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NUCLEOPHILIC REACTIVITY OF PHOSPHORIC AMIDES AND RELATED SYSTEMS

PhD UP 1992

NUCLEOPHILIC REACTIVITY OF PHOSPHORIC AMIDES AND RELATED SYSTEMS

by

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   Tetrahedron Lett., **30**, 2141 (1989);

2. S. Bauermeister, A. M. Modro, T. A. Modro, and A. Zwierzak,
   Phosphoric Amides. Part 11. Intramolecular Reactivity of Phosphorotriamidates,
   Can. J. Chem., **69**, 811 (1991);

3. S. Bauermeister, T. A. Modro, P. K. Psotta, and P. H. van Rooyen,
   The Chemistry and Structure of the P(O)NC(O) System. Part 2. Crystal and Molecular Structure of N-Diethoxyphosphorylformamidine,
   Phosphorus, Sulfur, and Silicon, **69**, 63 (1992);

4. S. Bauermeister and T. A. Modro,
   The Chemistry and Structure of the P(O)NC(O) System. Part 1. Trimethylsilylation of O,O-Diethyl-N-formylphosphoramidate and the Hexamethyldisilazane-Promoted Conversion to the N-Phosphorylated Formamidine,
   Phosphorus, Sulphur and Silicon, 1992 (in press);

5. S. Bauermeister, T. A. Modro, and A. Zwierzak,
   The Chemistry and Structure of the P(O)NC(O) System. Part 3. Preparation of O,O-Diethyl-N-Acylphosphoramidates and their Reactions with Electrophiles,
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1. S. Bauermeister and T. A. Modro,
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   Frank Warren Conference, Mpekweni, Eastern Cape, April 1988;

2. S. Bauermeister, A. M. Modro, and T. A. Modro,
   Base-catalyzed Cyclization in Phosphoric Triamides,
   30th Convention of the South African Chemical Institute, Southern Transvaal, January 1989;

3. S. Bauermeister, A. M. Modro, T. A. Modro, and A. Zwierzak,
   Reactivity Studies on Physiologically Active Phosphoric Amides,
   10th IUPAC Conference on Physical Organic Chemistry, Haifa, Israel, August 1990;

4. S. Bauermeister and T. A. Modro,
   Intramolecular Reactivity of Phosphoric Amides,
   Ontario Physical Organic Chemistry Mini-Symposium, Kingston, Canada, October 1990;

5. S. Bauermeister, T. A. Modro, and A. Zwierzak,
   The Ambident Nucleophilicity of the "OPNCO" System,
   31st Convention of the South African Chemical Institute, Grahamstown, June 1991.

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ABSTRACT

This thesis is focused on the nucleophilic reactivity of selected classes of phosphoryl compounds, *i.e.* systems of the general formula XYZP(O). In this study, at least one of the substituents X, Y, or Z, represents an electron-rich amino group, NHR (or NR_2), hence all systems studied belong to the family of phosphoric amides, or their derivatives. Two major groups of compounds have been investigated in detail: (i) Phosphoric triamides bearing the *N*-(2-chloroethyl) substituent (compounds **17**, Chapter 2), and (ii) *O*,*O*-diethyl-*N*-acylphosphoramidates (**21**, Chapter 3).

Substrates **17** have been synthesized and studied under strongly basic conditions, in order to evaluate their reactivity in the two possible intramolecular cyclization reactions. For *N*-alkyl derivatives (**17d**, **e**), base-promoted intramolecular displacement of chloride yielded the *N*-phosphorylated aziridines (**29'**) as exclusive cyclization products. For *N*-aryl derivatives (**17a** - **c**), both the aziridine, and the 1,3,2-diazaphospholidine products (**30'**) could be obtained in comparable yields. These products are mutually interconvertible under conditions of nucleophilic or base catalysis. The mechanisms of these interconversions are proposed and discussed.

In the second part, a number of *N*-acylated phosphoramidate derivatives (**21**) have been synthesized, and their reactivity towards electrophilic reagents was studied.

Haloalkanes and trimethylsilyl derivatives were used as electrophiles; neutral substrates **21**, or their conjugate bases were employed as the ambident nucleophiles. The reactions were studied under a variety of experimental conditions, including the application of phase-transfer catalysis. It has been found that the regioselectivity (*N*-, carbonyl *O*-, or phosphoryl *O*-substitution) varied greatly depending on the substrate, the electrophile, the base, and other reaction conditions. In some cases, however, the reaction can serve as a convenient synthetic route to a specific class of derivatives of **21**. In silylation reactions we observed an interesting behaviour of the intermediate product, which can either undergo a rearrangement, or substitution of the Me_3SiO group by nucleophilic species.

The reactivity studies have been followed by structural determinations, aimed at the evaluation of the intra- and intermolecular interactions operating in the systems containing the OPNCO molecular backbone. Cryctal structures of three compounds have been determined by X-ray diffraction, and the molecular parameters determined revealed a strong electron-donating effect of the amidine substituent. The molecular structures have then been compared with those reported previously for related systems. This analysis enabled us to arrive at two general models of the intramolecular effects (hence the conformation of the molecule in the solid state), involving mutual donor-acceptor interactions between the carbonyl and the phosphoryl functions.

Some extrapolation of the present results to further work is also presented.

SAMEVATTING

Hierdie tesis sentreer rondom die nukleofiliese reaktiwiteit van geselekteerde klasse van fosforielverbindings met die algemene formule XYZP(O). Die sisteme wat bestudeer is, word geklassifiseer as fosforamiede of hul derivate, aangesien ten minste een van die sustituente X, Y, of Z, 'n elektronryke aminogroep, NHR (of NR_2) verteenwoordig. Verbindings van twee hoofgroepe is ondersoek: (i) Fosfortriamiede met die *N*-(2-chlooretiel)-substituent, en (ii) *O*,*O*-dietiel-*N*-asielfosforamidate.

Die substrate wat behoort tot groep (i) is gesintetiseer en hul reaktiwiteit ten opsigte van twee moontlike intramolekulêre sikliseringsreaksies is bestudeer onder sterk basiese kondisies. In die geval van *N*-alkielderivate is gevind dat die intramolekulêre verplasing van die chloriedioon lei tot die vorming van die *N*-gefosforileerde asiridienderivate as uitsluitlike siklisasieprodukte. Hierteenoor het die *N*-arielderivate beide die asiridien- en 1,3,2-diazafosfolidienprodukte in vergelykbare opbrengste gelewer. Daar is gevind dat hierdie twee produkte onderling omskakelbaar is onder nukleofiliese en basiese katalitiese toestande. Die meganismes vir hierdie omskakeling word voorgestel en bespreek.

In die tweede hoofgroep is 'n aantal *N*-asileerde fosforamidaatderivate berei en hul reaktiwiteit ten opsigte van elektrofiliesereagense ondersoek. Haloalkane en trimetielsilielderivate is gebruik as elektrofiele. Neutrale substrate of hul gekonjugeerde basisse is gebruik as ambidente nukleofiele. Die reaksies is bestudeer

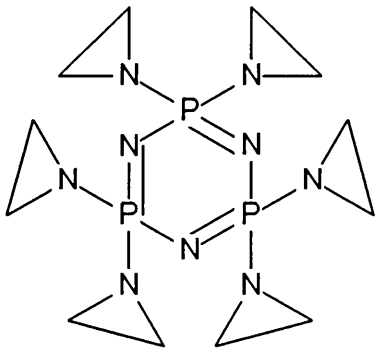
onder 'n verskeidenheid van reaksiekondisies, waaronder fase-oordragkatalise. Daar is gevind dat die regioselektiwiteit ten opsigte van die *N*-, karboniel *O*-, of fosforiel *O*-substitusie, afhanklik is van die substraat, elektrofiel en basis, asook ander reaksiekondisies. In sommige gevalle kan die reaksies egter gebruik word as 'n nuttige sintetiese roete na 'n spesifieke klas van derivate van die *O*,*O*-dietiel-*N*-asielfosforamidate. Met die sililering sreaksies is gevind dat die tussenproduk of 'n herrangskikking kan ondergaan, of dat substitusie van die Me_3SiO-groep deur 'n nukleofiele spesie plaasvind.

Die reaktiwiteitstudies is uitgebrei na struktuurbepalings om die intramolekulêre en intermolekulêre interaksies in sisteme met die OPNCO molekulêre "ruggraat", te bepaal. Kristalstrukture van drie verbindings is verkry deur middel van X-straal-diffraksie, en die molekulêre parameters het 'n sterk elektrondonerende effek in die geval van die amidiensubstituent aangetoon. Die molekulêre strukture is vergelyk met verwante sisteme wat reeds in die literatuur beskryf is. Hierdie analise het ons in staat gestel om twee algemene modelle voor te stel vir die intramolekulêre effekte wat betrekking het op die onderlinge donor-akseptor-wisselwerkings tussen die karboniel- en fosforielfunksies, en sodoende die konformasie van die molekule in die vaste toestand.

CHAPTER 1

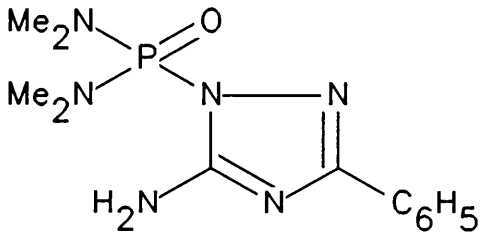
GENERAL INTRODUCTION

Phosphoryl derivatives containing a nitrogen atom in the P(O)—N function represent an important class of organophosphorus compounds.[1,2] The considerable interest in their chemistry lies in various practical applications of these compounds to everyday living.[3] Polymeric systems containing phosphazene units are used as carriers for chemically and biomedically reactive species. Aziridinyl derivatives of cyclophosphazenes, in particular Apholate (also called Myko 63) [hexaaziridinylcyclotriphosphazene] (**1**), have drawn attention as potential anti-cancer agents.[4,5]



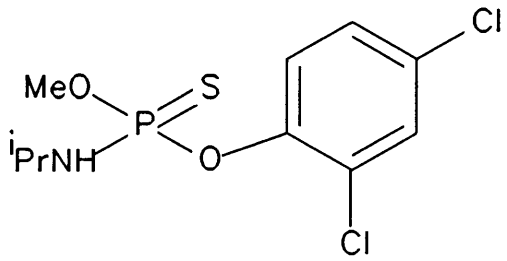
1

Many organophosphorus compounds containing N are known to act as fertilizers, fungicides (bactericides), herbicides, insecticides, as well as chemosterilants.[1,6] The phosphoramidate *N*,*N*,*N*′,*N*′-tetramethyl-*P*-(5-amino-3-phenyl-1,2,4-triazol-1-yl)-phosphonic diamide (also called Triamiphos or Wepsyn) (**2**),[7,8] which was discovered in 1960 by the firm Philips Duphar, is mainly fungicidally applied for the control of powdery mildew in roses and apple culture,[9] although it also has , at the same time, insecticidal and acaricidal activity.



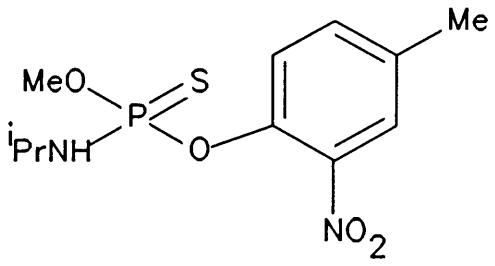
2

Zytron or DMPA [*O*-methyl-*O*-2,4-dichlorophenyl-*N*-isopropyl phosphoramidothioate] (**3**),[10] which was originally introduced as a systemic insecticide is now used as a herbicide which suppresses the growth of germinating seeds for the control of undesirable plant species (i.e. weeds).



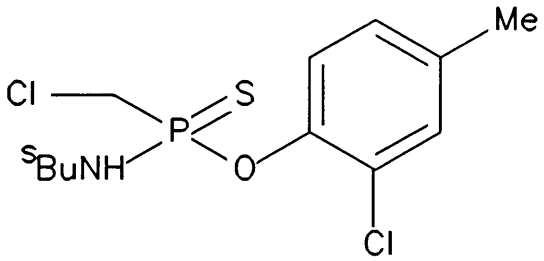
3

The corresponding and closely related *O*-nitrophenyl ester, Amiprofos-methyl (also called Tokunol M) [*O*-methyl-*O*-(4-methyl-2-nitrophenyl)-*N*-isopropyl phosphoramidothioate] (**4**), is an inhibitor of cell mitosis[11] and displays high activity against important broadleaf and grass weeds. The herbicidal activity may **partly** be due to a selective inhibition of tubulin synthesis,[12] as observed in *Chlamydomonas reinhardii*.[13]



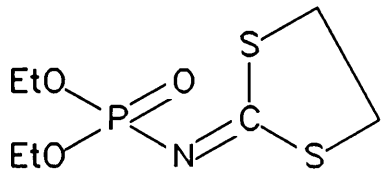
4

Isophos-3 [*O*-(2-chloro-4-methylphenyl)-*N*-^{s}butyl chloromethyl phosphonamidothioate] (**5**)[14] represents a herbicide which displays highly selective action in tomato and rice. Broadleaves as well as grass weeds can also be controlled. **5** apparently inhibits cell division and disrupts cell development systems.



5

Phosfolan (also called Cyolane) [*O*,*O*-diethyl-*N*-1,3-dithiolan-2-ylidene phosphoramidate] (**6**)[15,16,17] is a commercially available systemic insecticide which acts as a contact and stomach poison against biting and sucking insects as well as spider mites. Acephate [*O*,*S*-dimethyl-*N*-acetyl phosphoramidothioate] (**7**), which was synthesized by Lorenz in 1964, is useful for the control of various classes of insects.[18]



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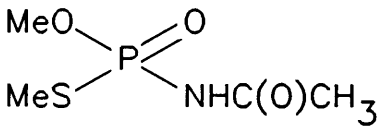
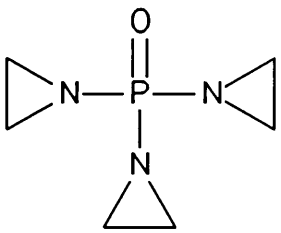


7

N-phosphorylated aziridines are known inhibitors of cell division, the property responsible for their application as insect chemosterilants. Their sterilizing, as well as carcinogenic action is attributed to the alkylation of biological centres.[1,6] Compound **1**, synthesized in 1954 by Rätz and Grundmann,[19] was the first example of a compound with sterilizing properties, which was tested successfully by Chamberlain[20,21,22] against *Callitroga hominivorax.* Other examples of commonly used contact sterilizing agents are TEPA or aphoxide [tris-(1-aziridinyl)-phosphine oxide] (**8**),[23,24,25,26,27,28] HEMPA (**9**) and aphamide [*N*,*N*'-ethy-lene-bis-(*P*,*P*-bis-(1-aziridinyl)-*N*-methyl)phosphoric triamide] (**10**); the latter described by Chance.[29]



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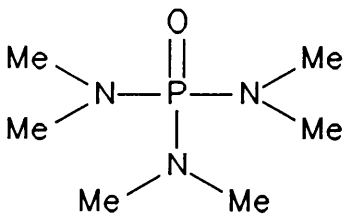

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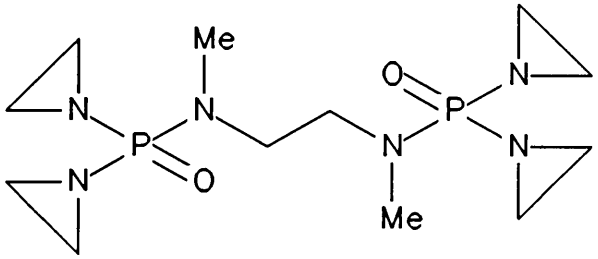
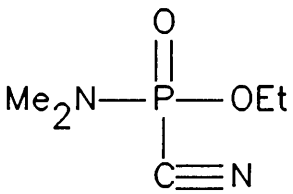


10

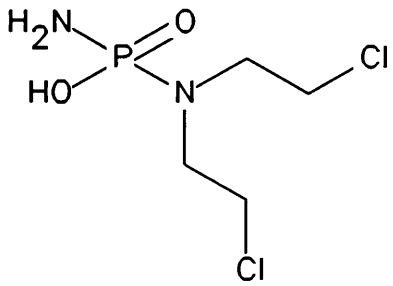
Chemical warfare agents[1,30,31,32,33] can be illustrated by the organophosphorus compound such as Tabun (**11**), which can be used as a harassing agent causing constriction of the pupils, blurred vision, pain behind the eyes and subsequently tightness of the chest, difficulty in breathing, sweeting, nausea, etc. develops. The biological activity of these compounds can be explained by their inhibition of enzymes involved in the function of the nervous system.



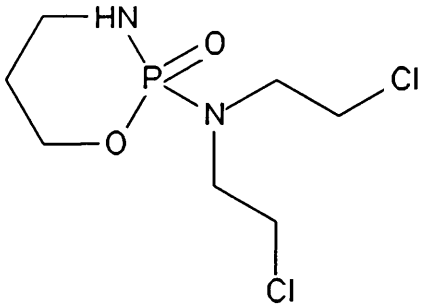
11

The clinical application of organophosphorus amides in chemotherapy, and in particular in cancer chemotherapy, has been under extensive investigation since the late 1960's. The phosphoramide mustard (**12**) is believed to be the active metabolite of the anti-tumor alkylating drug, [2-bis(2-chloroethyl)aminotetrahydro-

2H-1,3,2-oxazaphosphorin-2-oxide], or cyclophosphamide (also called Endoxan or Cytoxan) (**13**).[34]

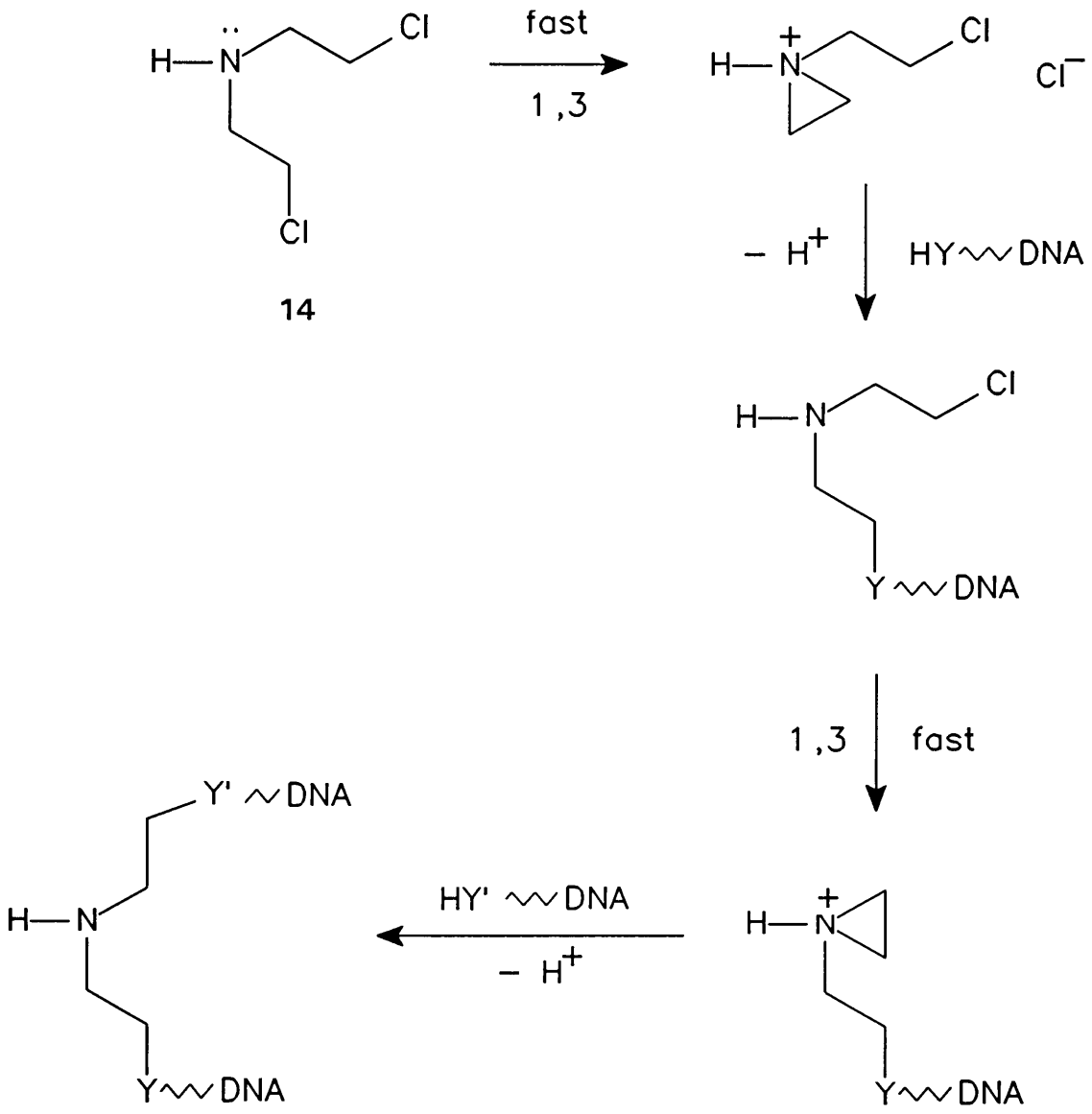


12



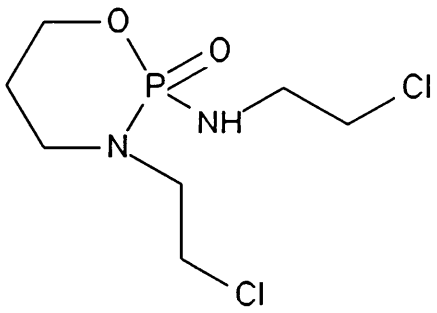
13

The anti-cancer activity of **13** (with the *R* stereoisomer being more readily metabolized in human body[35]) is based on the release of nornitrogen mustard $HN(CH_2CH_2Cl)_2$ **14**, (lability of the P(O)N linkage), after *in vivo* activation of the substrate molecule.[36] The alkylating reactivity , hence, cytotoxic activity (at physiological pH) of **12** is attributed to its intramolecular cyclization to the aziridinium ion, followed by the intermolecular reaction of that intermediate with a biological nucleophile (cross-linking) which causes the cellular growth to stop.[37] (See **Scheme 1**)



Scheme 1

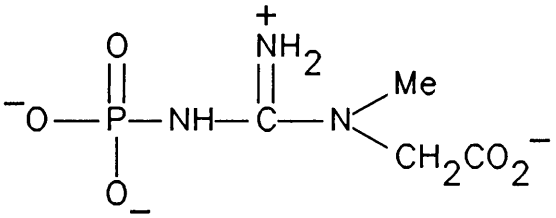
Ifosfamide (**15**) belongs to the group of most effective anti-cancer drugs currently used in cancer chemotherapy. Like isomeric **13**, **15** requires metabolic activation to exert its cytotoxic activity.[38]



15

The intra- and intermolecular nucleophilic displacements of the *β*-chlorine atom in systems of this type will be discussed in more details in the following chapter, in relation to our work.

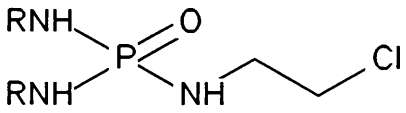
Energy-rich phosphorylated guanidines, such as phosphocreatine (**16**), ΔG°(hydr) - 43.1 kJmol^{-1} vs - 30.5 for ATP → ADP,[1,39] play a vital role as biological phosphorylating agents[40,41,42] in the regulation of the ATP[43] concentration in living cells. **16** acts as an alternative energy store containing an acid labile phosphoramidate linkage.[44]



16

The multifunctional character of P(O)N derivatives , results in the wide variety of chemical reactivity exhibited by compounds containing such function. For example, a simple amidoester moiety, (RO)(RHN)P(O)—, represents already a system where various reactions can proceed resulting in the formation of different reaction products (e.g. nucleophilic cleavage can involve the P—O or P—N bond, while reactions with electrophiles can involve the P═O or the P—N centre). Systems containing such multifunctional properties, have been a subject of the research carried out in our laboratories for some years and have been addressed in several projects, such as: (i) The nucleophilic cleavage of the P(O)—N bond;[45,46] (ii) Rearrangement reactions of mixed anhydrides involving P—N bond cleavage;[47] (iii) Nucleophilicity of the phosphoramidate function;[48] and (iv) Structure and reactivity of *N*-acyl phosphoramidates.[49] Projects (iii) and (iv) are directly related to this work where we attempted to advance our knowledge of the chemistry and structural features of various systems within the discussed class of organophosphorus compounds.

The work described in this Thesis concentrated on the multifunctional,nitrogen containing phosphoryl derivatives. The first part of the project was devoted to the intramolecular reactivity of *N*-(2-chloroethyl) substituted phosphorotriamidates **17**. The ambident reactivity of these systems can be aknowledged by recognizing that they can exhibit nucleophilic reactivity *via* two different amidate nitrogen atoms, as well as the phosphoryl oxygen atom. Apart from their nucleophilic properties, they can also offer more than one electrophilic (phosphorus and β-carbon atom of the β-chloroethyl group) centre.

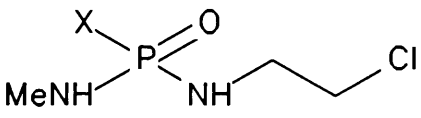


R = Ph, p–MeC_6H_4, p–$MeOC_6H_4$, Me, CH_2Ph

17

Intramolecular displacement of the *β*-chlorine atom can in principle involve one of the two chemically different nitrogen atoms resulting in the formation of a three- or five-membered cyclic compound, or the phosphoryl oxygen atom leading to another five-membered ring product.

