopy. Authentic anilinium ethylphosphate was added to the sample and the sample again subjected to n.m.r. spectroscopy. No new signals in the $^{31}P$ n.m.r. spectrum were observed, but only an increase in the intensity of a signal occurring at δ 1,24 ppm. A similar increase in a triplet at δ 1,15 ppm and a doublet of quartets at δ 3,81 ppm was observed in the $^{1}H$ n.m.r. spectrum.

**Conditions of gas-chromatography and the retention times of compounds**

Gas-chromatography was performed using a Carlo Erba Fractovap 2150 gas-chromatograph and a Spectra-Physics SP4290 integrator. The carrier gas was nitrogen, always used at a pressure of 1 $kg.cm.^{-2}$

The following columns were used:

1) A 2 m column with 3 mm inner diameter packed with 90-100 mesh Chromosorb WHP-SP using 5% by weight of SE-30 (GCG) as liquid phase (Column A).
2) A 1,9 m column with 3 mm inner diameter packed with 80-100 mesh Chromosorb WHP-SP using 3% by weight of OV-17 as liquid phase (Column B).

The oven temperature was varied as required for different samples. Individual runs were always conducted at a constant temperature. Retention times of compounds are given in table 1 for the various conditions used.

Table 1: Table of retention times of various compounds as function of the column used and oven temperature

| Column | Temperature/°C | Compound | $R_T$/min |
|---|---|---|---|
| B | 220 | 15b | 5,07 - 5,16 |
| | | Allylanisole | 0,63 - 0,67 |
| | | Sulfolane | 0,96 - 0,98 |
| | | $CF_3CO_2Et$ | 0,43 |
| | 210 | 15c | 4,11 - 4,17 |
| | | 4-Phenylbutene | 0,54 - 0,55 |
| | | Sulfolane | 1,08 |
| | | $CF_3CO_2Et$ | 0,43 - 0,45 |
| | 190 | 15a | 4,81 - 4,84 |
| | | Allylbenzene | 0,67 - 0,69 |
| | | Sulfolane | 1,50 - 1,52 |
| | | $CF_3CO_2Et$ | 0,42 |
| | | Diglyme | 0,53 - 0,55 |
| | | 18 | 11,78 - 11,99 |
| | 210 | 15f | 6,90 - 7,05 |
| | | Allylbenzene | 0,51 - 0,52 |
| | | Sulfolane | 1,08 |
| | | $CH_3CO_2Et$ | 0,43 - 0,44 |
| A | 193 | 15d | 6,39 - 6,44 |
| | | Allylbenzene | 0,83 - 0,84 |
| | | Sulfolane | 1,39 |
| | | $CF_3CO_2Me$ | 0,59 - 0,63 |
| | 180 | 15a | 9,29 - 9,32 |
| | | Allylbenzene | 1,03 |
| | | Sulfolane | 1,60 - 1,61 |
| | | $CF_3CO_2Et$ | 0,73 - 0,75 |
| | 196 | 15g | 8,68 - 8,77 |
| | | Allylbenzene | 0,83 - 0,85 |
| | | Sulfolane | 1,29 - 1,30 |
| | | $MeSO_3Et$ | 0,61 - 0,62 |

**N-Methylanilinium ethylphosphorofluoridate (19)**

19 was prepared from $PCl_3$ according to literature procedures.[143, 144] White powder. $^{31}P$ n.m.r.: $\delta$ -6,3 (d; $J_{PF}$932 Hz). $^{19}F$ n.m.r.: $\delta$ -83,6 (d; $J_{PF}$ 931 Hz). $^{1}H$ n.m.r.: $\delta$ 1,24 (3 H; t; $J_{HH}$ 7,0 Hz; $CH_3$ of OEt); 2,89 (3 H; s; MeN); 4,01 (2 H; m; $CH_2$ of OEt); 7,29 - 7,46 (5 H; m; Ph).