The intramolecular alkylation reactions of *β*-chloroethyl derivatives of phosphorodiamidates **18**, phosphoramidates **19** and phosphoric acid esters **20**, were investigated earlier under various reaction conditions.[48]



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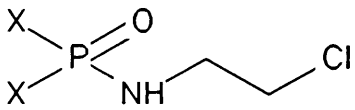
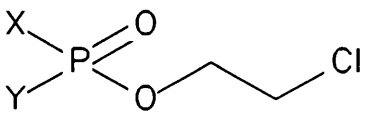


19



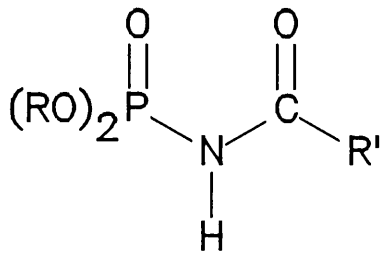
X = MeO, PhO, Et, Ph

Y = MeO, MeNH

20

Many studies on the nucleophilic reactivity of both, the nitrogen, and the phosphoryl oxygen atoms of phosphoric amides towards alkylating agents, concerned bimolecular (intermolecular) alkylations of these substrates.[50]

Another topic addressed in this Thesis is the structure and reactivity of the mixed phosphoric-carboxylic imides **21**. Both these compounds and their salts attract attention because they show antiviral activity[51] and also some interesting complexing properties.[52]



R = Et

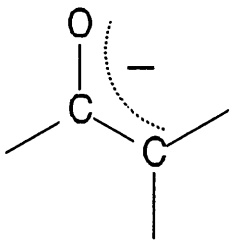
R' = H, Me, Et, Ph, OEt, NEt_2

21

The substrates **21a** - **f** were chosen in such a way in order to vary the structure only at the carbonyl carbon atom, while the resulting alkylated products which were obtained would introduce some structural variation at either the phosphorus, the nitrogen or carbon atom. From the reactivity point of view and as an extension of the first part of this work, these systems also may exhibit ambident properties, both in electrophilic, and nucleophilic reactions. Solvolysis of **21** can proceed with

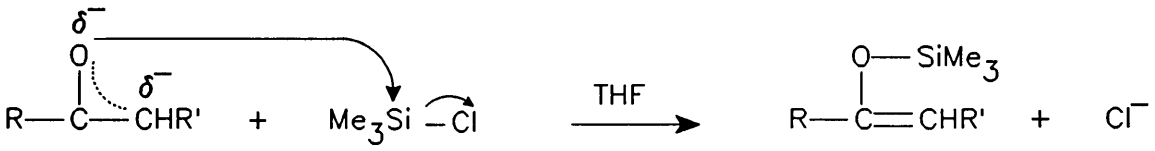
the cleavage of the N—P(O) (phosphorylation) or the N—C(O) (acylation) bond; our earlier studies indicated that the selectivity in solvolysis is primarily the function of medium acidity.[53] In reactions with electrophiles, imides **21** can offer two oxygen atoms (the carbonyl and the phosphoryl), and the nitrogen atom as nucleophilic centres. Alkylation of the conjugate base of **21** can therefore lead to more than one product.

Both systems **17** and **21** have in common a multifunctional character which can give rise to various products. A multi-directional reactivity is a characteristic property of a great majority of organic molecules, and it includes, among others, the so-called ambident reactivity, defined, in the case of nucleophiles, as follows:[54] "Species containing two or more nucleophilic centres of different types are known as **ambident** and, if each centre is a part of a conjugated system, the reactivity pattern can be analyzed by considering the distribution of the HOMO and the charge, if any." The typical, and very important example of an ambident nucleophile is an enolate ion, of the general structure **22**.



22

Enolate ions have a partial negative charge on an oxygen atom and can react in nucleophilic substitution reactions as alkoxide ions.[55] However, because they have a partial negative charge on a carbon atom, they can also react as carbanions. How an enolate or ambident nucleophile reacts, depends, in part, on the substrate with which it reacts. One substrate that tends to react almost exclusively at the oxygen atom of an enolate is chlorotrimethylsilane, Me_3SiCl, for example (Eq. ***(1)***):



enol trimethylsilyl ether

(1)

The reason for this regioselectivity is the very high energy of the Si—O bond.

Enolate ions display their carbanionic character when they react with alkyl halides (Eq. ***(2)***):

major product

(C-alkylated)

(2)

Alkylation reactions have an important limitation: Because the reactions are S_N2 reactions and because enolate ions are **strong bases**, successful alkylations occur only when primary alkyl, primary benzylic, and primary allylic halides are used. With secondary and tertiary alkyl halides, **elimination** becomes the main course of the reaction.

An interesting case, related to our work, is that of β-amino-α,β-unsaturated ketones, which may be alkylated on a carbon, oxygen, or nitrogen atom.[56]

It would be useful to have general rules as to which of an ambident nucleophile will attack a given substrate or reagent under a given set of reaction conditions. Unfortunately, the situation is complicated by the large number of variables. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by **thermodynamic** control, the major product is usually the one in which the atom of higher basicity has attacked (i.e., C > N > O > S). However, in most reactions, the products are **kinetically** controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. There are two major factors: The polarizability (hard-soft character) of the nucleophile and solvation effects.

Alkyl substrates are considered to act as Lewis acids towards the nucleophile (considered as a base). As alkyl substrates are known to be soft, we may expect them to prefer softer, more polarizable nucleophiles. For a given degree of basicity,

softness promotes nucleophilicity.[57] The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom.[56] In an S_N2 mechanism the nucleophile attacks the carbon atom of a molecule, which is a softer acid. Therefore, S_N2 conditions favour the ambident nucleophile to attack with its less electronegative atom. However, this will not always be the case as the position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions.

S_N1 character of the transition state is enhanced when the negatively charged nucleophile bears a positive counterion that specifically helps in removing the leaving group, like for example, Ag^+ rather than the more usual Na^+ or K^+ ions. Therefore, the use of Ag^+ promotes attack at the more electronegative atom.

In many cases the solvent influences the position of attack. The more free the nucleophile is, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or positive counterions, the more likely is attack by the less electronegative atom. In protic solvents the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus, in a polar aprotic solvent the more electronegative end of the nucleophile is more free, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom.

The freer the nucleophile, the greater the rate. The rate of attack by "Nu^-cat^+" in benzene will be increased by the addition of substances that specifically solvate the cat^+ and thus leave the anion freer. In a nonpolar solvent such as benzene, Na^+ salts of nucleophilic substrates exist as ion-pair aggregations of high molecular weight.

The reactions of **17** and **21** will be discussed later as separate topics as a part of "Results and Discussion."

CHAPTER 2

INTRAMOLECULAR REACTIVITY OF PHOSPHOROTRIAMIDATES

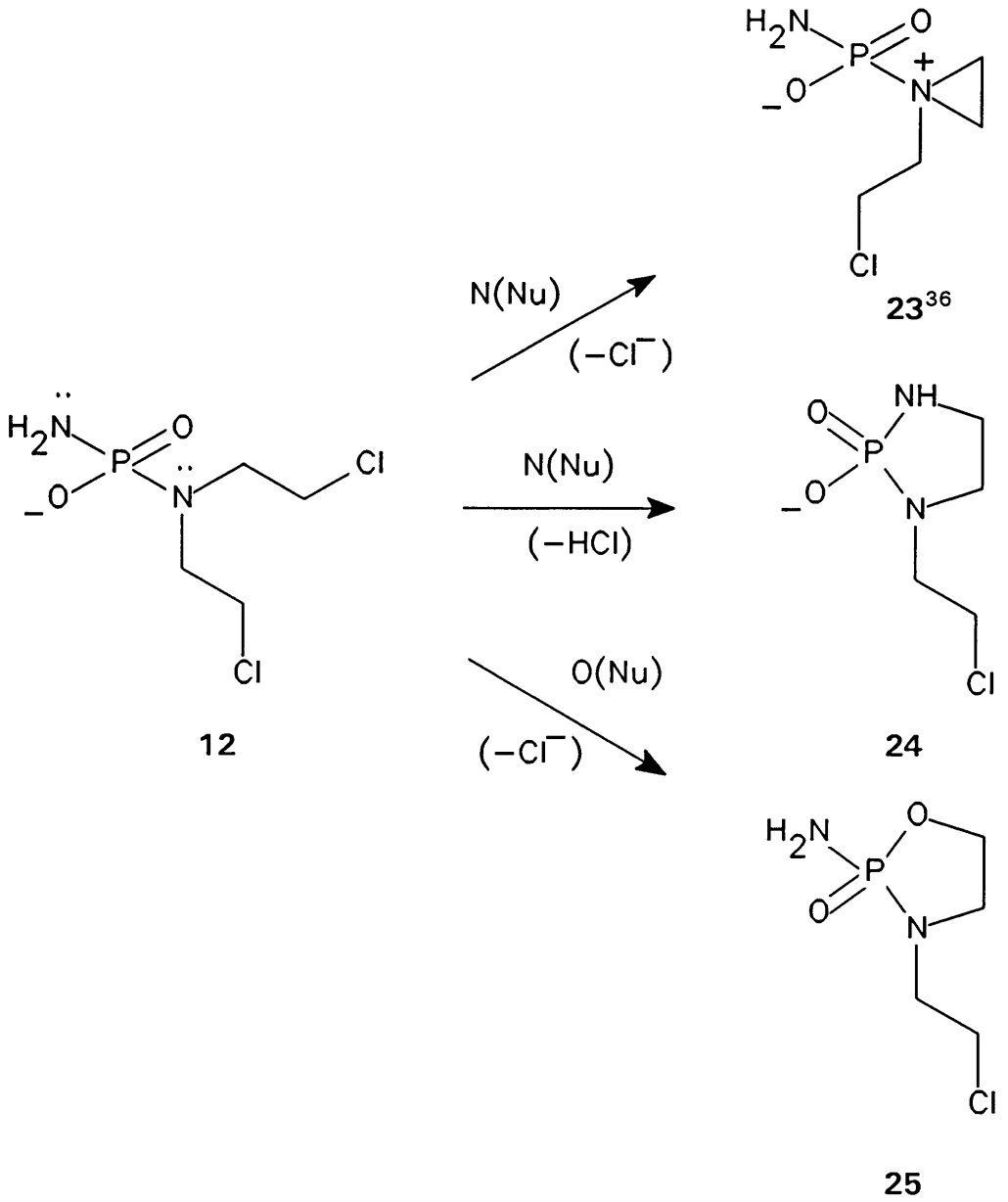
2.1 INTRODUCTION

2.2 RESULTS, DISCUSSION AND EXPERIMENTAL

2.1 INTRODUCTION

The conjugate base of phosphoramide mustard **12** can act intramolecularly and regioselectively to yield three different reaction products **23**, **24** and **25**, resulting from attack by either one of the two different amide nitrogen atoms (1,3 or 1,5 displacement of chloride ion, yielding the aziridinium ion or the 1,3,2-diazaphospholidine product respectively), *or* by the phosphoryl oxygen atom (1,5 substitution in the OPNCCCl system to give rise to the 1,3,2-oxazaphospholidine product), (Eq.*(3)*). Such cyclization was in fact postulated[58] and demonstrated[59] for the nonenzymatic hydrolysis of cyclophosphamide **13** itself.

The formation of compound **23** (aziridinium ion) attracts attention because the intermediate can react intermolecularly with a biological nucleophile which renders phosphoramide mustard **12** its biological activity.[37]



23[36]

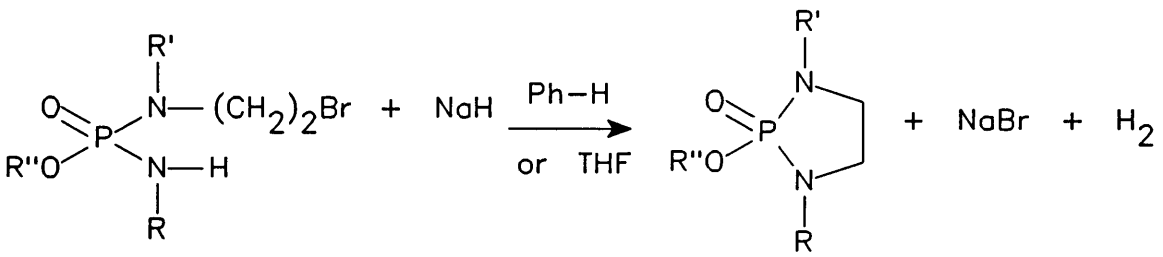
12

24

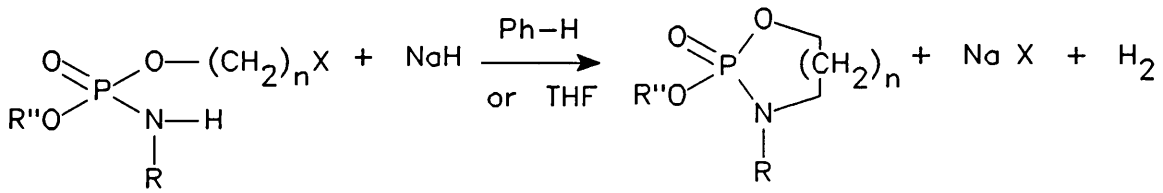
25

(3)

Intramolecular alkylation reactions of phosphoromono- and diamidates in the presence of strong bases such as NaH and alkoxides in alcohol, have been described by Savignac[60] and co-workers, (Eq.*(4)*, *(5)* and *(6)*).



(4)



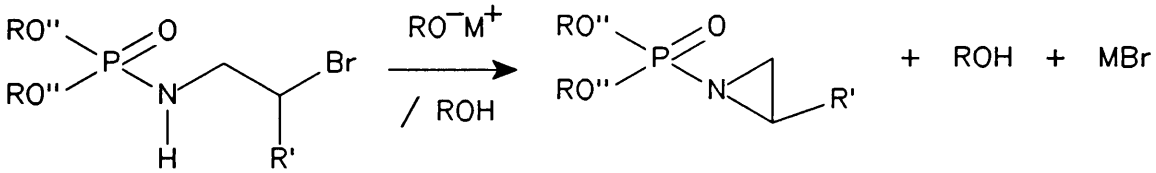
R, R' = alkyl group

R'' = Et, Ph

X = Br, Cl

n = 2, 3

(5)



R = alkyl group

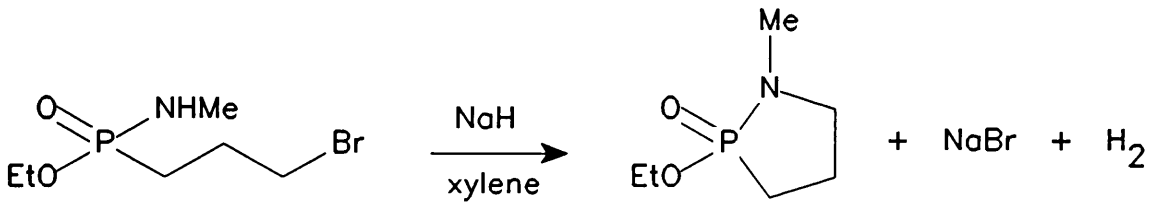
R' = H or alkyl group

R'' = Ph, ^{i}Pr

M = metal

(6)

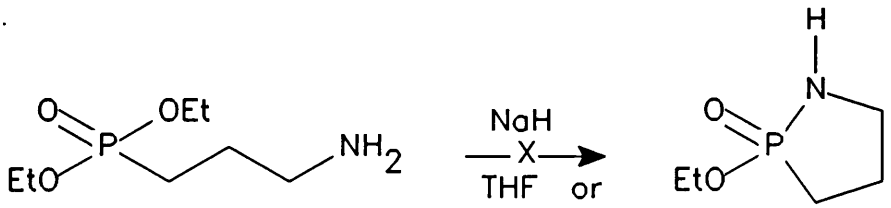
Collins and co-workers reported on the intramolecular nucleophilic reaction of phosphonamidate **26** with NaH in boiling xylene,[61] (Eq.*(7)*).



26 **27**

(7)

Their attempts to obtain N—P ring closure in diethyl-3-aminopropyl-phosphonate **28** using sodium hydride in boiling tetrahydrofuran or in hot dimethyl sulphoxide, failed (Eq.*(8)*).



28

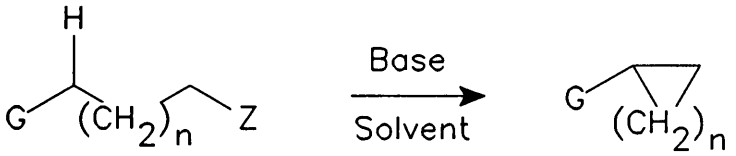
(8)

The failure could possibly be due to the unfavourable stereoelectronic constraints on the potential leaving group required during intramolecular nucleophilic substitution at the phosphorus atom in **28**. It is, however,

interesting to note that successful cyclization to the 1,3,2-diazaphospholidines of phosphoramidates of the type $(EtO)_2P(O)NH(CH_2)_2NHR$ (R = alkyl) in the presence of butyllithium as a base, has been achieved.[62]

Examples of heat-promoted and base-catalyzed ring closure of phosphorothioamidates, acting as ambident nucleophiles *via* either their nitrogen or sulphur atoms, are also available in the literature.[63]

Stirling *et al*[64] showed that for the intramolecular nucleophilic substitutions in which the internal nucleophile is a conjugatively stabilized carbanion, rates of formation of three-membered rings are much higher than those for five-membered rings (Eq.*(9)*).



G = $(CO_2R)_2$, p−tolyl−SO_2, PhCO, MeCO, $PhSO_2$

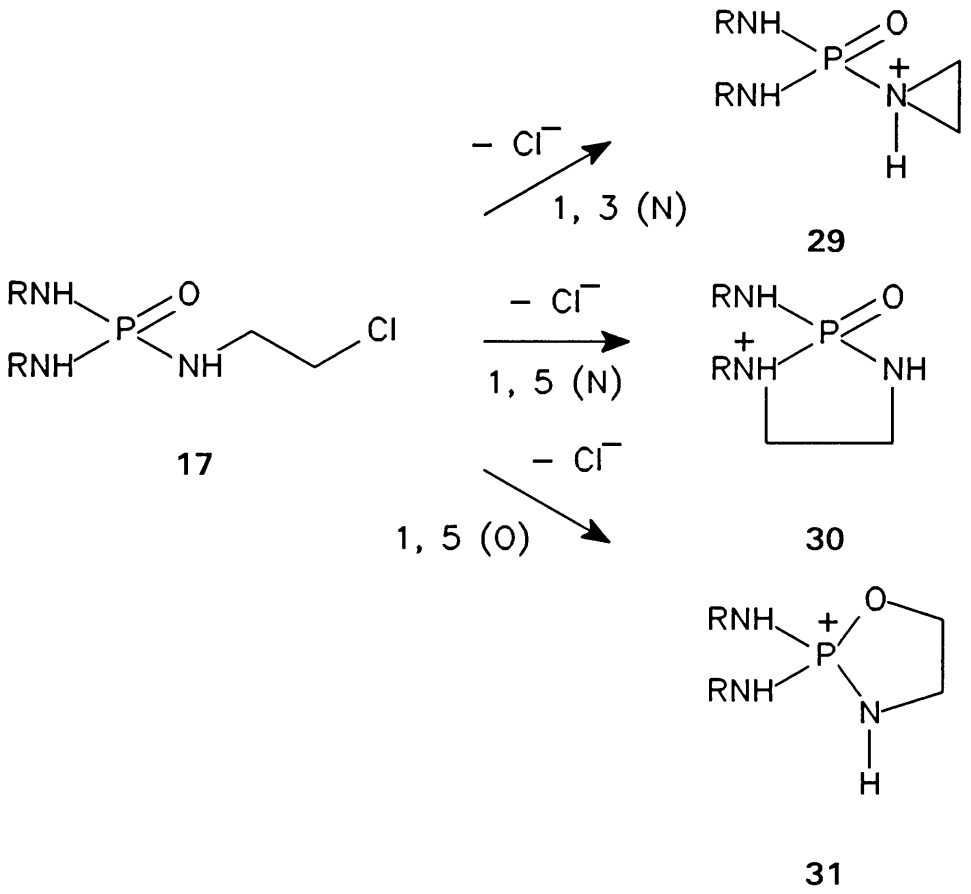
Z = Cl, Br, SAr, EtS^+−Ar, EtS^+−p−tolyl, $OSO_2C_6H_5$, OSO_2−p−tolyl

n = 1, 3

(9)

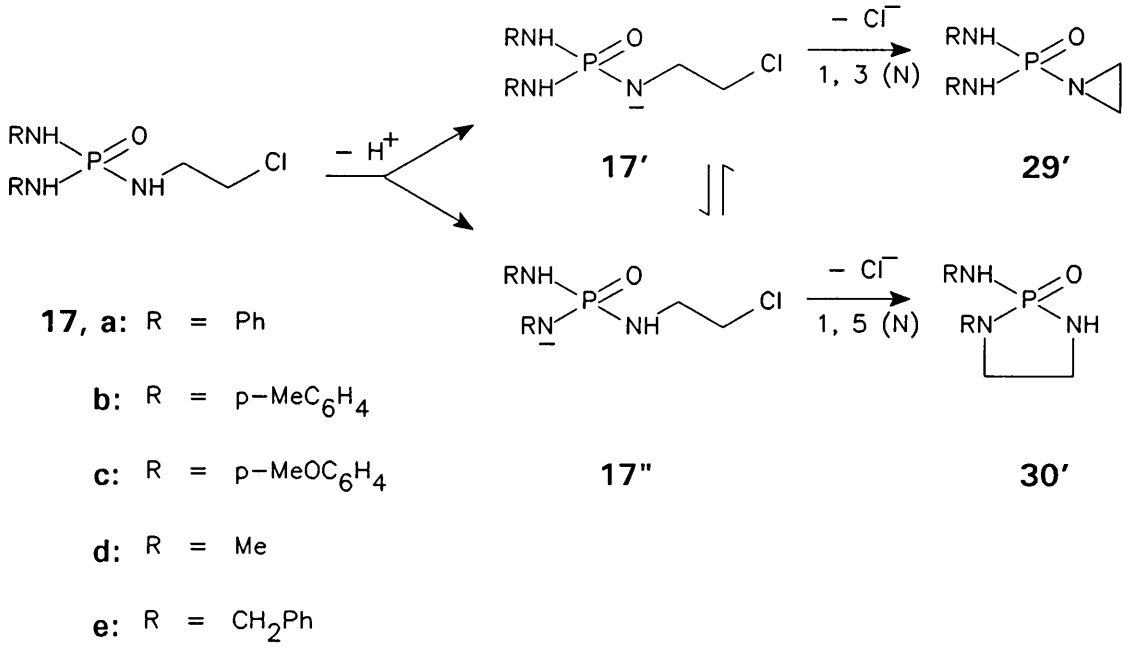
In our study on the intramolecular reactivity of the *N*-(2-chloroethyl) substituted phosphorotriamidates **17**, reaction *via* three potential nucleophilic centres could in principle give rise to the different products **29**, **30** and **31** as

illustrated in **Scheme 2**.



Scheme 2

Hence, the base-promoted cyclization *via* the nucleophilic displacement of chloride ion of the corresponding conjugate bases **17'** and **17"**, could therefore lead directly to the formation of the aziridine **29'** or 1,3,2-diaza-phospholidine **30'** derivatives (**Scheme 3**).



17, a: R = Ph

b: R = p–MeC_6H_4

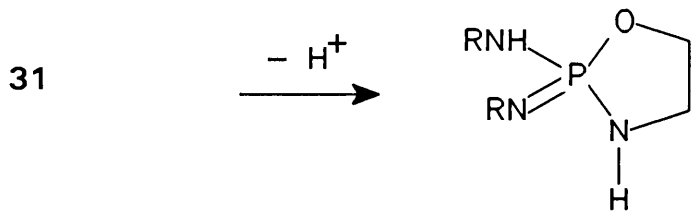
c: R = p–$MeOC_6H_4$

d: R = Me

e: R = CH_2Ph

Scheme 3

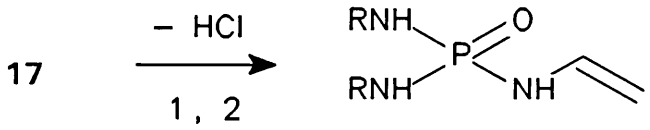
The attack *via* the phosphoryl oxygen (**Scheme 2**, pathway 1,5(O)) seems less likely, as the deprotonation of **31** (Equation ***(10)***) would lead to the 1,3,2-oxazaphospholidine system **31'**, with a loss of the phosphoryl group, replaced by the thermodynamically less stable imido function, $X_3P{=}NR$.



31'

(10)

It is worthwhile to note that a fourth product, the *N*,*N*'-dialkyl- or *N*,*N*'-diaryl-*N*"-vinylphosphorotriamidate **32** would be possible under basic conditions, resulting from the 1,2-dehydrohalogenation[60] reaction (Eq.*(11)*), which is not included in **Scheme 3**. Such a product was, however, never obtained under the maintained reaction conditions.



32

(11)

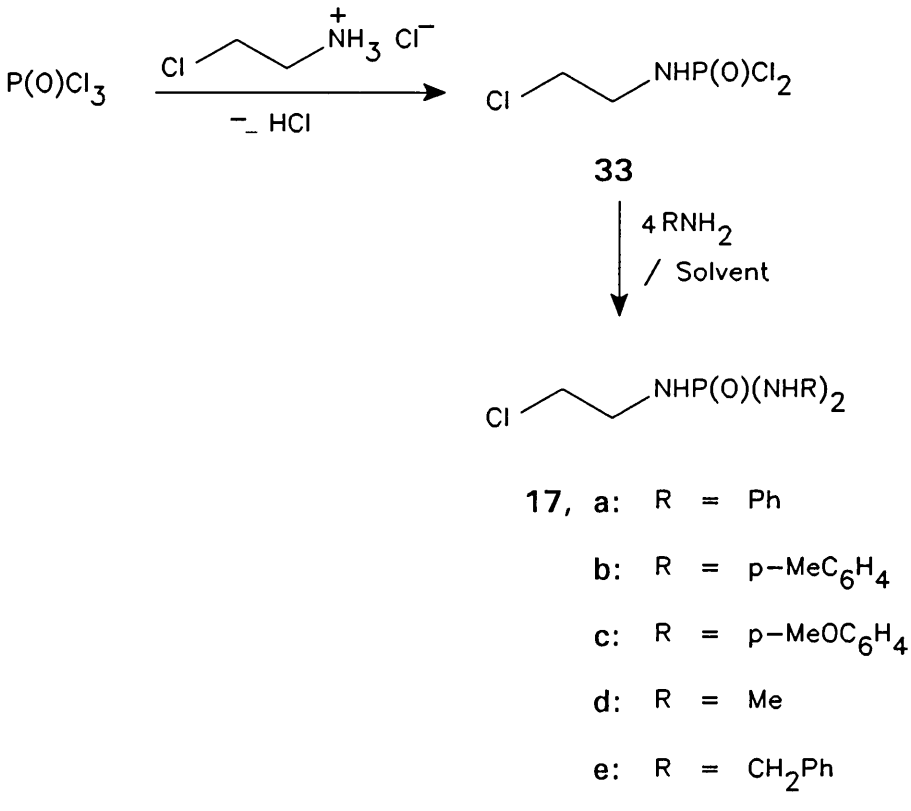
The proportion of the isomeric products **29'** and **30'** should be determined by more than one factor which will be discussed later in this chapter.

The other problems addressed in this part relate to the structural effects and reaction conditions required for the base- or nucleophile-promoted mutual isomerization of products **29'** and **30'** *via* the respective anionic intermediates.

2.2 RESULTS AND DISCUSSION

2.2.1 *N,N'*-DIARYL- AND *N,N'*-DIALKYL-*N"*-(2-CHLOROETHYL)PHOSPHOROTRIAMIDATES (17)

Two groups of aromatic and aliphatic substrates, **17a - e**, were prepared *via* a two step synthesis from phosphorus oxychloride, *β*-chloroethylammonium chloride and the corresponding amine in the appropriate solvent, according to Equation ***(12)***.[65]



17, **a**: R = Ph

b: R = p–MeC_6H_4

c: R = p–$MeOC_6H_4$

d: R = Me

e: R = CH_2Ph

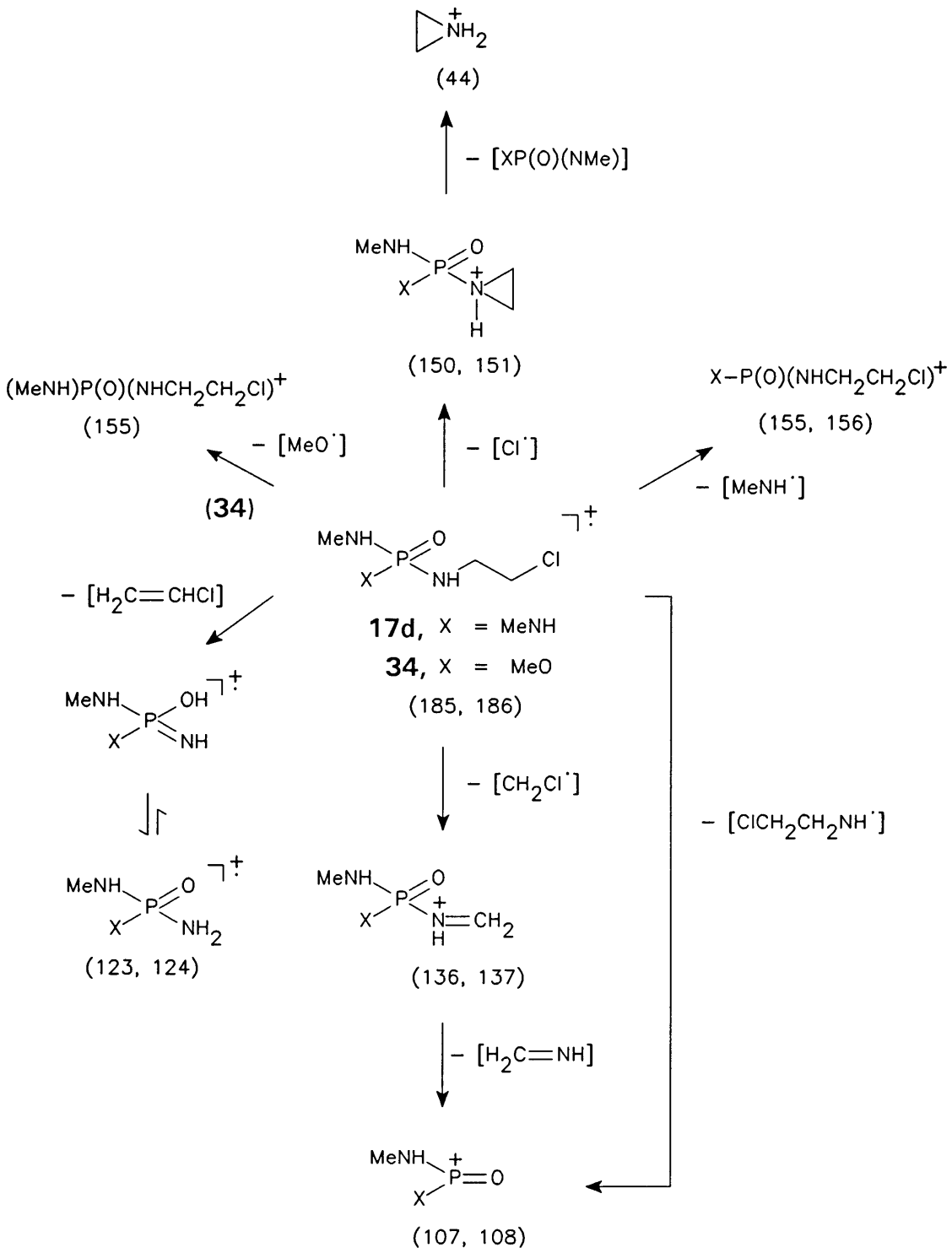
(12)

The hydrochloric salt of *β*-chloroethylamine was used in this

preparation in order to assure that the concentration of free amine is kept sufficiently low. This way the nucleophilic N atom of the free amine would react at the most electrophilic centre (P atom of $P(O)Cl_3$ *versus* β-carbon atom of amine) as it was slowly released from its salt to yield **33**, and would therefore reduce the possibility of the 1,3 ring closure leading to the formation of the aziridine ring.

The initial two-phase reaction mixture of hydrochloric salt and $P(O)Cl_3$ changed slowly with time as the reaction was progressing to a one-phase system.

All three aromatic compounds **17a** - **c** were easily obtained as powdery solids which could be purified, if required, by recrystallization. However, both aliphatic substrates **17d** and **e** were isolated as coloured, viscous oils (**17e** crystallized on standing), which had to be purified by column chromatography (**17d**) and recrystallization (**17e**). They were, however, obtained as pure compounds, as shown by their NMR spectra, elemental analysis, and, in some cases, mass spectrometry. Electron impact-induced fragmentation of the substrates can be illustrated by the behaviour of compounds **17d** and **34** (**Scheme 4**).

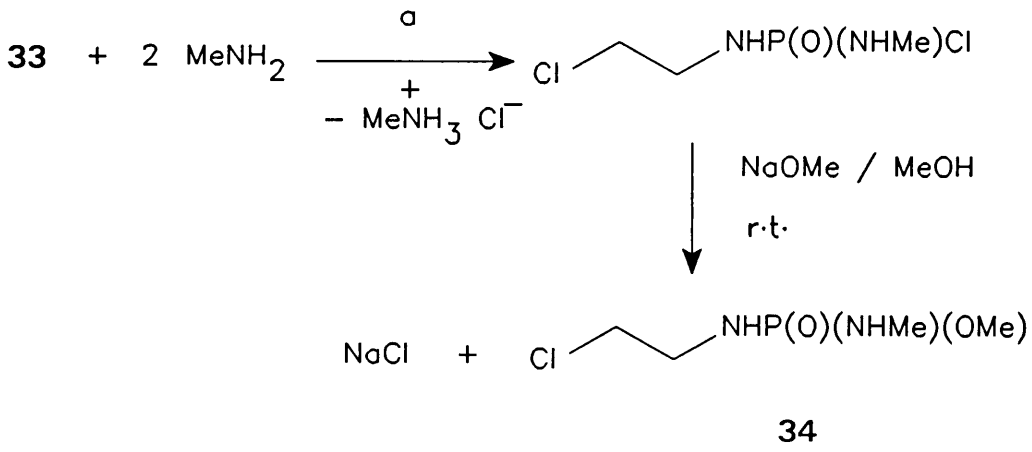


Scheme 4: MS of **17d** and **34**; only major fragmentation pathways shown.

It's interesting to note that both **17d** and **e** were found to deteriorate with time in the crude, non-crystalline form. Compounds **17a** - **c** were stable and could be stored for several months without any decomposition. Attempts to grow good quality crystals in order to determine the crystal structure of one of the crystalline substrates **17a** - **c** and **e**, failed.

2.2.2 *O*-METHYL-*N*-METHYL-*N'*-(2-CHLOROETHYL)DIAMIDOPHOSPHATE (34)

In order to extend the initial series of alkyl phosphorotriamidate substrates **17d**, **e**, the *N*-phosphorylated diamidoester **34** was prepared in two steps from *N*-(2-chloroethyl)phosphoroamidodichloridate **33** (Eq.*(12)*), methylamine and methanol, according to Equation *(13)*.



34

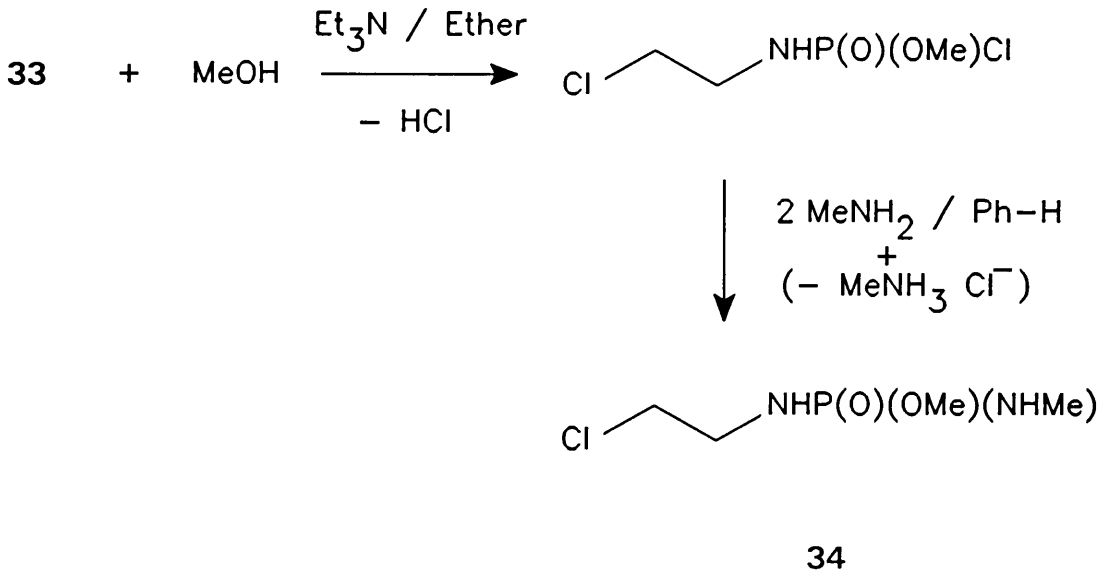
a = – 10 to – 5°C / Dioxane or
– 40 to – 30°C / $CHCl_3$

r·t = room temperature

(13)

The product (**34**) was obtained, after purification by column chromatography[48], as a reasonably stable, colourless oil. NMR spectroscopy, mass spectrometry as well as satisfactory elemental analysis results, confirmed its structure.

It's interesting to note that compound **34** was prepared previously[48] by changing the sequence of substitution of the two chlorine atoms at phosphorus (Eq.*(14)*).



34

(14)

2.2.3 FACTORS DETERMINING THE PROPORTION OF THE ISOMERIC PRODUCTS (29') AND (30')

As mentioned earlier, the proportion of the isomeric products **29'** and **30'** should be determined mainly by two factors: Firstly by the proportion of the respective conjugate bases **17'**, **17"**, which *per se* depends on the relative substituent effects of groups R and the *β*-chloroethyl group which determines the acidity of the adjacent NH function. The second (kinetic) factor, certainly more difficult to ascertain, being the relative rates of the 1,3 and 1,5 cyclization steps. These two factors can, of course, respond in a different way to the changes in the reaction conditions.

The relative acidity of the NH functions in substrates **17** was

qualitatively assessed by examining the chemical shifts of the NH proton signals in the ^{1}H NMR spectra of those compounds. Although the relationship between the δ value of a proton and its acidity is only an approximate one,[66] significant differences in the δ values found for the chemically non-equivalent NH groups in **17** were used to determine the relative acidity order. **Figure 1** shows the dependence of the shielding of the NH protons in **17** on Taft's polarity constants[a] σ^* of *N* substituents (**Table 1**).

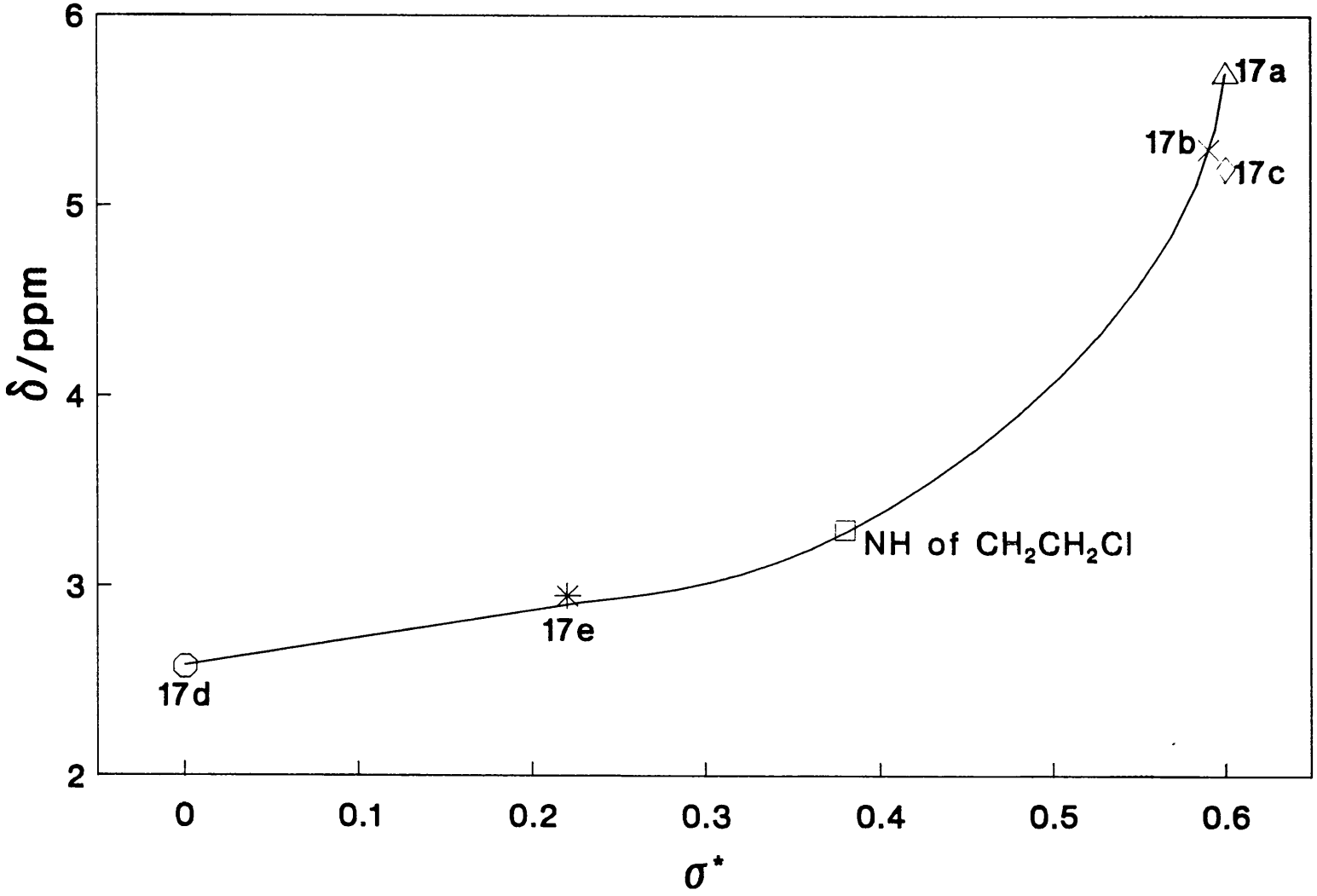
Table 1: Correlation of the chemical shifts of the NH protons in **17** with Taft's polarity constants σ^* of *N* substituents

Substrates **17**	δ_{NH} (ppm, $CDCl_3$, c = 0.2M)	σ^*_R (for substrates **17**)
d: R = Me	2.58[a]	0.00
e: R = CH_2Ph	2.95[a]	0.22
R = CH_2CH_2Cl	3.30[b]	0.38
c: R = *p*-$MeOC_6H_4$	5.20[c]	0.60[d]
b: R = *p*-MeC_6H_4	5.30[c]	0.59[d]
a: R = Ph	5.70[c]	0.60[d]

[a] High field signal (shielded).
[b] Average value taken from all compounds **17**.
[c] Low field signal (deshielded).
[d] Doesn't apply for resonance factor in aromatic systems.

[a] No proper parameters that describe ionization of the RNH function are available. The Taft's scale (in which σ^* values could be found[67] for all N substituents) ignores the resonance effects, as can be seen from the upward curvature of the plot for the NAr substituents.

Figure 1: δ_{NH} (ppm, $CDCl_3$, c = 0.2 M) *vs* σ^* for substrates **17**

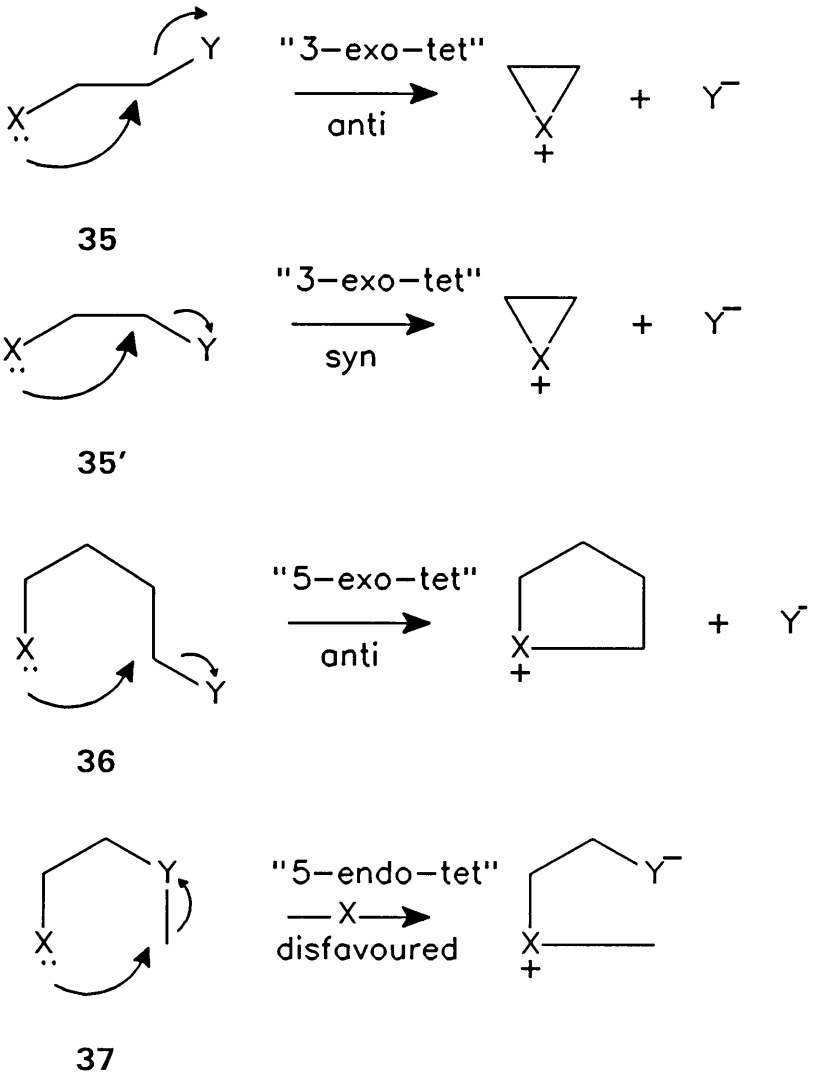


It should be pointed out that the observed upward curvature of the plot (**Figure 1**) results from the fact that the Taft's constants σ^* used for the correlation do not reflect resonance effects of a substituent. The aromatic groups in **17a - c** stabilize the respective conjugate bases by resonance effects, hence render the NH more acidic (greater δ_{NH} values) than indicated by the linear plot based on the aliphatic substituents alone. The relative order of decreasing acidity of the NH functions in substrates **17** was found to be: Ph > *p*-MeC_6H_4 > *p*-$OMeC_6H_4$ > CH_2CH_2Cl > CH_2Ph > Me. The observed trend indicates that for the *N*-aromatic substrates, **17a - c**, the conjugate base **17"**, and for **17d, e**, the conjugate base **17'** should represent the major form of the deprotonated substrate. It was expected therefore that substrates **17d, e** should yield aziridines **29'**, *unless* the 1,3 ring closure in this system is much **slower** than the alternative 1,5 cyclization. For **17a - c**, on the other hand, the 1,3,2-diazaphos-pholidine **30'** should be expected as the major product, *unless* the 1,3 cyclization is much **faster** than the direct cyclization of **17"** to **30'**.

Contrary to popular belief,[68,69] the closure of three-membered rings is not necessarily favoured over the formation of larger ring systems, and the k_3/k_5 ratio for different intramolecular reactions can vary from very high to very low values.[70] For example, in the formation of a carbocyclic ring by the intramolecular bromide displacement by the α-carbanion derived from the sulfone system *p*-

Tol—SO_2—$(CH_2)_n$Br, k_3/k_5 = 100,[71] while the cyclization of 1-bromo-*ω*-aminoalkanes, H_2N—$(CH_2)_n$—Br gives the value of k_3/k_5 = 1.2×10^{-3}.[72] A very small value of k_3/k_5 was also obtained for the base-promoted cyclization of the sulfonamides of the type *p*-Tol—SO_2—NH—$(CH_2)_n$—Cl.[73] Stirling and co-workers advanced their hypothesis[74] according to which three-membered ring closure is selectively promoted by electron-accepting (withdrawing) (- M) groups because the overlap in the transition state between the *π* (or d) orbitals of the conjugative group and the distorted, high p-character, ring bonds of the three-membered ring system[75,76] lowers the free energy of the transition state. Any effect of a conjugative group, however, should be less for the formation of aziridines than for cyclopropanes because in the former system the excess enthalphy associated with angle strain is less and the ring-bond distortion is reduced. Activation parameters undermine the assumption that formation of small rings is entropically favoured. Entropies of activation are actually **more negative** for the three-membered ring than for the five-membered ring systems.

According to Baldwin's rules for ring closure,[77] *3* (**35**), *4*, *5* (**36**), *6* and *7-exo-tet* processes are all favoured with the nucleophile and departing group in the *anti*-orientation to one another, whereas *5-endo-tet* (**37**) and *6-endo-tet* modes are disfavoured on stereo-electronic grounds[78] (**Scheme 5**).



35 **35'** **36** **37**

Scheme 5

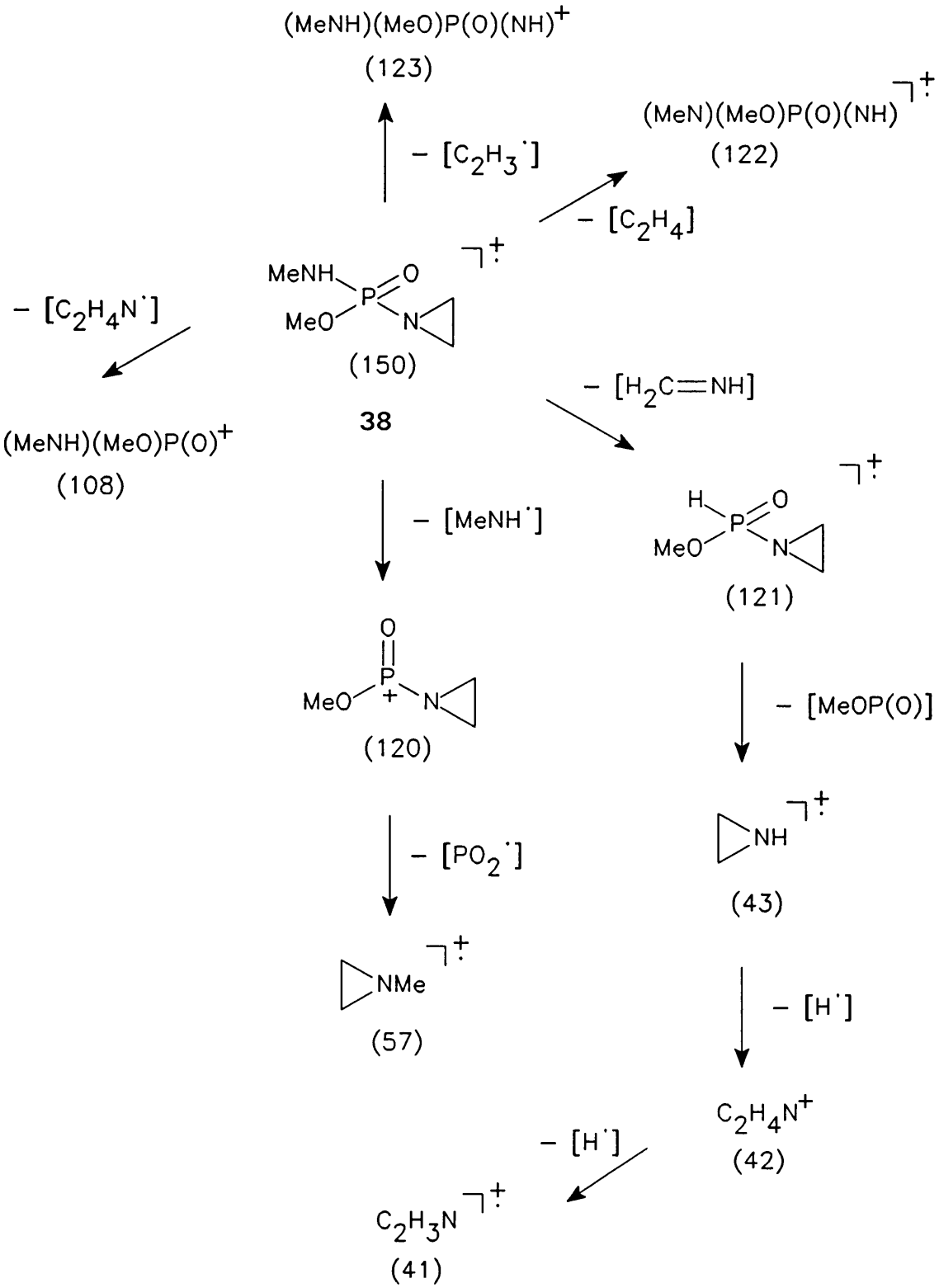
Anselme[79] and Fountain *et al*[80] reported that even the disfavoured process for a five-membered transition state such as *5-endo-trig*, can be obtained after modification of reaction conditions.

2.2.4 1,3 *VERSUS* 1,5 INTRAMOLECULAR NUCLEOPHILIC REACTIVITY OF THE CONJUGATE BASES OF THE *N,N'*-DIARYL-*N"*-(2-CHLOROETHYL)PHOSPHOROTRIAMIDATES, (17a - c), AND THE *N,N'*-DIALKYL ANALOGUES, (17d, e).