**Trapping of ethyl metaphosphate with fluoride**

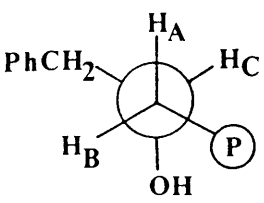
A mixture of 15a (0,14 g; 0,38 mmol), lithium fluoride (0,01 g; 0,4 mmol) and 0,1 m$\ell$ sulfolane was heated under reflux at 220°C for 5 hours. After cooling $CDCl_3$ was added and the solution transferred to two different n.m.r. tubes to one of which 19 was added. Both were subjected to $^{31}P$, $^{1}H$ and $^{19}F$ n.m.r. spectroscopy. The sample containing 19 showed no new peaks in the $^{31}P$ n.m.r. spectra and only and increase in intensity of the following signals: In the $^{31}P$ n.m.r. spectrum a doublet at $\delta$ - 6,8 ppm ($J_{PF}$ 935 Hz). In the $^{19}F$ n.m.r. spectrum a doublet at $\delta$ -83,8 ppm ($J_{PF}$ 931 Hz). In the $^{1}H$ n.m.r. spectrum an increase in intensity of a triplet at $\delta$ 1,1 ppm and a multiplet at $\delta$ 3,9 ppm and new peaks in the aromatic region are observed. The $CH_3N$-signal is obscured by a multiplet arising from sulfolane.

# APPENDIX

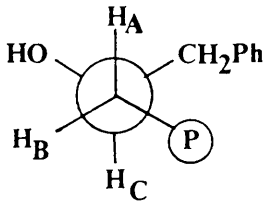
## Conformational Analysis using the Haasnoot-equation

The Haasnoot-equation[110] is $^3J_{HH} = P_1 \cos^2 \varnothing + P_2 \cos \varnothing + P_3 + \Sigma \Delta \chi_i \{P_4 + P_5 \cos^2 (\zeta_i \varnothing + P_6 \mid \Delta \chi_i \mid)\}$ where the $P_i$ are constants derived from datasets of coupling constants obtained for rigid systems. These constants vary depending on the number of substituents on the C-C bond under consideration. $\varnothing$ is the HCCH dihedral angle in the conformation for which $^3J_{HH}$ is being calculated. $\Delta\chi_i$ is the difference in electronegativity between the substituent group *i* and hydrogen i.e. $\Delta\chi_i = \chi_i - \chi_H$. $\zeta_i$ is a sign term that depends on the orientation of the group *i* relative to the hydrogen atom under consideration.

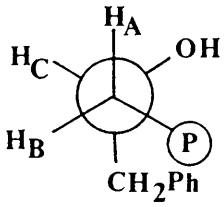
For 4a there are three substituents on the $C^{\alpha}$-$C^{\beta}$ bond, i.e. (P) ≡ $P(O)(NEt_2)_2$, OH and $PhCH_2$. The required $P_i$ values are $P_1$ = 13,22, $P_2$ = -0,99, $P_3$ = 0, $P_4$ = 0,87, $P_5$ = -2,46 and $P_6$ = 19,9°. The group electronegativities[111] are $\chi_P$ = 2,419, $\chi_{OH}$ = 3,494, $\chi_{PhCH_2}$ = 2,507 and $\chi_H$ = 2,176. $\Delta\chi_i = \chi_i - \chi_H$ and thus $\Delta\chi_P$ = 0,243, $\Delta\chi_{OH}$ = 1,318 and $\Delta\chi_{PhCH_2}$ = 0,331. The equation thus becomes $^3J_{HH} = 13{,}22 \cos^2 \varnothing - 0{,}99 \cos \varnothing + \Sigma\chi_i \{0{,}87 - 2{,}46 \cos^2 (\zeta_i \varnothing + 19{,}9 \mid \Delta\chi_i \mid)\}$. The equation is now used to calculate a coupling constant for a given conformation of 4a (fig. 1).