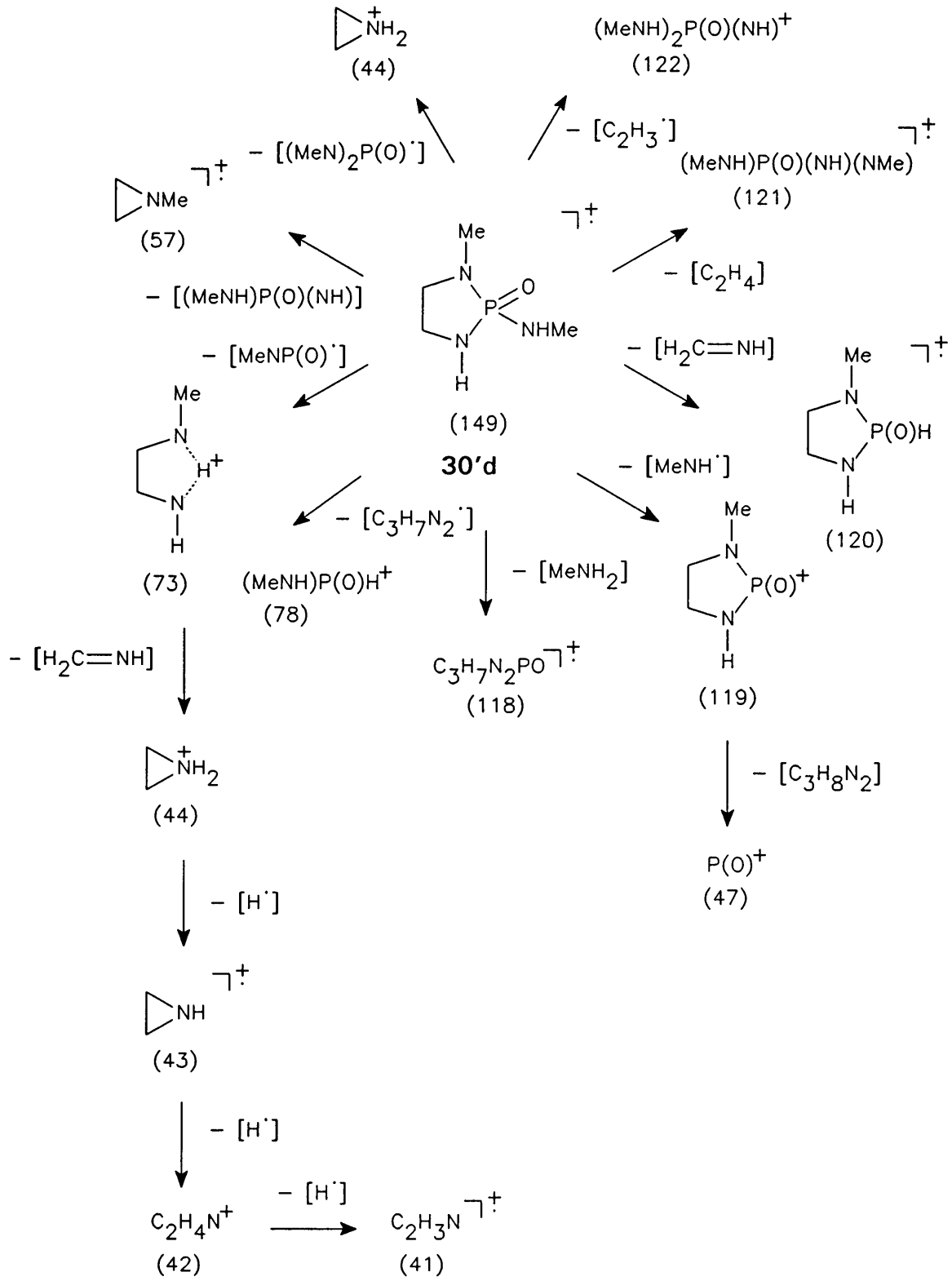
In the earlier work[48] done on the intramolecular reactivity of similar systems, promoted either *via* electrophilic catalysis (Ag^+), or deprotonation of the substrate (NaH, BuLi), it was shown that the displacement of the *β*-haloatom in **18** (X = Me, Ph) and **19** (X = MeO, Et, Ph) yielded exclusively the corresponding aziridines (no 1,5 cyclic products were obtained). Substrate **20** (Y = MeNH), for which no simple 1,3 cyclization would be possible, gave rise only to the 1,5 cyclic product. Under milder basic conditions (pyridine as the base), a reaction in which pyridine acted as an external **nucleophile** with respect to the alkyl (or ester) group, was obtained. It was also demonstrated that systems having the nucleophilic and electrophilic (*β*-carbon atom) centres within the same molecular framework, do not undergo thermally-induced intramolecular alkylation reactions. No nucleophilic displacement of the halogen atom by the phosphoryl oxygen atom was observed for the triester derivative **20** (Y = MeO).

During our study[65] it was found that substrates **17a - e**, upon treatment with bases (NaH, ^{t}BuOK and $NaOH/K_2CO_3$ respectively) in the presence of a phase-transfer catalyst (PTC, tetra-*n*-butylammo-

nium bromide (TBAB) or tetra-*n*-butylammonium hydrogen sulphate (TBAHS)), react smoothly according to **Scheme 3** and the product composition depends on the substrate as well as the reaction conditions. Since sodium (or potassium) salts of compounds **17** are insoluble in benzene (and other inert solvents tested), the addition of PTC was necessary for the reaction to proceed at reasonable rates. Similar rate acceleration upon the addition of tetraalkylammonium salts to the reaction medium was reported for alkylation of deprotonated phosphoramidates,[81] or some dehydrohalogenation reactions.[82] For each substrate the reaction products were isolated in the pure state and characterized by NMR (^{1}H, ^{31}P) spectroscopy and elemental analysis. Although the three- and five-membered ring compounds **29'a** - **e** and **30'a** - **e** were obtained as solids in the pure state, attempts to determine their structures by X-ray diffraction failed, since no suitable crystals could be obtained. For example, we found **30'd** a remarkably hygroscopic substance, very difficult to handle, to purify and to store without changing it into a syrupy liquid. In selected cases mass spectra of some of the products were also recorded since we were interested in the comparison of the MS of the products with those of their precursors. The MS behaviour of the aziridine product is illustrated by the spectrum of **38** (**Scheme 6**), while for the 1,3,2-diazaphospholidine product, **30'd** was chosen as a model (**Scheme 7**). The results of cyclization of substrates **17** are given in **Table 2.**



Scheme 6: MS of **38**; only major fragmentation pathways shown.



Scheme 7: MS of **30'd**; only major fragmentation pathways shown.

Table 2: Base-promoted cyclization of phosphorotriamidates **17**

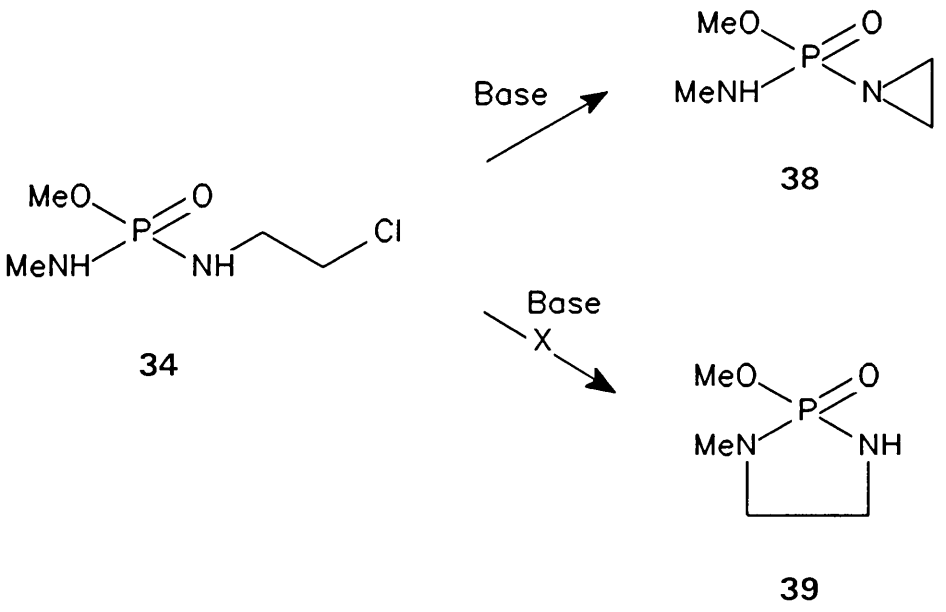
Substrate	Reaction conditions	Conversion (%)	**29′** (%)[a]	**30′** (%)[a]	**29′/30′**
17a	NaH (2.0 equiv.), TBAB[b] (5 mol%), Ph—H, r.t., 15 min	100	53	47	1.13
	NaH (1.0 equiv.), TBAB (5 mol%), Ph—H, reflux, 5 h	88	67	21	3.19
	NaH (1.0 equiv.), TBAB (5 mol%), THF[c]/Ph—H, reflux, 5.5 h	87	66	21	3.14
	NaH (2.0 equiv.), TBAB (5 mol%), Ph—H, reflux, 8 h	100	100		∞
17b	NaH (1.1 equiv.), TBAB (5 mol%), THF/Ph—H, reflux, 3 h	26	18	8	2.25
	NaH (1.1 equiv.), TBAB (10 mol%), Ph—H, reflux, 6 h	78	43	35	1.23
	NaH (1.5 equiv.), TBAB (10 mol%), Ph—H, reflux, 18 h	91	65	26	2.50
	$NaOH/K_2CO_3$ (4 equiv./5 equiv.), TBAB (10 mol%), Ph—H, reflux, 19 h	92	92		∞
	$NaOH/K_2CO_3$ (4 equiv./5 equiv.), TBAB (10 mol%), THF/Ph—H, reflux, 19 h	100	100		∞

Substrate	Reaction conditions	Conversion (%)	**29'** (%)[a]	**30'** (%)[a]	**29'/30'**
17b	$NaOH/K_2CO_3$ (4 equiv./5 equiv.), TBAB (10 mol%), CH_3CN, reflux, 19 h	99	99		∞
	^tBuOK (2.5 equiv.), TBAB (10 mol%), Ph—H, reflux, 18 h	93	92	1	92.0
17c	NaH (1.1 equiv.), TBAB (10 mol%), Ph—H, reflux, 5 h	85	48	37	1.30
	NaH (1.1 equiv.), TBAB (10 mol%), THF/Ph—H, reflux, 19 h	48	31	17	1.82
	NaH (1.5 equiv.), TBAB (10 mol%), Ph—H, reflux, 18 h	94	42	52	0.81
	$NaOH/K_2CO_3$ (4 equiv./5 equiv.), TBAB (10 mol%), THF/Ph—H, reflux, 17 h	100	100		∞
	$NaOH/K_2CO_3$ (4 equiv./5 equiv.), TBAB (10 mol%), CH_3CN, reflux, 22 h	100	100		∞
	^tBuOK (2.5 equiv.), TBAB (10 mol%), Ph—H, reflux, 18 h	100	100		∞
17d	NaH (1.1 equiv.), TBAB (10 mol%), Ph—H, 30 - 40°C, 6 h; r.t., 16 h	38	38		∞

Substrate	Reaction conditions	Conversion (%)	**29'** (%)[a]	**30'** (%)[a]	**29'/30'**
17d	$NaOH/K_2CO_3$ (4 equiv./5 equiv.), TBAHS[d] (10 mol%), Ph—H, r.t., 4.5 days	100	100		∞
	^tBuOK (2.5 equiv.), TBAHS (10 mol%), Ph—H, r.t., 4.5 days	87	87		∞
17e	NaH (1.1 equiv.), No TBAB, Ph—H, reflux[e, f], 64.5 h	100	100		∞
	NaH (1.0 equiv.), TBAB (10 mol%), Ph—H, r.t., 20 h	97	97		∞
	NaH (1.1 equiv.), TBAB (10 mol%), Ph—H, r.t., 26 h	100	100		∞
34	NaH (1.1 equiv.), No TBAB, Ph—H, r.t., 4 days	100	100[g]	[h]	∞[i]

[a] **29'/30'** ratio determined by ^{31}P NMR spectroscopy.
[b] Tetra-*n*-butylammonium bromide.
[c] Solubility of substrates **17a** - **c** higher in THF than in Ph—H.
[d] Tetra-*n*-butylammonium hydrogensulphate (or bisulphate).
[e] Under the same reaction conditions, but at r.t., a very low conversion was obtained.
[f] In the presence of TBAB, the formation of **30'e** became more prominent due to the secondary reaction of **29'e** with Br^- (*vide infra*).
[g] Compound **38**.
[h] Compound **39**.
[i] Ratio of **38**/**39**.

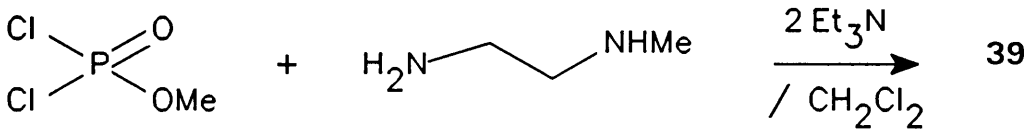
It is clear, that with respect to the reaction course, substrates **17** can be divided into two groups. For the *N*-alkyl substrates **17d,e**, the regioselectivity of the cyclization was complete; the corresponding *N*-phosphorylated aziridines **29'** (with characteristic high field doublet displayed by the aziridine NC_2H_4 group in the ^1H NMR spectrum) were the exclusive products which were found to be stable under the applied reaction conditions. We confirmed this preference for the 1,3 cyclization of *N*-alkylphosphoramidates on one additional example, *i.e.*, diamidoester, *O*-methyl-*N*-methyl-*N'*-(2-chloroethyl)diamidophosphate **34**. Again, this substrate yielded, upon treatment with base, exclusively the aziridine **38** (Eq. ***(15)***), with no trace of the corresponding 1,3,2-diazaphospholidine **39** being formed (see **Table 2**).



(15)

This result was confirmed by comparison of the reaction product with

a sample of the diazaphospholidine prepared directly from methylphosphorodichloridate[83] and *N*-methylethylenediamine in the presence of triethylamine (Eq. ***(16)***).

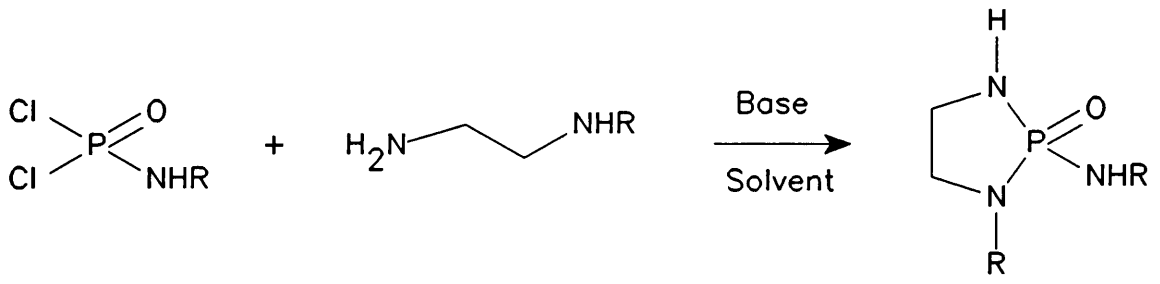


(16)

Although these results confirm the expected preferential (or exclusive) formation of **17'** (or the corresponding conjugate base of **34**) in the deprotonation step, they do not by themselves provide any conclusive information about the relative rates of the cyclization reactions.

For the *N*-aromatic substrates **17a - c**, on the other hand, the results obtained are more complex. When the reactions were carried out in the presence of only a small excess of the base (or for short periods of time), comparable quantities of both cyclization products, **29'** and **30'**, were formed. The presence of the isomeric products **30'** could be easily seen in the ^{1}H NMR spectra, as the methylene groups of the five membered ring give rise to a complex pattern, more low field from the doublet of the aziridine ring. The formation of both products (which were isolated as pure compounds and were found to be stable under neutral conditions) demonstrates that for **17a - c** the 1,5 cycli-

zation can compete successfully with the 1,3 ring closure. When a large excess of base was used, and when reactions were carried out under more drastic conditions, the aziridine derivatives **29'** were, however, formed as the exclusive products. It is clear therefore that those two types of cyclic compounds initially formed can undergo, under the reaction conditions, subsequent interconversion, finally yielding **29'** as the sole reaction product, most stable in this reaction system. Those secondary reactions involving products **29'** and **30'** were then tested by investigating independently the effect of the base (sodium hydride), and of tetrabutylammonium bromide on the individual cyclic products **29'a - e** and **30'a - e**, obtained either directly from the corresponding substrates **17** (**29'a - c**; **30'a - c**; **29'd, e**), or prepared by an independent route (**30'd, e**). The latter route involved formation of the 1,3,2-diazaphospholidine by the reaction of the corresponding *N*-substituted ethylenediamine with the *N*-substituted phosphoroamidodichloridate (Eq. ***(17)***).

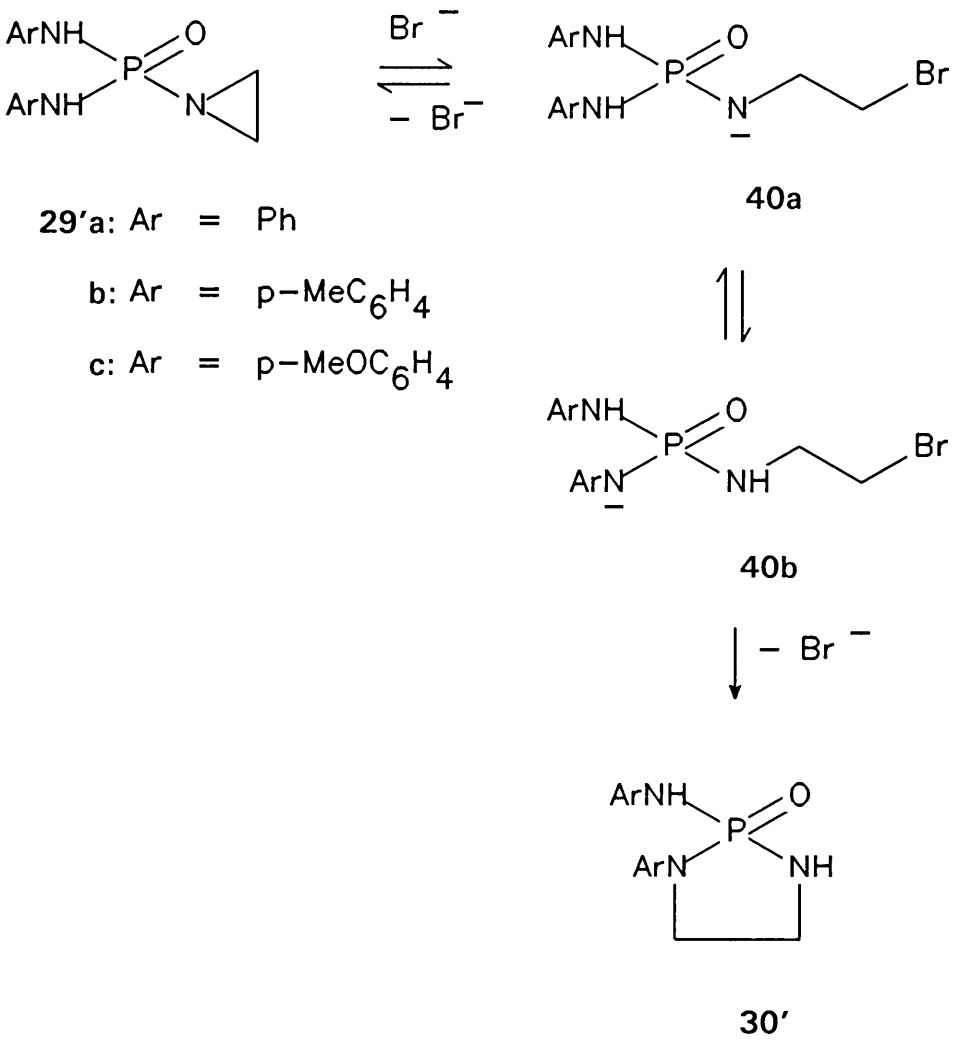


R = Me, CH_2Ph

30'd, e

(17)

With respect to the *N*-aromatic compounds, **29'a - c**, TBAB was found to catalyze their complete conversion to the 1,3,2-diazaphospholidine derivatives **30'a - c**. The reaction most likely proceeds *via* the nucleophilic opening of the aziridine ring by the bromide ion, internal proton transfer, and the 1,5 ring closure (**Scheme 8**).

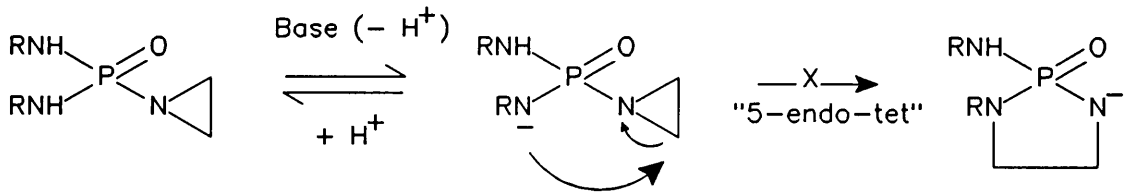


Scheme 8

When the reaction mixture was quenched with water, the ^{31}P NMR spectrum of the product always revealed, in addition to **30'** (and, in some cases, unreacted **29'**), small quantities of a product with the ^{31}P chemical shift almost identical to that of the corresponding **17**. We assigned this signal to the conjugate acid of the bromide analogue of **17**, **40a** (or **40b**); thus we took it as evidence for the first step of the interconversion. The driving force for the **40a** → **40b** proton transfer should stem of course, from the difference in the pK_a values of the NH groups of the ArNH and the $BrCH_2CH_2NH$ functions (*vide supra*). With **29'd** and **29'e**, although the bromide-induced opening of the aziridine ring (**Scheme 8**) should also take place, the subsequent proton transfer, prerequisite for the isomerization, is not favoured by the pK_a difference of the respective NH groups. As a consequence, when **29'd**, **29'e** were treated with TBAB in benzene, they gave, even after prolonged heating under reflux, only minor (less than 10%) quantities of the corresponding **30'**, the bulk of the substrate remaining unchanged.

With respect to the effect of the base, the situation is as follows. All *N*-phosphorylated aziridines **29'a** - **e** were stable upon prolonged treatment with sodium hydride. The absence of the isomerization results most likely from the reluctance of the conjugate base of **29'**, **29"** to undergo the intramolecular opening of the aziridine ring. Such a reaction, corresponding to the *5-endo-tet* cyclization process, should

be disfavoured on stereoelectronic grounds[77,78] (**Scheme 9**).



29'a: R = Ph **29"**

b: R = p–MeC_6H_4

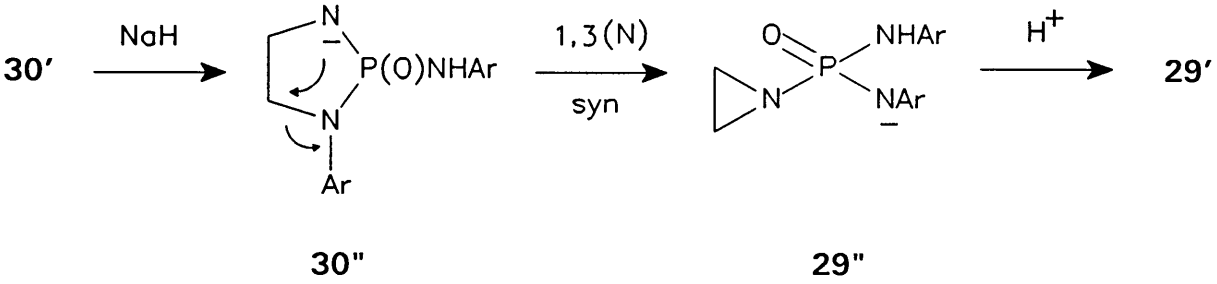
c: R = p–$MeOC_6H_4$

d: R = Me

e: R = CH_2Ph

Scheme 9

N,N'-Diaryl-1,3,2-diazaphospholidines **30'a** - **c** differ greatly in their reactivity under basic conditions from their *N*-alkyl (methyl, benzyl) analogues **30'd, e**. The former compounds, when heated in benzene solution in the presence of sodium hydride, undergo quatitative conversion to the corresponding isomeric products **29'**. This interconversion, also responsible for the gradual disappearance of products **30'**, initially formed by the base-promoted cyclization of **17a** - **c**, can be explained by the following sequence (**Scheme 10**):



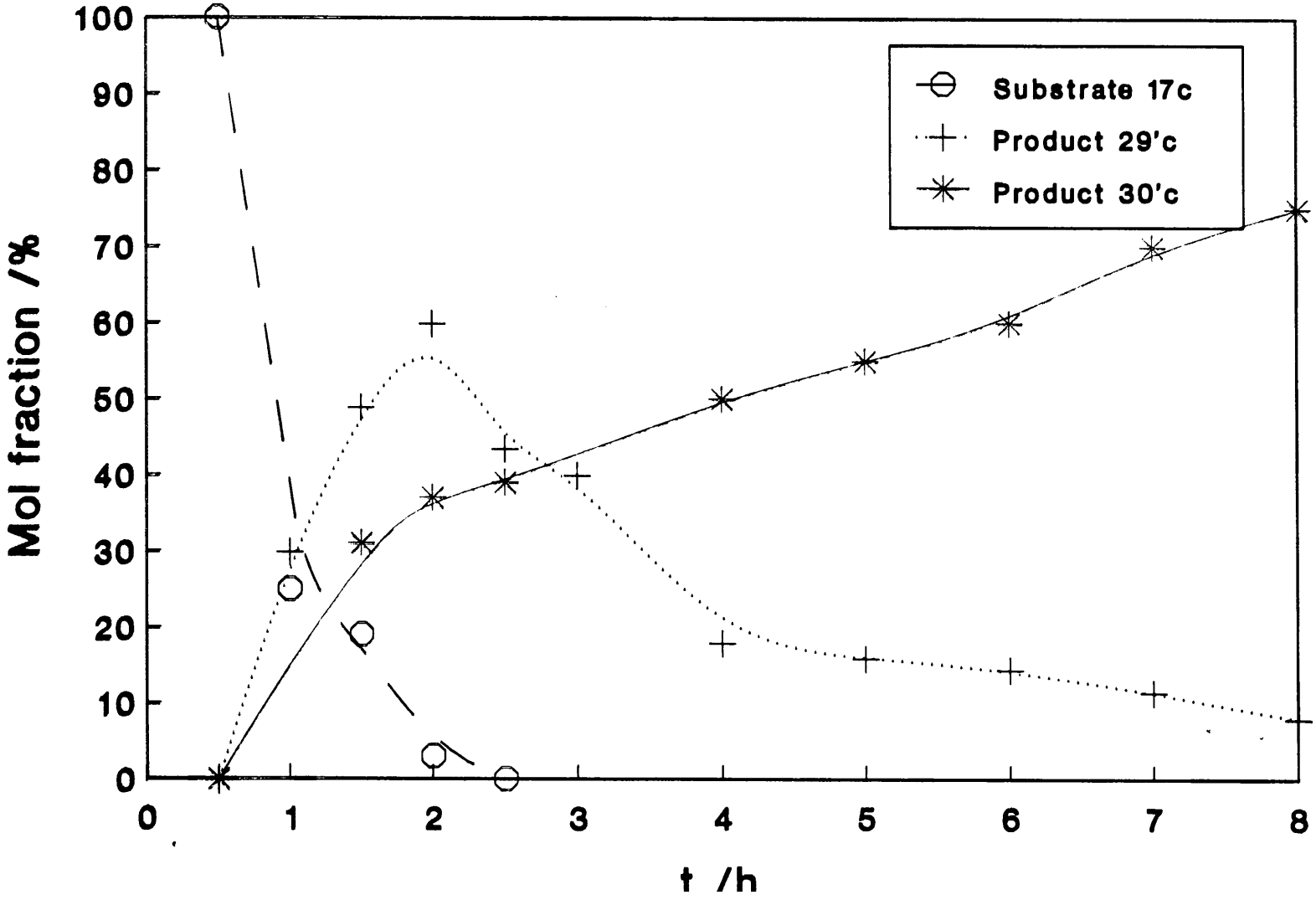
30" **29"**

Scheme 10

The **30"** → **29"** rearrangement illustrates the frequently observed[68,69] preference for the formation, if possible, of a three-membered ring. In this case, however, we observe a rather unusual example of a *3-exo-tet* ring closure proceeding *via* the *syn* (and not, as in most cases, *anti*) orientation of the nucleophilic centre (N^-) and the departing group (ArN^-), *vide supra*. The common examples of such *anti 3-exo-tet* ring closure (see **Scheme 5**) are the formation of epoxides[84] from halohydrins or aziridinium ions from 2-haloamines.[85]

The product composition in the case of the *N*-aromatic substrates can therefore result from both, the initial 1,3, or 1,5 ring closure of the 2-chloroethyl precursor, and from the secondary, mutual interconversion of the primary products. This behaviour can be illustrated by plotting the relative proportions of the substrate and the two isomeric products as a function of the reaction time. **Figure 2** represents such a plot for **17c**, which was treated with NaH (1.2 mol-equivalents) in

Figure 2: Reaction of **17c** with NaH; composition *vs* time



a presence of TBAB (10 mol%). It can be seen that after one hour at room temperature, followed by one hour of refluxing, the conversion of the substrate is virtually completed, with both, **29'c** and **30'c** appearing simultaneously in the reaction mixture. Under those conditions (small excess of the base) the conversion of **30'c** to **29'c** (**Scheme 10**) is negligible, but, because of the presence of the halide (Br^-, Cl^-) ions, the opposite conversion (**Scheme 8**) is in operation. As a result of this, the proportion of the aziridine derivative reaches a maximum (2h, 60%), then decreases yielding the increasing proportion of the 1,3,2-diazaphospholidine product. We expect therefore to be able to modify the final composition of the reaction mixture by altering the details of the experimental conditions for the primary, ring closure reaction.

Both *N*-alkyl substrates **30'd, e** were found to be unaffected by sodium hydride, even after long periods of treatment. We explain this difference in stability by the difference in the structural conditions for the rearrangement of the conjugate base of **30'** to the conjugate base of **29'** (see **Scheme 10**). For **30'a - c**, the 1,3 ring closure is facilitated by the departure of a relatively good leaving group, *i.e.*, the rearrangement would involve the departure of a much poorer (more basic) leaving group, such as the RN^- group. It is worthwhile noting that, in all substrates **30'**, the parallel deprotonation of the exocyclic NH function could, in principle, also lead to a rearrangement process, but

that pathway would again lead to the formation of a 1,3,2-diazaphospholidine system.

2.2.5 CONCLUSIONS

The proportion of the isomeric products **29'** and **30'** as well as **38** and **39** is, in fact, determined by the relative acidities of the respective NH functions, which *per se* depends on the substituents R and the 2-chloroethyl group. The subsequent interconversion of the ring products can directly be related to the substituent effect; therefore the great difference in selectivity for substrates in which R = aryl groups (**17a - c**) *vs* substrates where R = alkyl groups (**17d, e**).

It can be therefore expected that in biologically active systems of the Cyclophosphamide type (structure **13**, chapter 1), which lack any *N*-aromatic substituents, the 1,3-intramolecular displacement, leading to the reactive aziridinium intermediates, will be predominant or the exclusive behaviour.

2.2.6 EXPERIMENTAL

Solvents and commercially available substrates were purified by conventional methods immediately before use. The NMR spectra were

recorded on a Bruker AC 300 MHz spectrometer in $CDCl_3$, and the chemical shift values are given relative to $SiMe_4$ (TMS) (^1H) and trimethyl phosphate (^{31}P). Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionization potential of 70 eV and on a Finnigan MAT-8200 electron impact spectrometer. For column chromatography Merck Kieselgel 60 (0.063 - 0.200 mm) was used as a stationary phase. The products were collected as homogeneous (according to TLC) fractions. Elemental analysis (C/H/N) was carried out at the Council for Scientific and Industrial Research (Pretoria).

* ***Substrates***

N-(2-Chloroethyl)phosphoroamidodichloridate (33) (Eq. ***(12)***)

1 mol-equivalent of well-dried and finely powdered 2-chloroethylammonium chloride was added to freshly distilled phosphorus oxychloride (3.9 mol-equivalent). The reaction mixture was heated at reflux with good stirring and exclusion of moisture for 20 h. The excess $POCl_3$ was removed *in vacuo* and the residue was purified by distillation.

Yield: 94%;

b.p.: 98 - 99°C (0.05 Torr; 1 Torr = 133.3 Pa);

n_D^{25} 1.5031;

^{1}H NMR: δ: 3.43 (2H, m, NCH_2),
3.64 (2H, t, J_{HH} 5.9 Hz, CH_2Cl),
5.04 (1H, br s, NH);

^{31}P NMR: δ: 13.1.

Phosphorotriamidates* 17**; *general procedure* (Eq. ***(12))

A *ca* 5 M solution of *N*-(2-chloroethyl)phosphoroamidodichloridate (**33**) (1 mol-equivalent) in the appropriate solvent was added dropwise with stirring and cooling (- 5 to 0°C) to the *ca* 4 M solution of the required amine (4 mol-equivalent) in the same solvent. The mixture was then stirred at room temperature overnight, the amine hydrochloride was filtered off, and the organic solution was washed with water and dried ($MgSO_4$). After removal of the solvent the crude **17** was purified as indicated below.

17a: Prepared in $CHCl_3$; purified by two recrystallizations (Ph—H/$CHCl_3$ 1: 1, followed by EtOH).

Yield: 93%;
m.p.: 117 - 118°C;

^{1}H NMR: δ: 3.33 (2H, m, NCH_2),
3.50 (2H, t, J_{HH} 5.5 Hz, CH_2Cl),

3.59 (1H, br s, N*H*CH_2),

5.71 (2H, d, J_{HP} 7.8 Hz, 2 x N*H*Ph),

6.94 (4H, t, J_{HH} 7.2 Hz, H_{ortho}),

7.09 (6H, m, H_{meta}, H_{para});

^{31}P NMR: δ: 0.55;

Anal. calcd. for $C_{14}H_{17}ClN_3OP$: C 54.3, H 5.5, N 13.6;

found: C 54.5, H 5.4, N 13.5%.

17b: Prepared in ether; purified by recrystallization from EtOH/H_2O.

Yield: 67%;

m.p.: 154 - 155°C;

^{1}H NMR: δ: 2.24 (6H, s, 2 x ArC*H*$_3$),

3.33 (3H, m, $NHCH_2$),

3.52 (2H, t, J_{HH} 5.4 Hz, CH_2Cl),

5.26 (2H, d, J_{HP} 6.9 Hz, 2 x N*H*Ar),

6.94 (4H, d, J_{HH} 8.4 Hz, H_{meta}),

7.00 (4H, d, J_{HH} 8.4 Hz, H_{ortho});

^{31}P NMR: δ: 1.09;

Anal. calcd. for $C_{16}H_{21}ClN_3OP$: C 56.9, H 6.3, N 12.4;

found: C 56.7, H 6.1, N 12.4%.

17c: Prepared in $CHCl_3$; purified by recrystallization from EtOH.

Yield: 45%;

m.p.: 150 - 150.5°C;

^{1}H NMR: δ: 3.30 (3H, m, $NHCH_2$),

3.50 (2H, t, J_{HH} 5.6 Hz, CH_2Cl),

3.72 (6H, s, 2 x OCH_3),

5.24 (2H, d, J_{HP} 7.7 Hz, 2 x N*H*Ar),

6.74 (4H, d, J_{HH} 8.9 Hz, H_{meta}),

6.99 (4H, d, J_{HH} 8.9 Hz, H_{ortho});

^{31}P NMR: δ: 1.80;

Anal. calcd. for $C_{16}H_{21}ClN_3O_3P$: C 52.0, H 5.7, N 11.4;

found: C 51.9, H 5.5, N 11.3%.

17d: Prepared in Ph—H; purified by column chromatography (SiO_2;EtOH).

Yield: 63%;

MS: *m/z* 185 ($M^{\ddagger}$, 9%),

155 ($M^{\ddagger}$ - MeNH•, 2%),

150 ($M^{\ddagger}$ - Cl•, 7%),

136 ($M^{\ddagger}$ - $ClCH_2$•, 67%),

123 ($M^{\ddagger}$ - $H_2C{=}CHCl$, 6%),

107 ($(MeNH)_2PO^+$, 100%),

44 ($C_2H_6N^+$, 41%), see **Scheme 4**;

^{1}H NMR: δ: 2.55 (6H, d, J_{HP} 12.2 Hz, 2 x NCH_3),

2.60 (2H, br s, 2 x N*H*Me),

3.06 (1H, m, N*H*CH_2),

3.24 (2H, m, CH_2N),

3.58 (2H, t, J_{HH} 5.8 Hz, CH_2Cl);

^{31}P NMR: δ: 16.85;

Anal. calcd. for $C_4H_{13}ClN_3OP.2H_2O$: C 21.7, H 7.7, N 19.0;

found: C 21.3, H 7.3, N 18.6%.

17e: Prepared in ether; purified by recrystallization from ether/cyclohexane.

Yield: 97%;

m.p.: 63 - 64°C;

^{1}H NMR: δ: 2.95 (3H, br s, 3 x NH),
3.21 (2H, m, NCH_2),
3.50 (2H, t, J_{HH} 5.5 Hz, CH_2Cl),
4.07 (4H, dd, J_{HP} 10.1 Hz, J_{HH} 7.1 Hz, 2 x CH_2Ph),
7.28 (10H, br s, 2 x Ph);

^{31}P NMR: δ: 13.36;

Anal. calcd. for $C_{16}H_{21}ClN_3OP$: C 56.9, H 6.3, N 12.4;
found: C 56.5, H 6.7, N 12.0%.

O-Methyl-N-methyl-N′-(2-chloroethyl)phosphorodiamidate **(34)** (Eq. ***13)***)

(a) Dry methylamine was passed through the solution of *N*-(2-chloroethyl)phosphoroamidodichloridate (2.05 g, 0.010 mol) in dioxane (14 mL) with stirring and cooling (below 25°C). After the exothermic reaction subsided, 10 mL of dioxane was added, the mixture was filtered, the precipitate was washed with dioxane followed by chloroform, and the combined filtrates were concentrated under reduced pressure. Crude *N*-methyl-*N′*-(2-chloroethyl)diamidophosphorochloridate was obtained as a colourless oil and was used without further purification.

Yield: 1.73 g, 91%;

^{1}H NMR: δ: 2.68 (3H, d, J_{HP} 10.1 Hz, NMe),
3.31 - 3.44 (2H, m, NCH_2),
3.45 (1H, br s, NH),
3.64 (2H, t, J_{HH} 5.6 Hz, CH_2Cl),
4.25 (1H, br s, NH);

^{31}P NMR: δ: 20.7.

(b) A solution of this product (1.71 g, 0.091 mol) in dry methanol (4 mL) was added dropwise at room temperature to the solution of one mol-equivalent of CH_3ONa in methanol (8 mL). The mixture was stirred for 20 h, filtered, and evaporated under reduced pressure. A small volume of chloroform was added, the suspension was filtered through a layer of anhydrous $MgSO_4$ and evaporated, yielding the crude product. Pure **34** was obtained by column chromatography (SiO_2; $CHCl_3$/acetone, 3:1) as a colourless oil.

Yield: 1.39 g, 82% (crude);

MS: *m/z* 186 ($M^{\ddagger}$, 20%),
156 ($M^{\ddagger}$ - MeNH•, 5%),

155 ($M^{\ddagger}$ - MeO•, 1%),

151 ($M^{\ddagger}$ - Cl•, 10%),

137 ($M^{\ddagger}$ - $ClCH_2$•, 100),

124 ($M^{\ddagger}$ - $H_2C{=}CHCl$, 4%),

108 ((MeNH)(MeO)PO^+, 69%),

44 ($C_2H_6N^+$, 9%), see **Scheme 4**;

^{1}H NMR: δ: 2.52 (3H, dd, J_{HP} 12.3 Hz, J_{HH} 5.7 Hz, NMe),

2.90 (1H, br s, NH),

3.17 (2H, m, NCH_2),

3.29 (1H, br s, NH),

3.53 (2H, t, J_{HH} 5.8 Hz, CH_2Cl),

3.59 (3H, d, J_{HP} 11.2 Hz, OMe);

^{31}P NMR: δ: 15.5;

Anal. calcd. for $C_4H_{12}ClN_2O_2P$: C 25.7, H 6.5, N 15.0;

found: C 25.3, H 6.4, N 14.9%.

* ***Reactions of substrates* 17 *with bases*** **(Scheme 3)**

A *ca* 0.3 - 0.5 M solution of **17** in benzene was added to a suspension of the base in benzene (1 mL/mol), followed by the PTC,

and the mixture was stirred vigorously with exclusion of moisture. The proportion of the reagents and products, the reaction time, and temperature are given in **Table 2**. The reaction was stopped when the ^{31}P NMR spectrum of a sample showed complete disappearance of **17**. After filtration, the solution was washed with small portions of water until neutral, dried ($MgSO_4$), evaporated, and the residue was characterized and purified as described below. *N*-Phosphorylated aziridines **29'** were obtained by carrying out the reaction under conditions allowing for the exclusive formation of **29'**.

29'a: 2 mol-equivalent of NaH, 5 mol% TBAB, reflux, 8 h; purified by column chromatography (SiO_2; acetone/CH_2Cl_2, 2: 1).

Yield: 88%;

m.p.: 183 - 184°C;

^1H NMR: δ: 2.30 (4H, d, J_{HP} 16.2 Hz, C_2H_4N),
5.48 (2H, d, J_{HP} 8.4 Hz, 2 x N*H*Ar),
6.69 - 7.23 (10H, m, 2 x Ph);

^{31}P NMR: δ: 12.1;

Anal. calcd. for $C_{14}H_{16}N_3OP$: C 61.5, H 5.9, N 15.4;
found: C 61.2, H 5.9, N 15.4%.

29'b: $NaOH/K_2CO_3$ (4 mol-equivalent/5 mol-equivalent), 10 mol% TBAB, reflux, 19 h; purified by column chromatography (SiO_2; petroleum ether) (oil).

Yield: 92%;

^1H NMR: δ: 2.22 (6H, s, 2 x CH_3),
2.25 (4H, d, J_{HP} 11.4 Hz, C_2H_4N),
5.78 (2H, d, J_{HP} 8.7 Hz, 2 x N*H*Ar),
6.95 (4H, d, J_{HH} 8.4 Hz, 2 x H_{ortho}),
6.99 (4H, d, J_{HH} 8.4 Hz, 2 x H_{meta});

^{31}P NMR: δ: 12.8;

Anal. calcd. for $C_{16}H_{20}N_3OP$: C 63.8, H 6.7, N 13.9;
found: C 63.4, H 6.3, N 13.5%.

29'c: 2.5 mol-equivalent of ^tBuOK, 10 mol% TBAB, reflux, 18 h; crude foam purified by recrystallization from $CHCl_3$/petroleum ether (1: 1).

Yield: 55%;
m.p.: 47 - 51°C;

^{1}H NMR: δ: 2.22 (4H, d, J_{HP} 15.6 Hz, C_2H_4N),
3.68 (6H, s, 2 x OCH_3),
5.80 (2H, d, J_{HP} 8.7 Hz, 2 x N*H*Ar),
6.69 (4H, d, J_{HH} 8.8 Hz, 2 x H_{ortho}),
7.00 (4H, d, J_{HH} 8.8 Hz, 2 x H_{meta});

^{31}P NMR: δ: 13.4;

Anal. calcd. for $C_{16}H_{20}N_3O_3P$: C 57.7, H 6.1, N 12.6;
found: C 57.3, H 6.2, N 12.2%.

29'd: $NaOH/K_2CO_3$ (4 mol-equivalent/5 mol-equivalent), 10 mol% TBAB, room temperature, 108 h; purified by filtering the benzene solution through a Celite/$MgSO_4$ layer and evaporating the volatile material, affording a very hygroscopic oil.

Yield: 37%;

^{1}H NMR: δ: 2.02 (4H, d, J_{HP} 15.0 Hz, C_2H_4N),
2.48 (2H, br s, 2 x NH),
2.67 (6H, dd, J_{HP} 11.5 Hz, J_{HH} 5.4 Hz, 2 x NMe);

^{31}P NMR: δ: 26.0;

29'e: 1.2 mol-equivalent of NaH, 10 mol% TBAB, room temperature, 30 h; purified by recrystallization from benzene/petroleum ether (1: 1).

Yield: 85%;

m.p.: 58 - 60°C;

^{1}H NMR: δ: 2.04 (4H, d, J_{HP} 15.2 Hz, C_2H_4N),
3.01 (2H, m, 2 x NH),
4.13 (4H, 2 x dd, J_{HP} 9.2 Hz, J_{HH} 7.2 Hz, 2 x CH_2Ph),
7.29 (10H, br s, 2 x Ph);

^{31}P NMR: δ: 22.9;

Anal. calcd. for $C_{16}H_{20}N_3OP$: C 63.8, H 6.7, N 13.9;
found: C 63.4, H 6.5, N 13.9%.

* ***Reaction of substrate* 34 *with base*** (Eq. ***(15)***)

Substrate **34** (0.16 g, 8.6 x 10^{-4} mol) and NaH (9.4 x 10^{-4} mol) in benzene (5 mL) were stirred at room temperature for 96 h. Aqueous ethanol (1.5 mL) was added, the mixture was filtered through a layer of Celite/$MgSO_4$, washed with $CHCl_3$, and the volatile products evaporated. Aziridine derivative **38** was obtained as a pale yellow oil.

Yield: 65%;

MS: *m/z* 150 ($M^{\ddagger}$, 5%),

123 ($M^{\ddagger}$ - $C_2H_3\cdot$, 14%),

122 ($M^{\ddagger}$ - C_2H_4, 6%),

121 ($M^{\ddagger}$ - $H_2C{=}NH$, 18%),

120 ($M^{\ddagger}$ - $MeNH\cdot$, 5%),

108 ($M^{\ddagger}$ - $C_2H_4N\cdot$, 80%),

57 ($MeNC_2H_4^{\ddagger}$, 79%),

43 ($C_2H_5N^{\ddagger}$, 100%),

42 ($C_2H_4N^{+}$, 85%),

41 ($C_2H_3N^{\ddagger}$, 68%), see **Scheme 6**;

^{1}H NMR: δ: 2.03 (4H, d, J_{HP} 15.5 Hz, C_2H_4N),

2.60 (3H, dd, J_{HP} 11.4 Hz, J_{HH} 5.7 Hz, NMe),

3.00 (1H, br s, NH),

3.62 (3H, d, J_{HP} 11.0 Hz, OMe);

^{31}P NMR: δ: 23.7;

Anal. calcd. for $C_4H_{11}N_2O_2P.H_2O$: C 28.6, H 7.8, N 16.7;

found: C 28.7, H 7.3, N 16.5%.

1,3,2-Diazaphospholidines **30'** **(Scheme 3)**

N-Aryl derivatives **30'a** - **c** were isolated by column chromatography (SiO_2) from the mixtures obtained upon treatment of the corresponding substrates **17** with base under conditions that led to comparable quantities of both products.

30'a: Acetone/CH_2Cl_2, 2: 1; recrystallized from $CHCl_3$/petroleum ether (1: 1)

Yield: 36%;

m.p.: 203 - 205°C;

^{1}H NMR: δ: 2.87 (1H, d, J_{HP} 10.5 Hz, *endo*-NH),

3.40 - 3.54 (1H, m) and 3.58 - 3.64 (3H, m) (CH_2CH_2)

5.43 (1H, d, J_{HP} 6.6 Hz, *exo*-NH),

6.82 - 6.97 (5H, m, Ph)

7.08 - 7.25 (5H, m, Ph);

^{31}P NMR: δ: 13.1;

Anal. calcd. for $C_{14}H_{16}N_3OP$: C 61.5, H 5.9, N 15.4;

found: C 61.1, H 6.0, N 15.2%.

30'b: Acetone/CH_2Cl_2, 2: 1; recrystallized from $CHCl_3$/acetone (1: 1)

Yield: 26%;

m.p.: 180 - 182°C;

^{1}H NMR: δ: 2.20 (3H, s, Me),

2.23 (3H, s, Me),

2.85 (1H, br s, *endo*-NH),

3.34 (1H, m) and 3.65 (3H, m) (CH_2CH_2)

5.37 (1H, d, J_{HP} 6.6 Hz, *exo*-NH),

6.74 (2H, d, J_{HH} 8.1 Hz, H_{meta} of the *endo*-NAr),

6.94 (2H, d, J_{HH} 8.1 Hz, H_{ortho} of the *endo*-NAr),

7.02 (2H, d, J_{HH} 8.6 Hz, H_{meta} of the *exo*-NAr),

7.08 (2H, d, J_{HH} 8.6 Hz, H_{ortho} of the *exo*-NAr);

^{31}P NMR: δ: 13.6;

Anal. calcd. for $C_{16}H_{20}N_3OP$: C 63.8, H 6.7, N 13.9;

found: C 63.4, H 6.2, N 13.5%.

30'c: Acetone/CH_2Cl_2, (1: 1).

Yield: 37%;

m.p.: 200 - 202°C;

^{1}H NMR: δ: 2.73 (1H, d, J_{HP} 10.1 Hz, *endo*-NH),
3.36 (1H, m) and 3.56 (3H, m) (CH_2CH_2),
3.71 (3H, s, OMe),
3.74 (3H, s, OMe),
4.95 (1H, d, J_{HP} 7.5 Hz, *exo*-NH),
6.69 (2H, d, J_{HH} 8.8 Hz, H_{ortho} of the *endo*-NAr),
6.78 (2H, d, J_{HH} 8.4 Hz, H_{ortho} of the *exo*-NAr),
6.81 (2H, d, J_{HH} 8.4 Hz, H_{meta} of the *exo*-NAr),
7.11 (2H, d, J_{HH} 8.8 Hz, H_{meta} of the *endo*-NAr);

^{31}P NMR: δ: 14.6;

Anal. calcd. for $C_{16}H_{20}N_3O_3P$: C 57.6, H 6.0, N 12.6;
found: C 57.2, H 6.1, N 12.4%.

N-Alkyl derivatives **30'd**, e were prepared as follows (Eq. ***(17)***). A 0.3 - 0.5 M solution of the corresponding *N*-substituted ethylene-diamine (1 mol-equivalent) and triethylamine (2 mol-equivalent) in dioxane/ether (3: 1) was added dropwise with stirring and cooling at

0 - 5°C to the *ca* 1 M solution of the corresponding *N*-substituted phosphoroamidodichloridate in the same solvent. After addition the mixture was stirred at room temperature overnight and filtered. For **30'd** the filtrate was saturated with dry gaseous ammonia, filtered again, and evaporated.

30'd: Pure **30'd** was obtained as highly hygroscopic, colourless crystals.

Yield: 11%;

m.p.: 75 - 78°C (sealed capillary);

MS: *m/z* 149 ($M^{\ddagger}$, 61%),

122 ($M^{\ddagger}$ - $C_2H_3\cdot$, 8%),

121 ($M^{\ddagger}$ - C_2H_4, 8%),

120 ($M^{\ddagger}$ - $H_2C{=}NH$, 75%),

119 ($M^{\ddagger}$ - MeNH·, 50%),

118 ($M^{\ddagger}$ - $MeNH_2$, 7%),

78 ($M^{\ddagger}$ - $C_3H_7N_2\cdot$, 38%),

73 ($M^{\ddagger}$ - MeNP(O)·, 19%),

57 ($MeNC_2H_4^{\ddagger}$, 7%),

47 (PO^{+}, 17%),

44 ($C_2H_6N^+$, 100%),

43 ($C_2H_5N^{\ddagger}$, 68%),

42 ($C_2H_4N^+$, 57%),

41 ($C_2H_3N^{\ddagger}$, 5%), see **Scheme 7**;

^{1}H NMR: δ: 2.44 (3H, dd, J_{HP} 12.7 Hz, J_{HH} 5.5 Hz, *exo*-NMe),

2.54 (3H, d, J_{HP} 9.3 Hz, *endo*-NMe),

2.63 (2H, br s, 2 x NH),

2.98 - 3.37 (4H, m, CH_2CH_2);

^{31}P NMR: δ: 27.6;

Anal. calcd. for $C_4H_{12}N_3OP$: C 32.2, H 8.1, N 28.2;

found: C 32.3, H 8.5, N 27.8%.

For **30'e** the filtrate was evaporated under reduced pressure and the residue was dissolved in benzene and washed three times with water. After drying and evaporating of the solvent, the product was obtained in the crystalline state.

30'e: Recrystallization from Ph—H/petroleum ether (1: 1), yielded highly hygroscopic, colourless crystals.

Yield: 80% (crude);

m.p.: 101 - 103°C;

^{1}H NMR: δ: 2.38 (1H, d, J_{HP} 7.8 Hz, NH),
2.75 (1H, br s, NH),
2.88 - 3.37 (4H, m, CH_2CH_2),
3.90 - 4.19 (4H, m, 2 x CH_2Ph),
7.10 - 7.45 (10H, m, 2 x Ph);

^{31}P NMR: δ: 24.8;

Anal. calcd. for $C_{16}H_{20}N_3OP$: C 63.8, H 6.7, N 14.0;
found: C 63.4, H 6.5, N 13.9%.

N-Benzylethylenediamine (Eq. ***(17)***)

Ethylenediamine (4 mol-equiv.) and benzyl bromide (1 mol-equiv.) were mixed together and heated at reflux for 3 h. After washing with water and drying, the pure product was obtained by distillation.