I
$\varnothing_{AC}$ = 60°
$\varnothing_{BC}$ = 180°




II
$\varnothing_{AC}$ = 180°
$\varnothing_{BC}$ = 300°




III
$\varnothing_{AC}$ = 300°
$\varnothing_{BC}$ = 60°

Figure 1

The sign terms are $\zeta_{OH} = -1, \zeta_{PhCH_2} = +1, \zeta_P = +1$ (relative to $H_A$) and $\zeta_P = -1$ (relative to $H_B$). For conformation I we now first calculate the summation term. With regard to A, $\varnothing_{AC} = 60°$.

| | | | | |
|---|---|---|---|---|
| For P | : | $0,243\ \{0,87 - 2,46\ \cos^2\ [60 + 19,9\ (0,243)]\}$ | = | 0,103 |
| For $PhCH_2$ | : | $0,331\ \{0,87 - 2,46\ \cos^2\ [60 + 19,9\ (0,331)]\}$ | = | 0,159 |
| For OH | : | $0,318\ \{0,87 - 2,46\ \cos^2\ [-60 + 19,9\ (1,318)]\}$ | = | -1,094 |
| | | $\Sigma$ | = | -0,832 |

$$^3J_{AC}{}^{I} = 13,22\ \cos^2\ 60 - 0,99\ \cos\ 60 - 0,832 = 1,98\ Hz$$

With regard to B, $\varnothing_{BC} = 180°$.

| | | | | |
|---|---|---|---|---|
| For P | : | $0,243\ \{0,87 - 2,46\ \cos^2\ [-180 + 19,9\ (0,243)]\}$ | = | 0,382 |
| For $PhCH_2$ | : | $0,331\ \{0,87 - 2,46\ \cos^2\ [180 + 19,9\ (0,331)]\}$ | = | 0,516 |
| For OH | : | $1,318\ \{0,87 - 2,46\ \cos^2\ [-180 + 19,9\ (1,318)]\}$ | = | -1,462 |
| | | $\Sigma$ | = | -2,360 |

$$^3J_{BC}{}^{I} = 13,22\ \cos^2\ 180 - 0,99\ \cos\ 180 - 2,36 = 11,85\ Hz$$

For conformation II. With regard to A, $\varnothing_{AC} = 180°$.

| | | | | |
|---|---|---|---|---|
| For P | : | $0,243\ \{0,87 - 2,46\ \cos^2\ [180 + 19,9\ (0,243)]\}$ | = | 0,382 |
| For $PhCH_2$ | : | $0,331\ \{0,87 - 2,46\ \cos^2\ [180 + 19,9\ (0,331)]\}$ | = | 0,516 |
| For OH | : | $1,318\ \{0,87 - 2,46\ \cos^2\ [-180 + 19,9\ (1,318)]\}$ | = | -1,462 |
| | | $\Sigma$ | = | -2,360 |

$$^3J_{AC}{}^{II} = 13,22\ \cos^2\ 180 - 0,99\ \cos\ 180 - 2,36 = 11,85\ Hz$$

With regard to B, $\varnothing_{BC} = 300°$.

| | | | | |
|---|---|---|---|---|
| For P | : | $0,243\ \{0,87 - 2,46\ \cos^2\ [-300 + 19,9\ (0,243)]\}$ | = | 0,103 |
| For $PhCH_2$ | : | $0,331\ \{0,87 - 2,46\ \cos^2\ [300 + 19,9\ (0,331)]\}$ | = | -0,001 |
| For OH | : | $1,318\ \{0,87 - 2,46\ \cos^2\ [-300 + 19,9\ (1,318)]\}$ | = | +1,133 |
| | | $\Sigma$ | = | 1,235 |

$$^3J_{BC}{}^{II} = 13,22\ \cos^2\ 300 - 0,99\ \cos\ 300 + 1,24 = 4,05\ Hz$$

For conformation III. With regard to A, $\varnothing_{AC} = 300°$.