Yield: 47%;

b.p.: 100°C (0.1 Torr);

n_D^{20} 1.5417;

^{1}H NMR: δ: 1.35 (3H, s, disappears in D_2O, NH),
2.61 (2H, t, J_{HH} 5.7 Hz, CH_2N),
2.73 (2H, t, J_{HH} 5.7 Hz, CH_2N),
3.73 (2H, s, C*H*$_2$Ph),
7.25 (5H, br s, Ph);

Anal. calcd. for $C_9H_{14}N_2$: C 72.0, H 9.4, N 18.6;
found: C 72.4, H 9.1, N 18.8%.

N-Methylphosphoroamidodichloridate (Eq. ***(17)***)

Prepared from phosphorus oxychloride and methylammonium chloride.[86]

Yield: 98%;
b.p.: (bulb-to-bulb distillation, oven temperature 110°C/0.2 Torr);
n_D^{22} 1.4732;

^{1}H NMR: δ: 2.72 (3H, d, J_{HP} 19.5 Hz, NMe),
5.07 (1H, br s, NH);

^{31}P NMR: δ: 16.8.

N-Benzylphosphoroamidodichloridate (Eq. ***(17)***)

Prepared in the same manner from phosphorus oxychloride and benzylammonium chloride in almost quantitative yield (crude product).

^{1}H NMR: δ: 4.25 (2H, d, J_{HP} 14.7 Hz, CH_2),
5.20 (1H, br s, NH),
7.31 (5H, br s, Ph);

^{31}P NMR: δ: 13.6.

The product was thermally unstable and could not be distilled without decomposition. It was therefore used for preparation of **30'e** without purification.

O-Methyl-1-methyl-1,3,2-diazaphospholidine (39) (Eq. ***(15)***)

Methylphosphorodichloridate (2.0 g, 0.013 mol) in dichloromethane (10 mL) was added dropwise with stirring and cooling at - 5 to - 10°C to the solution of *N*-methylethylenediamine (0.99 g, 0.013 mol) and triethylamine (2.72 g, 0.027 mol) in dichloromethane (25 mL). The mixture was then stirred at room temperature for 22 h and filtered. The residual triethylammonium chloride was removed from the filtrate by stirring it with a mixture of solid $NaOH/K_2CO_3$, filtering, and evaporating the solvent under reduced pressure. The product was obtained as a viscous oil.

Yield: 0.82 g, 42%;

^{1}H NMR: δ: 2.57 (3H, d, J_{HP} 9.5 Hz, NMe),
2.98 (1H, br s, NH),
3.10 - 3.38 (4H, m, CH_2CH_2),
3.58 (3H, d, J_{HP} 11.9 Hz, OMe);

^{31}P NMR: δ: 27.2;
The ^{31}P NMR spectrum showed absence of any other phosphorus containing products, and the ^{1}H NMR spectrum revealed only the presence of some residual triethylammonium chloride.

***Interconversions of* 29' *and* 30'**

Individual compounds **29'** or **30'** were dissolved in benzene, the required amount of NaH or TBAB was added, and the mixture was stirred at the temperature and for the duration identical to those applied to the corresponding substrates **17**. After filtration and evaporation of the solvent, the products were examined by NMR (^{1}H and ^{31}P) spectroscopy and identified by comparison with the spectra of the authentic samples.

CHAPTER 3

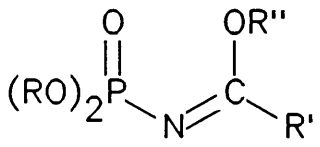
THE CHEMISTRY AND STRUCTURE OF THE P(O)NC(O) SYSTEM

3.1 INTRODUCTION

3.2 RESULTS, DISCUSSION, MOLECULAR STRUCTURE AND EXPERIMENTAL

3.1 INTRODUCTION

As was mentioned before, *N*-acylphosphoramidates **21** represent multifunctional systems, both in electrophilic (offering both phosphorus and carbonyl carbon atoms), and nucleophilic (providing one nitrogen and two oxygen atoms of the Y=O groups; Y = P, C) reactions. The nucleophilic reaction of the conjugate base of substrates **21** can therefore lead to three isomeric products, **41**, **42**, **43**, one of which (**41**) can exist as a pair of *syn/anti* stereoisomers (Equation *(18)*).



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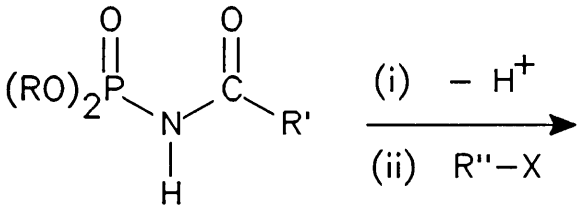
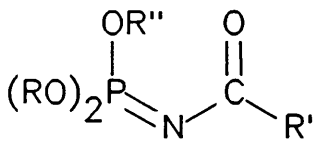


21 **42**

R = Et, a: R' = H
b: R' = Me
c: R' = Et
d: R' = Ph
e: R' = OEt
f: R' = NEt_2

R'' = Me, Et, ^{n}Pr, ^{n}Bu, ^{n}Hex, ^{i}Pr, $SiMe_3$



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(18)

Alkylation of simple phosphoramidates, $(RO)_2P(O)NH_2$, $(RO)_2P(O)NHR'$, as well as of phosphinic hydrazides, $R_2P(O)NHNH_2$, was studied in detail,[81,87] and was shown to occur at the *nitrogen* atom of the N—P(O) function; some evidence for the competitive alkylation of the phosphoryl oxygen is, however, also available.[88]

N-Acylation of a deprotonated phosphoramidate by acyl chlorides has also been reported,[89] and offers a synthetic route to systems **21**. Glidewell [90] demonstrated that *O,O*-diisopropyl-*N*-benzylphosphoramidate reacts with Me_3SiCl at nitrogen, but the possibility of the equilibration between the *N*- and *O*-trimethylsilylated tautomers of *N,O,O*-triphenylphosphoramidate had been considered.[91]

Literature data on the nucleophilic reactivity of the mixed *di*acyl systems **21** are much more scarce. In our earlier work [92] on the ethylation of *O,O*-dimethyl-*N*-benzoylphosphoramidate (**21**, R = Me, R' = Ph), we observed the reaction at both *oxygen* atoms (but *not* at the nitrogen), the selectivity being a function of the "hardness" of the ethylating agent.

N-Benzyloxyureas, on the other hand, undergo, after deprotonation, alkylation exclusively at nitrogen, thus offer a synthetic route to *N*-substituted-*N*-hydroxyureas.[93] Zabirov *et al* recently reported [94] that methylation of the potassium salt of *O,O*-diisopropyl-*N*-benzoylphosphoramidate (**21**, R = ^{i}Pr, R' = Ph) with iodomethane occurs selectively at the *phosphoryl* oxygen. Due

to our results obtained for the *O,O*-diethyl analogue **21d** (*vide infra*), we have reasons to believe that in this case the structural assignments of the product may be incorrect.

While in earlier work[53] it was showed that the selectivity in the nucleophilic cleavage depends on the acidity of the medium, we found that the direction of the alkylation reaction of the conjugate base of **21** depends on various factors, such as the bulk of the alkyl group, the nature of the solvent, the counterion of the base, as well as on phase transfer catalysis.

This chapter deals with the chemistry and structure of the P(O)NC(O) system.[95] We report on our studies on the trimethylsilylation reactions (using trimethylsilyl chloride or chlorotrimethyl silane (TMSCl)) with a selected substrate **21**, *O*, *O*-diethyl-*N*-formylphosphoramidate (**21a**, R = Et; R′ = H) and hexamethyldisilazane (HMDS) with a series of neutral *O,O*-diethyl-*N*-acylphosphoramidates **21a** - **f**). We also studied the alkylation reactions (using haloalkanes) of the conjugate bases of the same series of *O,O*-diethyl-*N*-acylphosphoramidates **21a** - **f**. The *N*-acyl groups in substrates **21** were varied in order to establish the importance of both, steric, and electronic effects at the carbonyl centre in the regioselectivity of the reaction. The structure of the alkylating agents was also varied in such a way as to evaluate the effect of the increasing size of the alkyl group on the product's structure. Finally, taking into account the well known effect of a cation on the selectivity in reactions of ambident anions with electrophiles,[96] as well

as the successful application of PTC in alkylations of various N—P(O) systems,[87,97] we compared the alkylations of sodium and lithium salts of substrates **21** with those carried out in the presence of the phase transfer catalyst, tetrabutylammonium bromide (TBAB).

We have recently observed that the regioselectivity in the reaction of Me_3SiCl (TMSCl) with ambident allylic anions derived from alkenylphosphonates is opposite to that observed for the reaction with haloalkanes.[98] Glidewell[90] demonstrated that *O,O*-diisopropyl-*N*-benzylphosphoramidate reacts with TMSCl at nitrogen, and calculated (using for the O—Si bond energy the value of 445 kJ mol-1)[99] that the enthalpy change for the migration of the Me_3Si group from oxygen to nitrogen is negative (- 30 kJ mol^{-1}). Taking, however, the more recent value of 531 kJ mol^{-1},[100] one arrives at the *positive* (+ 56 kJ mol^{-1}) ΔH value for that reaction. Mono-*N*-silylation, or di-*N,O*-silylation,[101] as well as the equilibrium between the *O*- and *N*-silylated tautomers[91] have been reported for some phosphoramidates. Tikhonina *et al*[102] reported on the migration of the $SiMe_3$ group from nitrogen to oxygen when diethylphosphoramidate was treated with TMSCl and triethylamine. Whereas in the previous case the possibility exists of the second molecule of TMSCl to go directly on to the phosphoryl oxygen, the authors confirmed the *N*→*O* migration of the $SiMe_3$ group by another example in which diethylphosphorochloridate was reacted with the sodium derivative of 2H-hexamethyldisilazane. It was therefore difficult to predict regioselectivity in the trimethylsilylation of **21**, and, as reported below, the final product depends critically on

the detailed conditions of the reaction. Recently Stec and Baraniak reported on the TMSCl-catalyzed *N*→*O* migration of the phosphoryl group in *N*-benzoyl-*N*-phenylphosphoramidate.[103] For that substrate no substitution leading to a stable product is possible, but the rearrangement was explained in terms of the initial attack of the *phosphoryl* oxygen at silicon, followed by the *N*→*O* migration *via* a pentacoordinated, P^{V} intermediate.

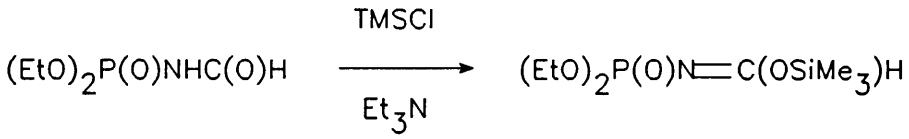
3.2 RESULTS AND DISCUSSION

3.2.1 REACTIONS OF THE NEUTRAL *O,O*-DIETHYL-*N*-ACYLPHOSPHORAMIDATES (21a - f) WITH ELECTROPHILIC SILICON

3.2.1.1 REACTIONS OF 21a WITH TRIMETHYLSILYL CHLORIDE (TMSCl)

The substrate, *O,O*-diethyl-*N*-formylphosphoramidate (**21a**: R = Et, R′ = H), was prepared from *O,O*-diethylphosphoramidate[104] and triethyl orthoformate. Acid catalyzed hydrolysis of the ethyl-[*N*-(diethoxyphosphoryl)]-formimidate intermediate (**41a**)[105] yielded the desired phosphoramidate in reasonable high yield and *ca* 95% purity (see Equation ***(19)*** (*vide infra*)). The substrate **21a** could, however, never be obtained in 100% pure state, as some decomposition to *O,O*-diethylphosphoramidate and *O,O,O′,O′*-tetraethyl pyrophosphate was always observed in the final purification step by distillation.

When neutral **21a** was treated with some excess of TMSCl and triethylamine, it was quantitatively converted into a single phosphorus-containing product (single signal in the ^{31}P NMR spectrum). Attemps to purify the product led to extensive decomposition; when exposed to the atmosphere, the compound was converted completely to the starting material **21a**. NMR spectroscopy (^{31}P, ^{1}H) allowed us to identify the product as *O*-trimethylsilyl-*N*-diethoxyphosphorylformimidate **(44)**, thus the nucleophilic attack at silicon in TMSCl occurred *via* the carbonyl oxygen atom (**Scheme 11**).

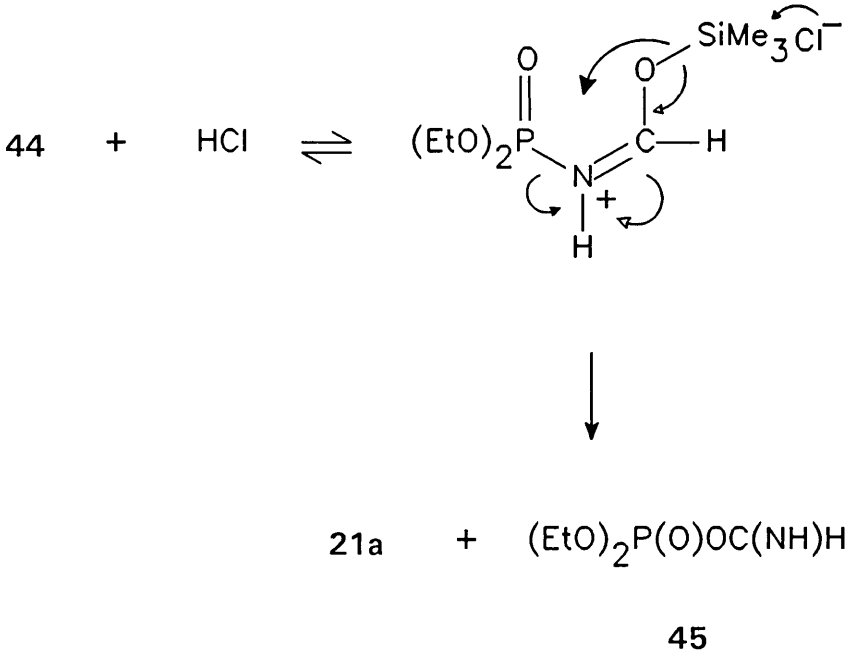


21a **44**

Scheme 11

The ^{31}P chemical shift of the product (3.23 ppm) corresponds closely to that observed for the C—O-ethyl (δ_P 3.54) and C—O-isopropyl (two stereoisomers, δ_P 3.70, 3.44) analogues of **44**.[95] The ^{1}H NMR spectrum contained, in adittion to the signals of the ethoxyphosphoryl group, a signal indicating the incorporation of the Me_3Si group (δ_H 0.11, s, 9 H), and the signal of the C(sp^2)—H (δ_H 8.27, d, J_{HP} 13.9 Hz, 1 H), corresponding to the analogous

signals (δ_H 8.12, 7.97, 7.93; J_{HP}15.3, 15.3, 15.5 Hz) of the C—OEt and C—O^{i}Pr derivatives.[95] Upon hydrolysis, formimidate **44** underwent simple desilylation back to the starting material. When treated with dry HCl, **44** underwent, however, not only simple desilylation, but also the desilylation accompanied by the rearrangement, yielding the *O*-phosphorylated formimidate **45.** Under those conditions, the protonation pre-equilibrium activates the P—N bond, so it can also be cleaved in the desilylation step (**Scheme 12**).



Scheme 12

Compound **45** was identified by NMR (^{31}P, ^{1}H) spectroscopy: its ^{31}P chemical shift (δ_P - 15.6) corresponds well to that (δ_P - 16.4) reported for the analogous rearrangement product.[103] The ^{1}H NMR

spectrum showed disappearance of the Me_3Si signal, and the low-field shift of the $C(sp^2)H$ signal (δ_H 8.60, br. s). It seems therefore that the *N→O* migration of the phosphoryl group can result not only from the electrophilic catalysis operating *via* the phosphoryl oxygen (as reported[103]), but also *via* a reaction occuring at the carbonyl oxygen.

Reaction of **21a** with TMSCl in the absence of a base led to a mixture of three products, proportions of which varied from experiment to experiment. None of the products contained the Me_3Si group incorporated into the molecule, and, on the basis of the NMR (^{31}P, ^1H) spectroscopy, those products were identified as the starting material (**21a**), *O*-phosphorylated formimidate **45**, and *N*-diethoxyphosphorylformidoyl chloride **46**. We believe that all three compounds result from the reaction of HCl with the common intermediate **44**, formed directly by the *O*-silylation of the carbonyl group of the substrate (**Scheme 13**).

21a + TMSCl → [**44**] + HCl

→ **21a** + **45** + $(EtO)_2P(O)N{=}C(Cl)H$

46

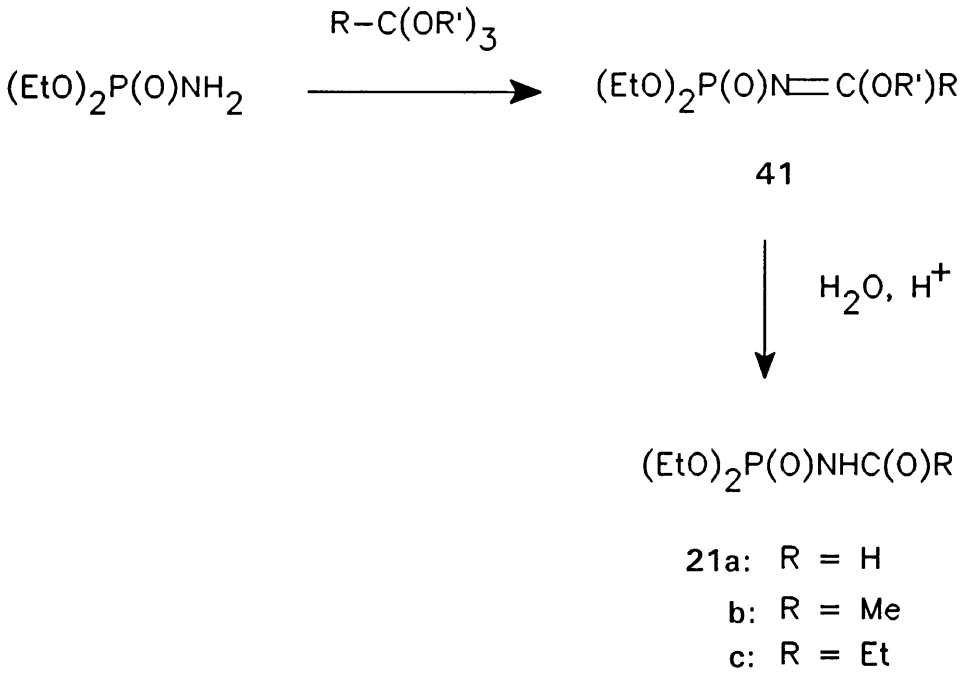
Scheme 13

The variation of the proportion of products **21a**, **45**, and **46** with the reaction time clearly showed that **21a** present in the reaction mixture does not result from an incomplete conversion, but from a subsequent reaction of the intermediate. The desilylation-rearrangement of **44** to **45**, promoted by HCl, has been demonstrated in the experiment described before (**Scheme 12**). We have also shown in an independent experiment that when **21a** was treated with dry HCl, it rearranged to **45**, probably *via* the mechanism analogous to that proposed by Baraniak and Stec[103] for the rearrangement of the tertiary substrate. It is therefore possible that at least some of **45** has been formed directly *via* this route. The structure of product **46** is tentative and based on the spectroscopic evidence, as we were unable to isolate this compound from the reaction mixture. ^{1}H NMR spectroscopy demonstrated for this compound the presence of only two ethoxy groups and one C(sp^{2})H atom (δ_H 8.16, br s). ^{31}P chemical shift (δ 8.50) indicated the presence of the P—N bond, and corresponds well to the δ_P value of 8.20 ppm obtained for the structurally analogous *N*-phosphorylated formamidine (*vide infra*). The formation of **46** can be envisaged as a result of the nucleophilic displacement of the trimethylsilyloxy group by Cl^- in the *unprotonated* **44**. In the presence of the excess of HCl (**Scheme 12**), the fully protonated **44** undergoes exclusively the cleavage of the O-Si bond leading to the formation of the starting material, or the rearranged product **45**.

3.2.1.2 REACTIONS WITH HEXAMETHYLDISILAZANE (HMDS)

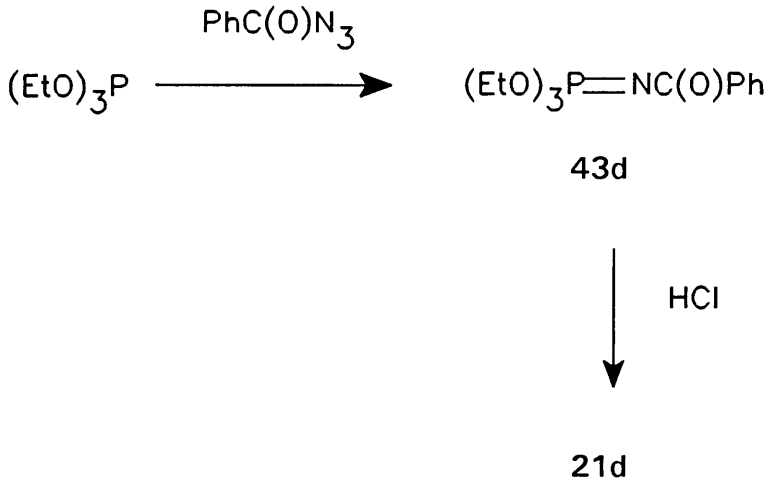
Apart from *O,O*-diethyl-*N*-formylphosphoramidate (**21a**: R = Et, R′ = H) (*vide supra*), five additional *O,O*-diethyl-*N*-acylphosphoramidates (**21**, R = Et): **21b** (R′ = Me), **21c** (R′ = Et), **21d** (R′ = Ph), **1e** (R′ = OEt), **1f** (R′ = NEt_2) were synthesized and their reactions with hexamethyldisilazane under neutral conditions, were studied.

The *O,O*-diethyl-*N*-acylphosphoramidates **21** were synthesized using three different procedures. Substrates **21b** and **21c** were prepared from diethylphosphoramidate,[104] *via* the hydrolysis of the corresponding intermediate **41**[105] (Equation ***(19)***) in analogy to **21a**.



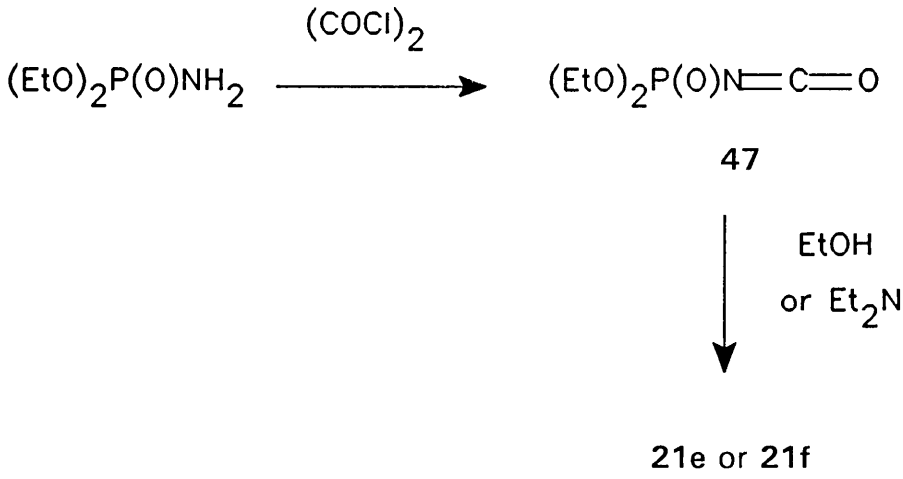
(19)

Substrate **21d** was prepared from freshly made benzoyl azide and triethyl phosphite to give the intermediate **43d**, which was on treatment with hydrogen chloride, converted into the product (Equation *(20)*).



(20)

Finally, compounds **21e** and **21f** were synthesized by treating diethylphosphorisocyanatidate **47**[106] with ethanol or diethylamine (Equation *(21)*). It is worthwhile to note that the corresponding intermediates could also serve as standards for the silylation products (see Equations *(18)*, *(19)*, *(20)*).

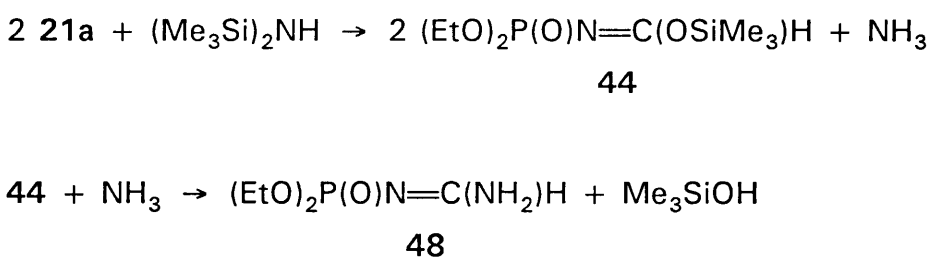


(21)

We have recently studied in detail reactions of *O,O*-diethyl-*N*-formylphosphoramidate (**21a**) with trimethylsilylating agents[95], and in particular with HMDS, and found that silylation occured exclusively at the carbonyl oxygen atom. The *N*-trimethylsilylation of phosphoramidates achieved by the action of HMDS has been reported,[107] and was used in synthetic work[108] to enhance the acidity of the NH function. When **21a** was treated with HMDS as an electrophile, a new, crystalline, product was formed which did not contain the Me_3Si group. ^{31}P NMR spectrum (δ_P 8.2) indicated that no rearrangement took place, as the chemical shift value was in the range of that observed for *N*-phosphoryl derivatives. ^{1}H NMR spectroscopy demonstrated the presence of two ethoxy groups, one C(sp^2)H atom (δ_H 8.41, d, J_{HP} 22.2 Hz),

and a strong signal for the N—H hydrogens (δ_H 8.26, br s). In the ^{13}C NMR spectrum, in addition to the signals derived from the OEt groups, we observed only one signal of the C(sp^2) atom (δ_C 161.9, d, J_{CP} 5.5 Hz). The chemical shift value of that signal corresponds closely to that reported[109] for the amidine carbon in *N*-methyl-*N'*-(2,6-dichlorophenyl)acetamidine (δ_C 158.6). The IR spectrum indicated the retention of the phosphoryl group (ν_{PO} = 1223 cm^{-1}), the presence of the NH groups (ν_{NH} = 3279, 3150 cm^{-1}), and contained the absorption at 1668 cm^{-1}, which was identified as the C=N stretching band, very close to the value of $\nu_{C=N}$ = 1657 cm^{-1} observed before[92] for $(MeO)_2P(O)N{=}C(Ph)OEt$. Elemental analysis clearly demonstrated the presence of **two** nitrogen atoms in the molecule, and the structure of the product was finally proved by the X-ray diffraction[95] (and confirmed by MS), as that of *N*-diethoxyphosphorylformamidine **48**.

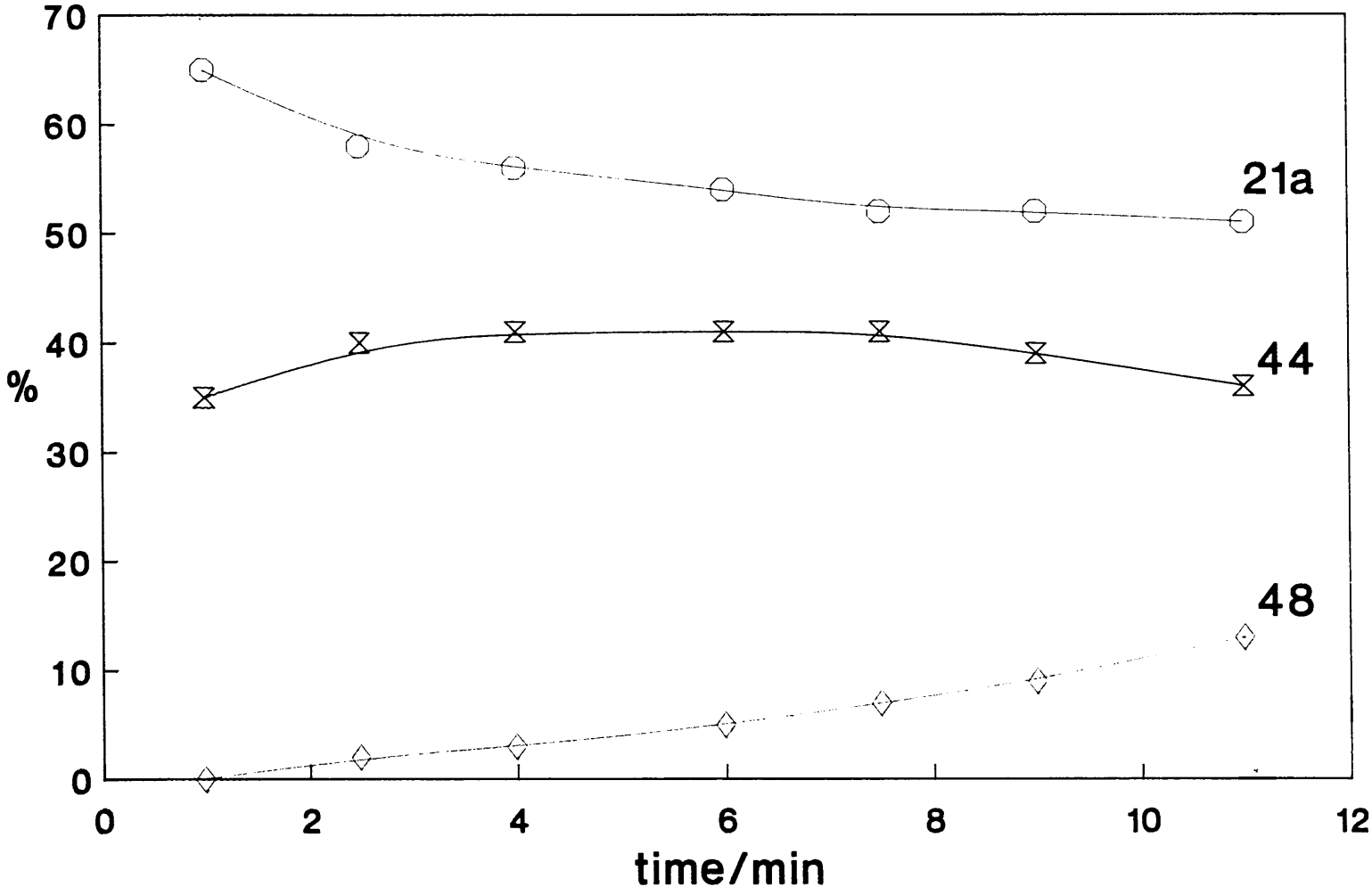
The formation of product **48** is presented in **Scheme 14** and involves a sequence of C=O group silylation, followed by the addition-elimination reaction with ammonia, released in the first step.[107,108,110] As demonstrated before in the reaction of **21a** with TMSCl/Et_3N, the derivative **44** can easily lose Me_3SiO group in reaction with nucleophiles; in **Scheme 14** HMDS acts as both, activating (silylating) agent, and as a precursor of a nucleophile (NH_3). The formamidine **48** was, in fact, prepared previously[111]



Scheme 14

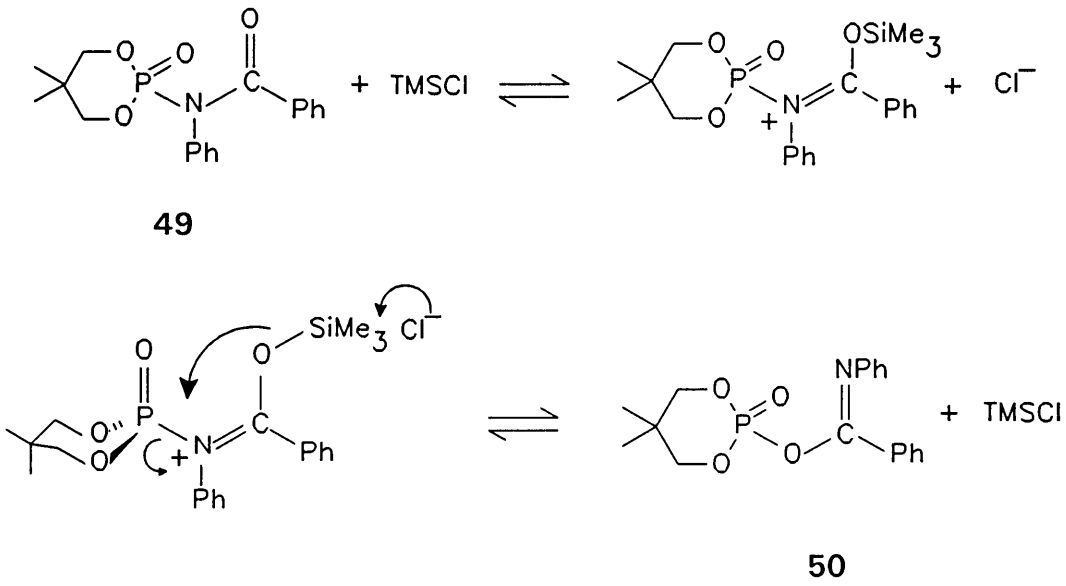
by treating *O*-^{i}butyl-*N*-diethoxyphosphorylformimidate with ammonia, and similar reactions with amines have been reported recently.[112] Although intermediate **44** was unstable under reaction conditions (**Scheme 14**), its intermediacy was demonstrated when the reaction was carried out at low temperature (- 5°C). ^{31}P NMR spectra (also recorded at - 5°C) of the reaction mixture showed the formation (followed by the disappearance) of the species with δ_P in the range of 3.20 - 3.30, corresponding to that of **44** (*vide supra*). The variation of the relative concentrations of **21a**, **44**, and **48** at - 5°C (measured by the relative intensities of the corresponding signals in the ^{31}P NMR spectra) with time is presented in **Figure 3**. When **21a** itself was treated with an excess of ammonia at elevated temperature, we observed very slow (*ca* 4% conversion after 4.5 h) formation of amidine **48**, thus confirmed the activating effect of the *O*-silylation in the formation of the amidine derivative.

Figure 3: Reaction of **21a** with HMDS at - 5°C; composition *vs* time



In conclusion, we have demonstrated that the reaction of **21a** with electrophilic silicon occurs exclusively *via* the carbonyl oxygen. The fate of the *O*-silylated derivative depends on the reaction conditions. In the presence of nucleophiles (water, Cl^-, NH_3, etc.) it can undergo displacement of the Me_3SiO group without (**Scheme 13**, **14**) or with (**Scheme 12**) rearrangement involving the *N*→*O* phosphoryl migration. In view of our results, we suggest that the TMSCl-catalyzed rearrangement of 2-*N*-benzoyl-*N*-phenylamino-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane **49** to the correspon-ding (5,5-dimethyl-1,3,2-dioxaphosphorinyl)(*N*-phenyliminoben-zoyl)oxide **50**, reported by Baraniak and Stec,[103] also involves the carbonyl (and not, as proposed, the phosphoryl) oxygen atom. For that reaction we propose the mechanism (**Scheme 15**) that corre-sponds closely to the formation of product **45** (see **Scheme 12**).

It is worth to note at this stage that the retention of configuration at phosphorus, demonstrated for the *N*→*O* phosphoryl rearrange-ment[113] is also compatible with the mechanism presented in **Scheme 15** (equatorial/apical stereochemistry of bond-making and bond-breaking steps).



Scheme 15

In view of the interesting result obtained when **21a** was treated with HMDS (as electrophile) and the initial silylation product underwent a subsequent nucleophilic displacement with ammonia (released as side product), we decided to apply the reaction of HMDS to all substrates **21a** - **1f** in order to establish their reactivity towards a common, Si-containing electrophile.

In all cases reactions with HMDS were reversible and the final product contained variable proportions of unreacted **21**. Only for **21a**, where the subsequent reaction with ammonia[114] removed the initial product from the reaction mixture, could we achieve the

full conversion. The reaction with ammonia was not, however, observed for any of the remaining substrates. It seems that the subsequent attack by a nucleophile is, for steric reasons, feasible only for the product with the unhindered, formamide centre. As can be seen from **Table 3**, both, conversion, and selectivity vary widely for individual substrates. Compounds **21b** - **1f** react much more slowly than **21a**, indicating the importance of steric effects for the reaction involving a bulky electrophile.

Table 3: Trimethylsilylation of **21a** - **1f** with HMDS[a]

Substrate	Conversion (%)	**41**[b] (%)	**42**[b] (%)	**43**[b] (%)
21a	100	100[c]		
21b	47	4	43	
21c	0[d]			
21d	71	71		
21e	95	25	48	22
21f	24	14	5	5

[a] Benzene, reflux, 3 - 6 h.

[b] For structures, see Equation *(18)*; R" = $SiMe_3$.

[c] Under reaction conditions converted quantitatively to $(EtO)_2P(O)N{=}C(NH_2)H$.

[d] Only unreacted **21c** was observed in the ^{31}P NMR spectrum.

In conclusion, as will be seen for the alkylation reactions in the next section, substrates **21** vary greatly with respect to HMDS in their reactivity and regioselectivity, with only some reactions being of real synthetic value.

3.2.2 REACTIONS OF THE CONJUGATE BASES OF *O,O*-DIETHYL-*N*-ACYL-PHOSPHORAMIDATES (21a - f) WITH HALOALKANES

The base-promoted reactions of substrates **21** with iodomethane and with five bromoalkanes, R"—Br (R" = Et, ^{n}Pr, ^{n}Bu, $^{n}C_6H_{13}$, ^{i}Pr), were studied. Substrates **21a - f** were converted into their sodium salts by treating them with sodium hydride in 1,2-dimethoxyethane (DME); the solution of the salt was then treated with the alkylating agent, and the reaction mixture was stirred at room temperature (for reactions with MeI), or under reflux, for several hours. The reaction products were identified mainly by the NMR (^{31}P, ^{1}H, ^{13}C) spectroscopy; in some cases IR spectroscopy, MS, and elemental analysis were additionally used. ^{31}P NMR spectroscopy was found to be invaluable in both, qualitative, and quantitative identification of the reaction products. The types of phosphorus compounds involved in this work (**21, 41, 42, 43**) are characterized by relatively narrow ranges of their ^{31}P chemical shift values, with the increasing *deshielding* of the ^{31}P nuclei in the order **21** < **42** < **41** < **43** (**Table 4**). It is important to note again, that, as in the case of the silylation reactions, the corre-

sponding intermediates formed during the preparation of substrates **21** were used as standards for either phosphoryl or carbonyl oxygen alkylation product identification.

Table 4: ^{31}P chemical shifts for compounds **21**, **41**, **42**, **43** ($CDCl_3$, ppm, relative to trimethyl phosphate)

R′	**21**	R"	**42**	**41**	**43**
H	- 4.46	Me	- 0.49		8.05
		Et	- 0.06	3.54	
		Pr	- 0.20		
		Bu	- 0.20	3.96	
		Hex	- 0.08	4.20	
		^{i}Pr		3.40, 3.70	8.00
		Me_3Si		3.23	
Me	- 4.50	Me	- 0.03	0.73	
		Et	0.00	0.61	
		Hex	0.45	0.93	6.60
		Me_3Si	- 0.26	2.34, 3.81	
Et	- 4.90	Me	- 0.02		
		Et	0.23	0.56	6.30
		Hex		0.56	6.60
		Me_3Si			
Ph	- 4.50	Me	- 0.88		

R′	**21**	R"	**42**	**41**	**43**
Ph		Me_3Si		4.40	
OEt	- 4.50	Me	- 1.50		
		Et	- 2.00		
		Hex	- 1.50		
		Me_3Si	- 2.70	4.50	7.90
NEt_2	- 3.00	Me	0.20		
		Et	- 0.20		
		Hex	- 0.80		
		Me_3Si	- 2.60	2.40, 4.60	7.80

Alkylation reactions of substrates **21** (Equation ***(18)***) gave very diverse results from the point of view of the reactivity of the substrates, the purity of the products, and the regioselectivity of the alkylation. In some cases reactions were regiospecific, yielding single products in high yield and purity, thus offered useful synthetic routes to some alkyl derivatives of **21**. In other cases, the full conversion of a substrate into the product could not be achieved, and/or the regioselectivity was low, so the mixture of isomeric alkyl derivatives was obtained. In these cases it was not possible to separate individual components, and they were identified in a mixture of products by spectroscopic techniques. These reactions have little synthetic value

and show that small changes in substrates structure can have profound effect on the course of the alkylation. For that reason it was difficult to arrive at any general description of the reaction represented by Equation *(18)*, so the results are discussed below separately for individual substrates **21**.

3.2.2.1 ALKYLATION OF 21a

The results obtained for the six haloalkanes are summarized in **Table 5**.

Table 5: Alkylation of the conjugate base of **21a**

Haloalkane R"—X	Conditions[a]	TBAB[b]	Conversion (%)	**41a** (%)[c]	**42a** (%)[c]	**43a** (%)[c]
MeI		no	87		87	
	in THF	no	92		92	
	LDA in benzene	no	35		18	17
EtBr		no	50	trace	> 48	
		yes	64		64	
	LDA in benzene	no	35			35
PrBr		yes	35		35	
BuBr		yes	27	2	25	

Haloalkane R"—X	Conditions[a]	TBAB[b]	Conversion (%)	**41a** (%)[c]	**42a** (%)[c]	**43a** (%)[c]
HexBr		no	66	12	54	
	2 h	yes	67	4	63	
	13.5 h	yes	67	31	36	
^{i}PrBr		no	22			22
		yes	26	26 (E/Z)		

[a] Unless otherwise stated, the conditions were: NaH, DME, room temperature (for the methylation) or reflux; 16 - 24 h.

[b] "yes" denotes the addition of 5 mol% of TBAB.

[c] Related to the percentage of conversion. The absence of a given product means that it was not detected by ^{31}P NMR spectroscopy.

It is clear that the *sodium* salt of **21a** behaves as a *nitrogen* nucleophile, yielding exclusively, or almost exclusively, the *N*-alkyl derivatives, **42a**. For methylation, ethylation, and ^{n}propylation, the reaction is of practical value, since the products could be isolated in high yield and fully characterized. For higher alkyl groups (^{n}butylation, ^{n}hexylation) the reaction is, probably for steric reasons, slower, and the competitive formation of the (carbonyl) *O*-alkylated products **41a** can be observed. The formation of **41a** is, in some cases, enhanced by the phase transfer catalyst. We have found, by examining the effect of the reaction time on the

42a/**41a** ratio in ^{n}hexylation, that this effect is mostly due to the TBAB-promoted subsequent rearrangement of **42a** to **41a**. The rearrangement is *not* a thermal reaction, since the ^{n}hexylation product could, after the work-up, be distilled (bulb to bulb, oven temp. 115 - 120°C/ 2 Torr) without any change of the **42a**/**41a** ratio.

For the reaction with a secondary haloalkane (^{i}PrBr) we observed a dramatic change in the regioselectivity. In the absence of TBAB only one product was formed which could not be purified by distillation or column chromatography without extensive decomposition. When the reaction work-up was carried out with rigorous exclusion of moisture, the crude product was identified by NMR spectroscopy as the *phosphoryl O*-^{i}Pr derivative **43a** (**43**, R′ = H; R" = ^{i}Pr). In the presence of TBAB the regioselectivity was again changed drastically: although the *N*-alkylation product was still absent, the alkylation occurred exclusively at the *carbonyl* oxygen, yielding two stereoisomers (*syn*/*anti*) of **41a** (**41**, R′ = H; R" = ^{i}Pr). This remarkable change in the *N vs O* regioselectivity observed for the secondary substrate as compared with primary haloalkanes suggests a change in the reaction mechanism. It is possible that for ^{i}PrBr the reaction has more of an S_N1 character, thus involves a "harder" electrophile of the 2-propylcarbonium ion type. Such an electrophile would be expected to show marked

preference to react with "hard" nucleophilic centres (oxygen atoms) rather than with a "soft" nitrogen centre.

The change in the orientation of the alkylation could also be achieved *via* the change of the counterion of the conjugate base of **21a**. While the sodium salt underwent methylation exclusively at nitrogen, the anion generated by LDA in THF yielded equal proportions of the N—Me derivative, **42a**, and the P—OMe derivative, **43a**. In the ethylation, Li^+ counterion shifted the regioselectivity completely from the substitution at nitrogen to the reaction at the phosphoryl oxygen. In conclusion, with respect to primary haloalkanes, the Na^+ salt of **21a** behaves as a nitrogen nucleophile, although the *N*/*O* selectivity decreases in the order Me > Et > Bu > $^nC_6H_{13}$. This order reflects most likely the increasing steric hindrance for the reaction to occur at the congested nitrogen centre. With respect to a secondary halide, the same sodium salt demonstrates its nucleophilic reactivity exclusively *via* its two oxygen atoms.

3.2.2.2 ALKYLATION OF 21b - f

Table 6 lists the results of the alkylation of the remaining substrates by three primary haloalkanes (MeI, EtBr, HexBr).

Table 6: Alkylation of the conjugate bases of **21b - 1f**[a]

Substrate	Haloalkane R"—X	TBAB	Conversion (%)	**41** (%)	**42** (%)	**43** (%)
21b	MeI	no	90		69[b]	
		yes	99		83[b]	
	EtBr	no	87	16	71	
		yes	58	19	39	
	HexBr	no	60	6	25	29
		yes	59	56	trace	3
21c	MeI	no	100		100	
		yes	100		100	
	EtBr	no	51		38	13
		yes	68		54	14
	HexBr	no	43	19		24
		yes	51	45		6
21d	MeI	no	40		40	
		yes	43		43	
	EtBr	no/ yes	[c]			
	HexBr	no/ yes	[c]			
21e	MeI	no	100		100	
		yes	100		100	

Substrate	Haloalkane R"—X	TBAB	Conversion (%)	**41** (%)	**42** (%)	**43** (%)
21e	EtBr	no	79		79	
		yes	97		97	
	HexBr	no	47		47	
		yes	61		61	
21f	MeI	no	77		77	
		yes	99		99	
	EtBr	no	21[d]		21	
		yes	27[d]		27	
	HexBr	no	19[d]		19	
		yes	20[d]		20	

[a] In all reactions the conditions were: NaH, DME, room temperature (for the methylation), or reflux; 16 - 24 h. For other information, see footnotes [b], [c], **Table 5.**

[b] The remaining products were: diethyl *N*-methyl-, and *N,N*-dimethyl-phosphoramidates; *vide infra*.

[c] Extensive decomposition leading to a complex mixture of products.

[d] Partial decomposition during the course of reaction.

With respect to iodomethane all substrates **21** behave as highly regiospecific *nitrogen* nucleophiles. The yields vary from medium (**21d**) to quantitative (**21c**, **21e**); TBAB usually improves the con-

version to the corresponding **42**. For the *N*-acetyl substrate (**21b**) we observed in the methylation reaction the formation of two unexpected phosphoramidates: $(EtO)_2P(O)NHMe$ and $(EtO)_2P(O)NMe_2$. These compounds, accompanying the major product **42b** (**42**, R′ = R" = Me), could be easily identified by their ^{31}P chemical shift values (δ_P 7.30 and 7.90, respectively) and by the characteristic signals of their N—Me groups in the ^1H NMR spectra (δ_H 2.48, dd, J_{HP} 12.0, J_{HH} 5.0 Hz, and δ_H 2.53, d, J_{HP} 10.2 Hz, respectively); those assignments were confirmed by the addition of the authentic samples of **51** and **52**, and by the absence of any additional acetyl methyl signal in the ^1H NMR spectra. We do not believe that **51** and **52** are formed *via* the direct cleavage of the C(O)—N bond by sodium hydride, observed for some formates and formamides,[114] as we did not observe these products in alkylations of **21a**. One can speculate that the formation of *N*-methylphosphoramidates results from the base-promoted deprotonation of one of the three *α*-hydrogens in **21b**, yielding ketene and the conjugate base of diethyl phosphoramidate, which can then undergo subsequent *N*-methylation.[87]

With higher haloalkanes **21b** and **21c** gave increasing proportions of the oxygen (both, carbonyl and phosphoryl) alkylated products; this low selectivity limited synthetic applicability of the reaction. The *N*-benzoyl substrate **21d** proved to be the most unstable

under the reaction conditions; extensive decomposition was observed in all alkylations, except for the methylation, which has been carried out at room temperature. The latter reaction resulted in the formation, albeit in poor yield, of a single alkylation product, identified as the *N*-methyl derivative, **42d** (**42**, R' = Ph, R" = Me). The δ_P value (-0.88) obtained for this product is well within the range observed for other compounds **42**. Similarly, the methyl group signal in the ^{1}H NMR spectrum (δ_H 3.06, d, J_{HP} 7.7 Hz) is very typical for all *N*-methyl derivatives **42** obtained in this work (see Experimental). Zabirov *et al*[94] identified the product of the methylation of *O,O*-diisopropyl-*N*-benzoylphosphoramidate as the corresponding P—OMe derivative of the type **43**. The NMR spectroscopic data reported for that product (δ_P - 3; methyl group δ_H 3.10, d, J_{HP} 7 Hz) correspond closely to those observed by us for the *N*-methyl products **42**. We think therefore that Zabirov's product is, in fact, the *O,O*-diisopropyl analogue of compound **42d**, since for the P—OMe derivative the ^{31}P NMR chemical shift would be expected to be in the range of + 6 to + 8 ppm (see **Table 4**).

The *N*-phosphorylated ethylcarbamate **21e** showed to be the most regioselective among all substrates **21**. With all three haloalkanes it gave exclusively *N*-alkyl derivatives **42** with good or excellent yields and in a high state of purity; TBAB increasing the overall

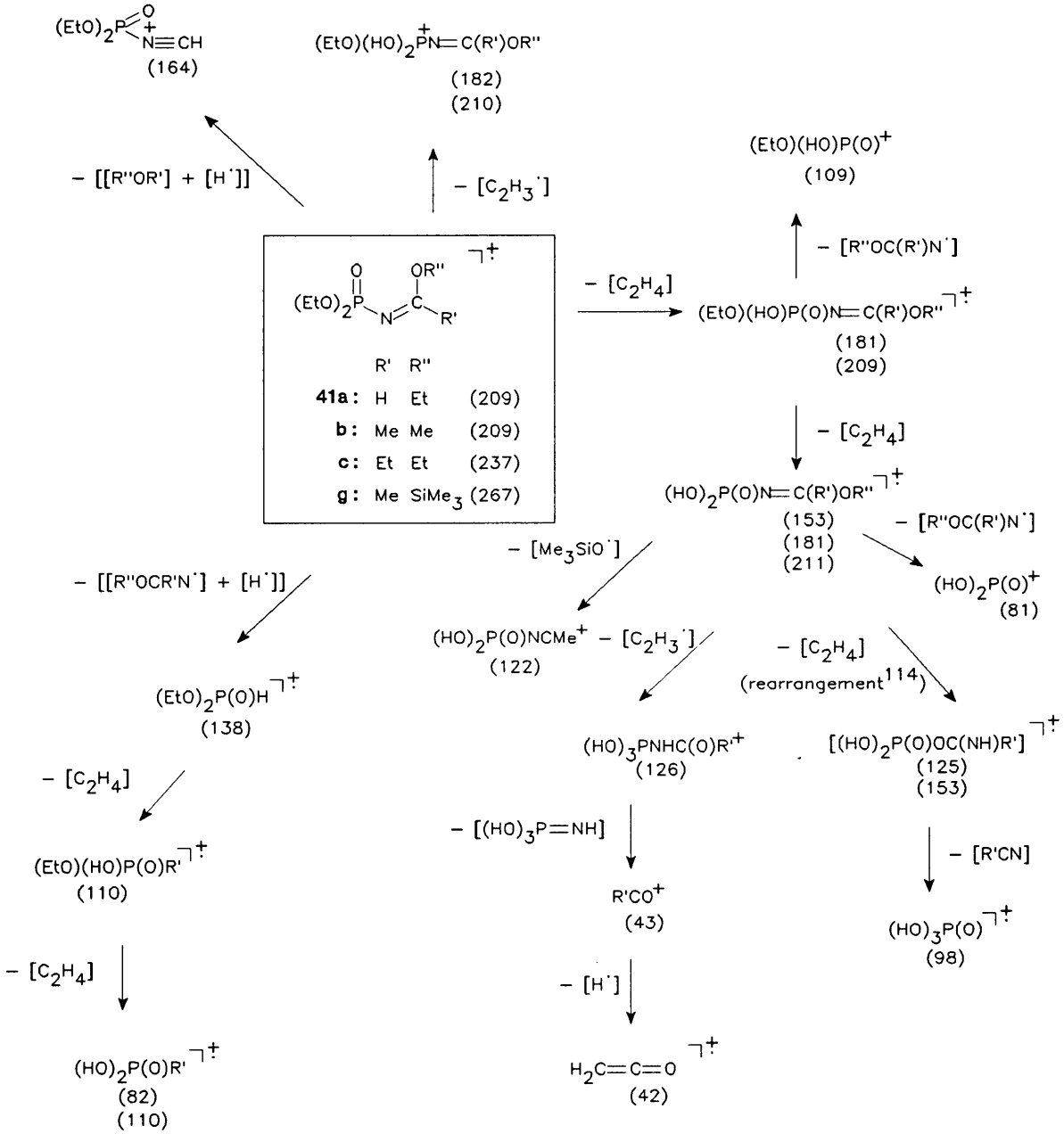
yield of the reaction. **21e** is, in fact, the only substrate capable of giving efficient and regiospecific results in the ^{n}hexylation reaction. The urea derivative **21f** behaves very similarly to **21e**, the only difference being its lower stability, thus lower yields of alkylation and partial decomposition. It is clear, however, that both hetero-atom-containing substituents R' (OEt, NEt_2) markedly increase the regioselectivity of the corresponding conjugate base in favour of the *nitrogen* nucleophilicity.