| | | | | |
|---|---|---|---|---|
| For P | : | $0,243\ \{0,87 - 2,46\ \cos^2\ [300 + 19,9\ (0,243)]\}$ | = | 0,016 |
| For $PhCH_2$ | : | $0,331\ \{0,87 - 2,46\ \cos^2\ [300 + 19,9\ (0,331)]\}$ | = | -0,001 |
| For OH | : | $1,318\ \{0,87 - 2,46\ \cos^2\ [-300 + 19,9\ (1,318)]\}$ | = | +1,133 |
| | | $\Sigma$ | = | 1,148 |

$$^3J_{AC}{}^{III} = 13,22\ \cos^2\ 300 - 0,99\ \cos\ 300 + 1,15 = 3,96\ Hz$$

With regard to B, $\varnothing_{BC} = 60°$.

| | | | | |
|---|---|---|---|---|
| For P | : | $0,243\ \{0,87 - 2,46\ \cos^2\ [-60 + 19,9\ (0,243)]\}$ | = | 0,016 |
| For $PhCH_2$ | : | $0,331\ \{0,87 - 2,46\ \cos^2\ [60 + 19,9\ (0,331)]\}$ | = | -0,159 |
| For OH | : | $1,318\ \{0,87 - 2,46\ \cos^2\ [-60 + 19,9\ (1,318)]\}$ | = | -1,094 |
| | | $\Sigma$ | = | 0,919 |

$$^3J_{BC}{}^{III} = 13,22\ \cos^2\ 60 - 0,99\ \cos\ 60 - 0,92 = 1,89\ Hz$$

$J_{AC}^{obs}$ = 2,0 Hz $J_{BC}^{obs}$ = 10,0 Hz

If a, b and c are the relative contributions of conformations I, II and III respectively we can set up the following set of equations.

$$a\,{}^3J_{AC}^{I} + b\,{}^3J_{AC}^{II} + c\,{}^3J_{AC}^{III} = {}^3J_{AC}^{obs}$$

$$a\,{}^3J_{BC}^{I} + b\,{}^3J_{BC}^{II} + c\,{}^3J_{BC}^{III} = {}^3J_{BC}^{obs}$$

$$a + b + c = 1$$

Substituting the relevant values we obtain

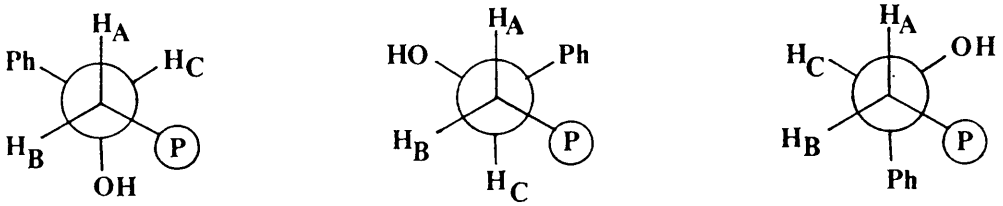
$$1{,}98\,a + 11{,}85\,b + 3{,}86\,c = 2{,}0$$

$$11{,}85\,a + 4{,}05\,b + 1{,}89\,c = 10{,}0$$

$$a + b + c = 1$$

and solving a = 0,82; b = -0,04; c = 0,22

For 4b we have the following conformations, (fig. 2).




I II III

**Figure 2**

$\chi_{Ph}$ = 2,717 : $\Delta\chi_{Ph}$ = 0,541

We only need to recalculate those terms for 4a in which $PhCH_2$ was involved.

For I: $H_A$: $0,541\ \{0,87 - 2,46\ \cos^2\ [60 + 19,9\ (0,541)]\} = 0,326$

$^3J_{AC}{}^{I} = 2,15$

$H_B$: $0,541\ \{0,87 - 2,46\ \cos^2\ [180 + 19,9\ (0,541)]\} = 0,814$

$^3J_{BC}{}^{I} = 11,55$

For II: $H_A$: $0,541\ \{0,87 - 2,46\ \cos^2\ [180 + 19,9\ (0,541)]\} = -0,814$

$^3J_{AC}{}^{II} = 11,55$

$H_B$: $0,541\ \{0,87 - 2,46\ \cos^2\ [300 + 19,9\ (0,541)]\} = -0,097$

$^3J_{BC}{}^{II} = 3,95$

For III: $H_A$: $0,541\ \{0,87 - 2,46\ \cos^2\ [300 + 19,9\ (0,541)]\} = -0,097$

$^3J_{AC}{}^{III} = 3,86$

$H_B$: $0,541\ \{0,87 - 2,46\ \cos^2\ [60 + 19,9\ (0,541)]\} = 0,326$

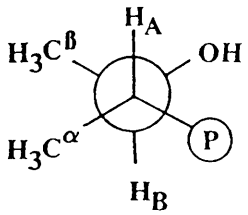
$^3J_{BC}{}^{III} = 2,06$

The system of equations thus become

$$2,15\ a + 11,55\ b + 3,86\ c = 1,77$$
$$11,55\ a + 3,95\ b + 2,06\ c = 11,09$$
$$a + b + c = 1$$

and solving we have $a = 0,96$; $b = -0,06$; $c = 0,10$

For 4f we have four substituents and a further set of $P_i$ has to be used. $P_1 = 13,24$, $P_2 = -0,91$, $P_3 = 0$, $P_4 = 0,53$, $P_5 = -2,41$ and $P_6 = 15,5°$. The relevant group-electronegativities, (fig. 3), are




(1R,2R)

**Figure 3**

$\chi_{CH_3}$ = 2,472, $\chi_{OH}$ = 3,494 and $\chi_P$ = 2,419. Thus $\Delta\chi_{CH_3}$ = 0,296, $\Delta\chi_P$ = 0,243, $\Delta\chi_{OH}$ = 1,318. However, now the group electronegativities of the substituents have to be corrected as follow, $\Delta\chi_i = \Delta\chi_i^{\alpha} - P_7\Sigma\Delta\chi_i^{ß}$. For three substituents $P_7$ = 0 and thus no correction was required. For four substituents $P_7$ = 0,19. $\Delta\chi_{CH_3}^{\alpha}$ = 0,296 - 0,19 (1,318 + 0,296) = -0,011, $\Delta\chi_P$ = 0,243 - 0,19 (1,318 + 0,296) = -0,064, $\Delta\chi_{CH_3}^{ß}$ = 0,296 - 0,19 (0,296 + 0,243) = 0,194, $\Delta\chi_{OH}$ = 1,318 - 0,19 (0,296 + 0,243) = 1,216. For the conformation shown in figure 3 we have, $\zeta_{CH_3}^{\alpha}$ = -1, $\zeta_{CH_3}^{ß}$ = -1, $\zeta_P$ = +1, $\zeta_{OH}$ = +1 and $\varnothing_{AB}$ = 180°.

First we calculate the summation terms.

| | | | | |
|---|---|---|---|---|
| For P | : | -0,064 {0,53 - 2,41 $\cos^2$ [180 + 15,5 (0,064)]} | = | 0,120 |
| For $CH_3^{\alpha}$ | : | -0,011 {0,53 - 2,41 $\cos^2$ [-180 + 15,5 (0,011)]} | = | 0,021 |
| For $CH_3^{ß}$ | : | 0,194 {0,53 - 2,41 $\cos^2$ [-180 + 15,5 (0,194)]} | = | -0,363 |
| For OH | : | 1,216 {0,53 - 2,41 $\cos^2$ [180 + 15,5 (0,216)]} | = | -1,980 |
| | | $\Sigma$ | = | -2,202 |

$$^3J_{AB} = 13,24 \cos^2 180 - 0,91 \cos 180 - 2,20 = 12,0 \text{ Hz}$$

The other conformation of 4f we considered is shown in figure 4.

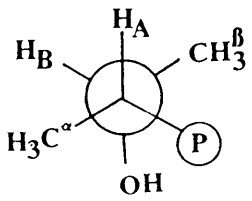



**Figure 4**

Now $\varnothing_{AB}$ = 300°. Again we first calculate the summation terms.

| | | | | | |
|---|---|---|---|---|---|
| For P | : | -0,064 {0,53 - 2,41 $\cos^2$ [300 + 15,5 (0,064)]} | = | 0,007 | [1] |
| For $CH_3^{\alpha}$ | : | -0,011 {0,53 - 2,41 $\cos^2$ [-300 + 15,5 (0,011)]} | = | 0,001 | [2] |
| For $CH_3^{\beta}$ | : | 0,194 {0,53 - 2,41 $\cos^2$ [-300 + 15,5 (0,194)]} | = | 0,007 | |
| For OH | : | 1,216 {0,53 - 2,41 $\cos^2$ [300 + 15,5 (0,216)]} | = | -1,017 | |
| | | | $\Sigma$ = | -1,002 | |

$^3J_{AB}$ = 13,24 $\cos^2$ 300 - 0,91 cos 300 - 1,0 = 1,9 Hz

$^3J_{AB}^{obs}$ = 9,1 Hz. We thus have the set of equations.

9,1 = 12,0 a + 1,9 b

1 = a + b

and solving a = 0,71, b = 0,29

For the conformation of (1S,2R)-4g shown in figure 5,

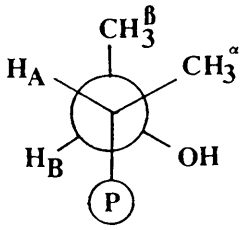



**Figure 5**

the only things that change are $\zeta_{CH_3}{}^{\alpha} = +1$ and $\zeta_P = -1$. We thus only have to recalculate the terms given in [1] and [2] above. We then obtain $^3J_{AB} = 1{,}85$ Hz. For the conformation shown in figure 6, the angle $\varnothing_{AB}$ is now 60°.

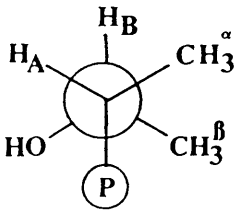


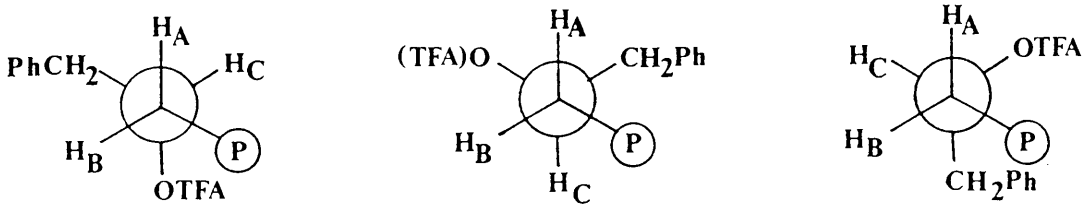

**Figure 6**

The summation terms thus become:

| | | | | |
|---|---|---|---|---|
| For P | : | -0,064 {0,53 - 2,41 $\cos^2$ [-60 + 15,5 (0,064)]} | = | 0,002 |
| For $CH_3{}^{\alpha}$ | : | -0,011 {0,53 - 2,41 $\cos^2$ [60 + 15,5 (0,011)]} | = | 0,001 |
| For $CH_3{}^{\beta}$ | : | 0,194 {0,53 - 2,41 $\cos^2$ [-60 + 15,5 (0,194)]} | = | 0,036 |
| For OH | : | 1,216 {0,53 - 2,41 $\cos^2$ [60 + 15,5 (0,216)]} | = | 0,535 |
| | | $\Sigma$ | = | 0,502 |

$$^3J_{AB} = 13,24 \cos^2 60 - 0,91 \cos 60 + 0,50 = 3,4 \text{ Hz}$$

For 15a we can consider the three configurations shown in figure 7, ( P = $P(O)(OEt)_2$).




I II III

**Figure 7**

$\chi_P$ = 2,419, $\chi_{CH_2Ph}$ = 2,507 and $\chi_{OTFA}$ = 3,510. We assume $\chi_{OTFA} = \chi_{OAC}$. Thus $\Delta\chi_P$ = 0,243; $\Delta\chi_{CH_2Ph}$ = 0,331 and $\Delta\chi_{OTFA}$ = 1,334. The sign terms $\zeta_i$ and $P_i$ are the same as for 4a.

The summation terms for I with regard to $H_A$, $\varnothing_{AC}$ = 60, are:

| | | | | |
|---|---|---|---|---|
| For P | : | 0,243 {0,87 - 2,46 $\cos^2$ [60 + 19,9 (0,243)]} | = | 0,103 |
| For $PhCH_2$ | : | 0,331 {0,87 - 2,46 $\cos^2$ [60 + 19,9 (0,331)]} | = | 0,159 |
| For OTFA | : | 1,334 {0,87 - 2,46 $\cos^2$ [-60 + 19,9 (1,334)]} | = | -1,124 |
| | | $\Sigma$ | = | -0,862 |

$$^3J_{AC}{}^{I} = 13,22 \cos^2 60 - 0,99 \cos 60 - 0,862 = 1,95 \text{ Hz}$$

For B, $\varnothing_{BC}$ = 180°

| | | | | |
|---|---|---|---|---|
| For P | : | 0,243 {0,87 - 2,46 $\cos^2$ [-180 + 19,9 (0,243)]} | = | -0,382 |

For $PhCH_2$ : $0,331\ \{0,87 - 2,46\ \cos^2\ [+180 + 19,9\ (0,331)]\}$ = -0,516

For OTFA : $1,334\ \{0,87 - 2,46\ \cos^2\ [-180 + 19,9\ (1,334)]\}$ = -1,466

$\Sigma$ = -2,364

$$^3J_{BC}{}^{I} = 13,22\ \cos^2 180 - 0,99\ \cos 180 - 2,36 = 11,85\ Hz$$

We only need to calculate the OTFA term and replace the OH terms calculated for 4a with these new values.

Thus for II.

$\varnothing_{AC} = 180°$ : $1,334\ \{0,87 - 2,46\ \cos^2\ [-180 + 19,9\ (1,334)]\} = 1,466$

$\therefore \quad \Sigma = -2,364 \quad \therefore\ ^2J_{AC}{}^{II} = 11,85\ Hz$

$\varnothing_{BC} = 300°$ : $1,334\ \{0,87 - 2,46\ \cos^2\ [-300 + 19,9\ (1,334)]\} = 1,149$

$\therefore \quad \Sigma = 1,251 \quad \therefore\ ^3J_{BC}{}^{II} = 4,06\ Hz$

And for III.

$\varnothing_{AC} = 300°$ : $1,334\ \{0,87 - 2,46\ \cos^2\ [-300 + 19,9\ (1,318)]\} = 1,149$

$\therefore \quad \Sigma = -1,164 \quad \therefore\ ^3J_{AC}{}^{III} = 3,97\ Hz$

$\varnothing_{BC} = 60°$ : $1,334\ \{0,87 - 2,46\ \cos^2\ [-60 + 19,9\ (1,334)]\} = 1,124$

$\therefore \quad \Sigma = 0,949 \quad \therefore\ ^3J_{BC}{}^{III} = 1,86\ Hz$

$J_{AC}{}^{obs} = 5,6\ Hz$ $\qquad$ $J_{BC}{}^{obs} = 7,1\ Hz$

Thus the system becomes

$$1,95\ a + 11,85\ b + 3,97\ c = 5,6$$

$$11,85\ a + 4,06\ b + 1,86\ c = 7,1$$

$$a + b + c = 1$$

Solving we have $a = 0,45$, $b = 0,32$, and $c = 0,22$.

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