3.2.3 ELECTRON IMPACT - INDUCED FRAGMENTATION BEHAVIOUR

While preparing our substrates and investigating their reactions, we have recorded mass spectra of the intermediates, substrates, and products. The purpose of those determinations was two-fold: we used the mass spectra as an additional structural confirmation, and we were interested in the fragmentation patterns for these types of organophosphorus compounds. In the interpretation of the mass spectra we relied heavily on the detailed MS study carried out previously in our Laboratory for the phosphoric-carboxylic imides and related systems.[115] The compounds studied in this work can be divided into four groups, and the MS behaviour of each group will be discussed separately.

(i) Compounds $(EtO)_2P(O)NC(R')OR''$ (**41**). The diagram summarizing the

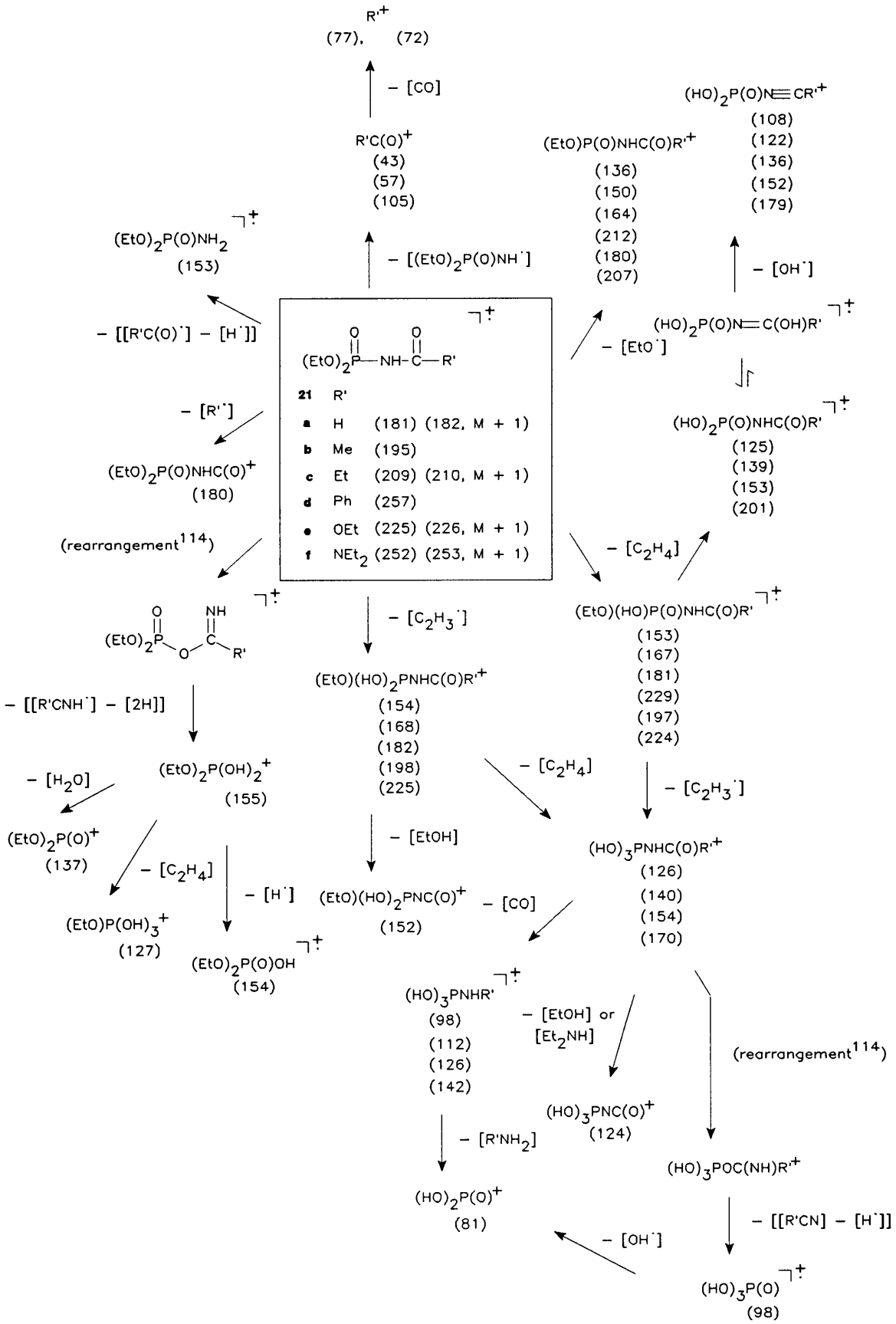
mass spectra of the intermediates **41** is shown in **Scheme 16.**



Scheme 16: Major fragmentations of **41a, b, c** and **g.**

The fragmentation of **41** (like of all other systems studied) involves the usual reactions of the $(EtO)_2P(O)$ group (McLafferty rearrangement, double hydrogen migration, etc.), which will not be discussed here, as we were specifically interested in the behaviour of the variable *N*-substituent. The P-N bond cleavage (with a hydrogen migration) yields a common molecular ion of diethyl phosphite (*m/z* 138), or occurs after a loss of one or two molecules of ethene, yielding the $EtOPO_2H^+$ (*m/z* 109), or the $H_2PO_3^+$ ion (*m/z* 81). We did not see any evidence of the gas-phase rearrangement of substrates, but we believe that the phosphorus *N* to *O* migration takes place after two McLafferty rearrangements, that is from the *m/z* 153 molecular ion. Such a migration is necessary to explain the formation of the molecular ion of orthophosphoric acid (*m/z* 98), a molecule in which the phosphorus atom is bonded to four oxygens.

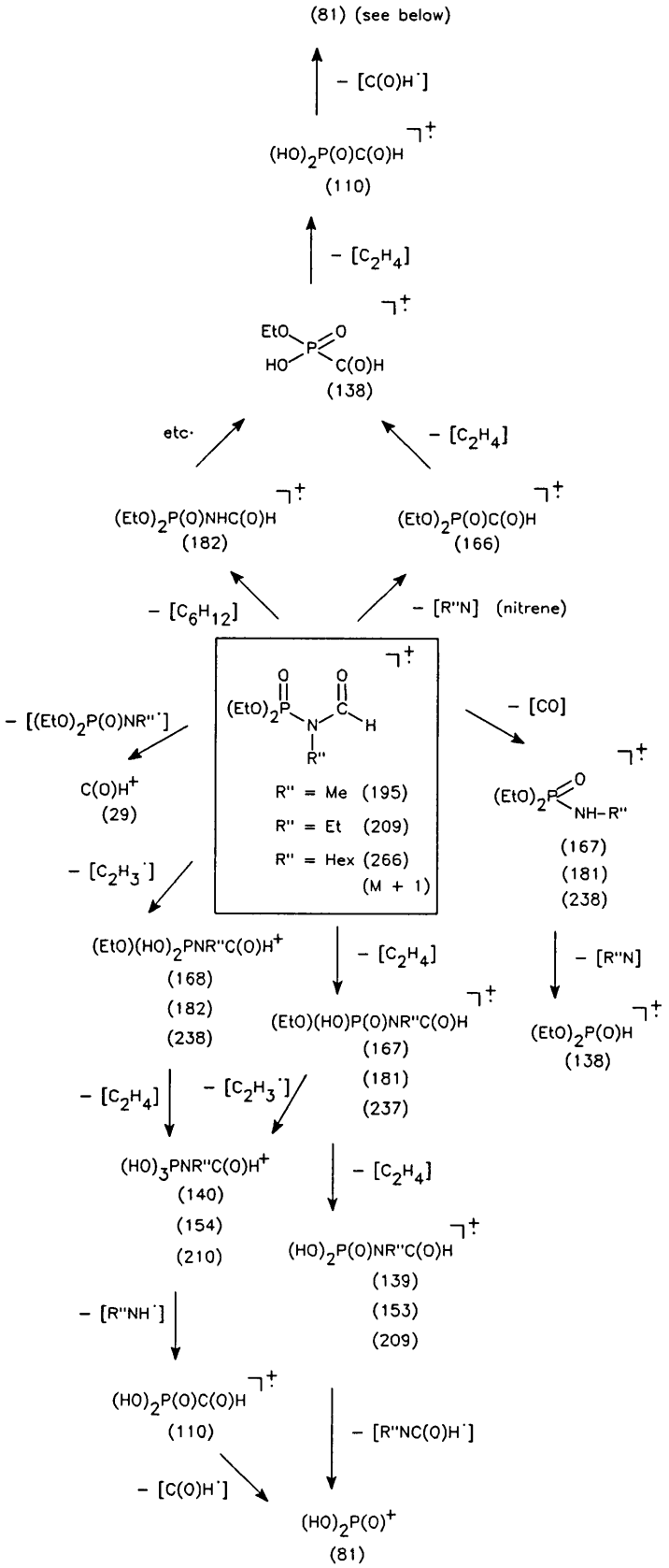
(ii) Substrates $(EtO)_2P(O)NHC(O)R'$ (**21**) (**Scheme 17**).



Scheme 17: Major fragmentations of substrates **21**.

As far as the molecular ion itself is concerned, the most interesting reaction is its rearrangement to the P—O isomer, which then gives rise to the tetraoxygenated phosphorus species (*m/z* 155, 154, 137, 127). Depending on the resulting acylium ion stabilty, the cleavage of the N—C bond can also occur (**21b**, **21c**, **21d**). An interesting fragmentation involving the same bond fission is the loss of the R'CO fragment, together with hydrogen migration, resulting in the formation of the molecular ion of diethylphosphoroamidate (*m/z* 153). For the secondary fragmentations, we found it interesting that the products of the loss of two C_2H_4 molecules (*m/z* 125, 139, 153, 201) can lose the hydroxyl radical, presumably *via* the tautomerization indicated in the **Scheme 17**. The latter fragmentation produces a system which represents the *N*-phosphorylated nitrylium cation (*m/z* 108, 122, 136, 152, 179). The same molecular ion can, like the full diester **21**, rearrange to the derivative of orthophosphoric acid, which can then undergo further transformation, until the level of orthophosphoric acid itself (*m/z* 98) is achieved.

(iii) Alkylation products $(EtO)_2P(O)NR"C(O)H$ (**42**) (**Scheme 18**).

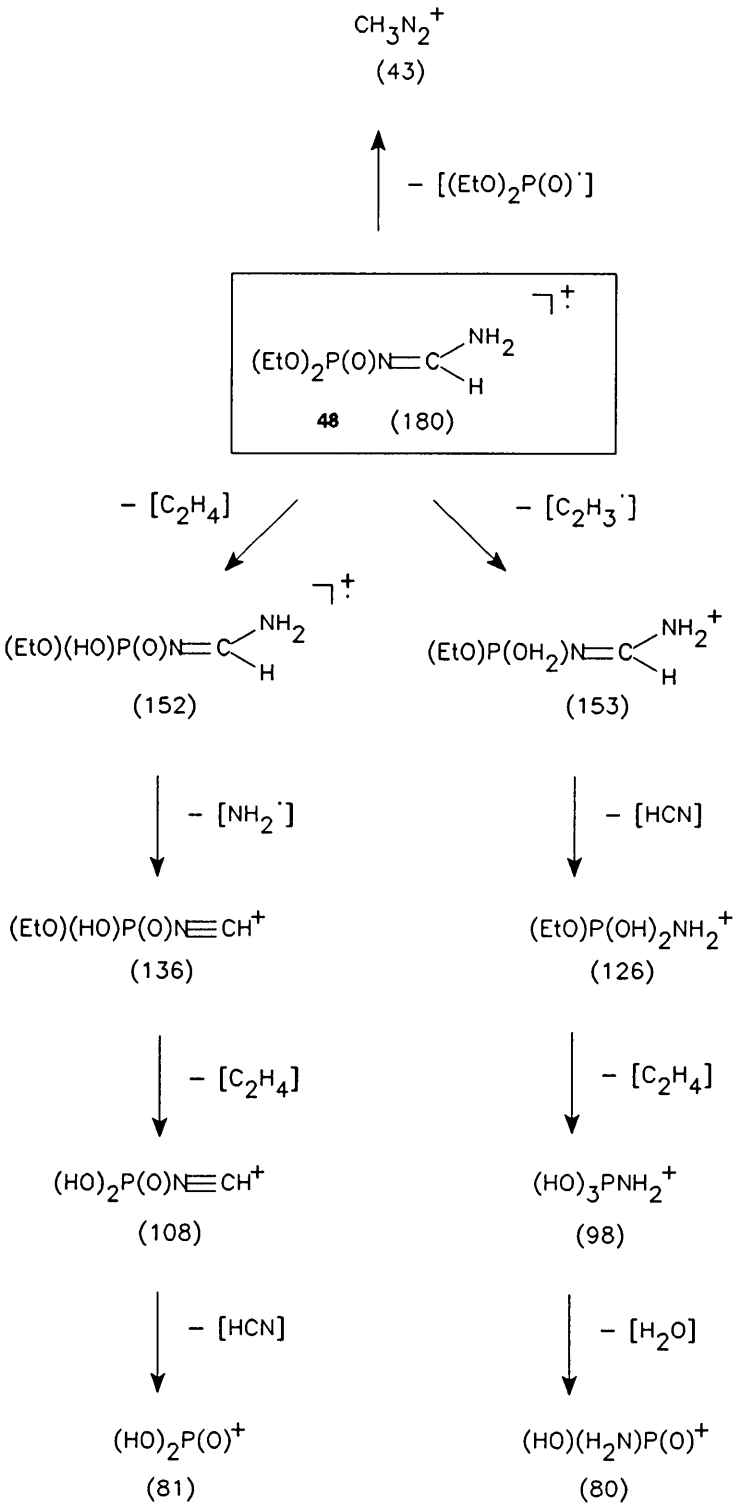


Scheme 18: Major fragmentations of *N*-alkylated **21a**.

The most striking difference observed for the *N*-alkyl, *N*-formyl derivatives, as compared with the previously studied[115] other *N*-acyl imides, is that we did not observe any obvious evidence of the *N* to *O* migration of the phosphoryl moiety. This difference is reminiscent of the silylation reaction, in which the *N*-formyl substrate behaved very differently from all other analogues (*vide supra*). Instead, all three compounds eject the formylium ion (*m/z* 29) *via* simple N—C bond cleavage. All products give the *m/z* 138 ion; we show in the **Scheme** two possible routes to the two different species of that value of *m/z*. In two cases we were able to see the intermediate species expected for one route (*m/z* 166), but for another route the expected intermediates, *O,O*-diethyl-*N*-alkylphosphoramidates (*m/z* 167, 181, 238) have the same *m/z* value as the products of the first McLafferty rearrangement of the parent molecular ions. Additional studies, involving determination of metastable peaks, are necessary to resolve this problem. No other new types of fragmentations were observed for products **42**.

(iv) *N*-diethoxyphosphorylformamidine (**48**). As this compound represents a unique reaction product, its MS is discussed separately. Apart of the obvious reactions of the $(EtO)_2P(O)$ group, the molecular ion can undergo the P—N bond cleavage with the extrusion of the diethoxyphosphoryl radical, yielding protonated cyanamide (*m/z* 43). In general, however, the fragmentation pattern for **48** is not complex and involves loss of such simple species as C_2H_4, $C_2H_3\cdot$, HCN, or $NH_2\cdot$.

The corresponding pathways are illustrated in **Scheme 19.**



Scheme 19: Major fragmentations of **48**.

3.2.4 CRYSTAL AND MOLECULAR STRUCTURE STUDIES

In our current studies on the ambident nucleophilicity of phosphoric-carboxylic imides, $(RO)_2P(O)NHC(O)R'$ (**21**), we investigated the trimethylsilylation reaction of diethyl *N*-formylphosphoramidate (**21a**) (**21**, R = Et; R' = H).[95] The reaction of **21a** with hexamethyldisilazane involved the initial silylation of the carbonyl oxygen, followed by the nucleophilic displacement of the Me_3SiO group by ammonia, released in the first step of the reaction (**Scheme 14**). The *N*-phosphorylated formamidine (**48**), reported previously by Khyat and Al-Isa,[111] is a crystalline compound, and we decided to determine its crystal and molecular structure for the following reasons. Firstly, neither NMR (^1H, ^{13}C, ^{31}P) nor IR spectroscopy could unambiguously distinguish between structure (**48**) and its tautomeric form, $(EtO)_2P(O)—NH—C(NH)H$. For a similar *N*-sulfonylformamidine system, the tautomer containing the $RSO_2—N{=}C$ bonding was preferred on the basis of the ^{13}C NMR spectra.[116] In the crystal structure analysis, however, the NH hydrogens were located experimentally and refined, thus we were able to determine unequivocally the solid state structure of the compound. Secondly, molecular parameters obtained for (**48**) could be compared with those available for a variety of related structures, hence could provide additional information about the bond order, hybridization, geometry, hydrogen bonding, etc., for the nitrogen-substituted phosphoryl

derivatives. For the most closely related structures, *i.e.* the *N*-acylated phosphoramidates **21**, one crystal structure was previously determined in our Laboratory.[117] We have now additionally determined the structures of two other representatives of **21** (**21b** and **21d**) in order to arrive at the more typical molecular parameters characteristic for this class of compounds. We also intended to include to the structural discussion some of the *products* of the reactions of **21** with electrophiles (compounds **41**, **42**, or **43**), as the reaction changes the hydrogen bonding abilities of the system by removing the proton of the N—H functional group. Unfortunately, although some products of the alkylation of substrates **21** are solid substances, all attempts to prepare crystals suitable for X-ray diffraction failed. It will be necessary to prepare some of the products *via* different routes hoping to improve in this way the quality of the crystals (see Conclusions).

The perspective view of (**48**), together with atomic nomenclature, is given in **Figure 4**, while **Figure 5** represents the unit cell for the compound. **Figures 6, 7** and **8, 9** show the respective views and the unit cells for compounds **21b** and **21d**.

The location of the NH hydrogens (hence the detailed molecular structure of (**48**)) is evident; it is also clear that the molecules of **48** are arranged into the infinite chains *via* intermolecular P═O···H—N

hydrogen bonds, with the O···N distance of 2.775 Å. Selected molecular parameters are listed in **Table 7** together with the available data for such related structures as phosphoric-carboxylic imides (**21**) (in the following discussion the molecular parameters used for system **21** represent the average values for **21b**, **21d**, and **21h**), *N*-phosphorylated urea (**53**), *N*-phosphorylated dimethylsulfoximides (**54**), and simple phosphoramidates (**55**).

Figure 4: A perspective view of **48** with atomic numbering

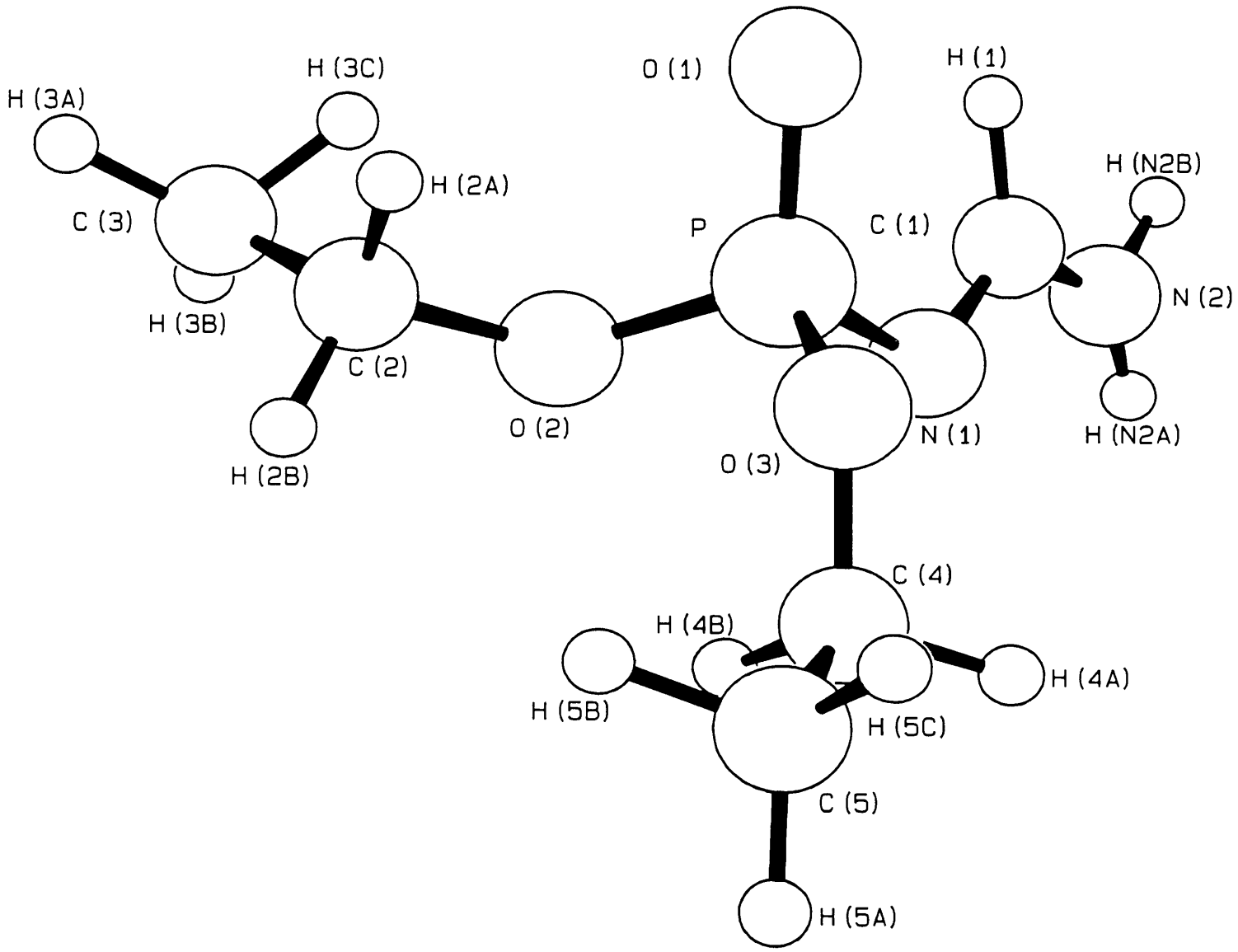


Figure 5: Packing diagram for **48**; hydrogen bonding indicated by dotted lines

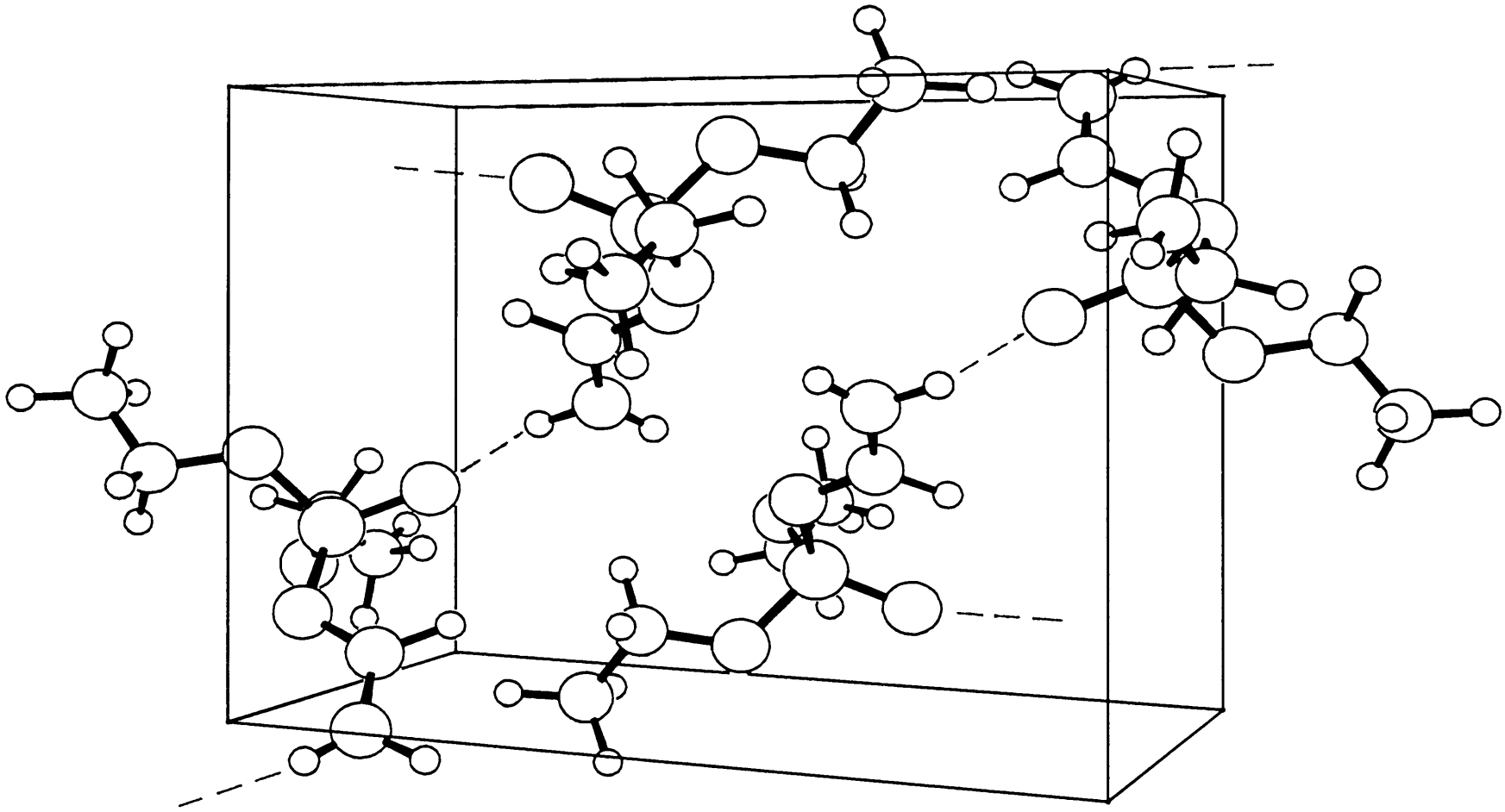


Figure 6: A perspective view of **21b** with atomic numbering

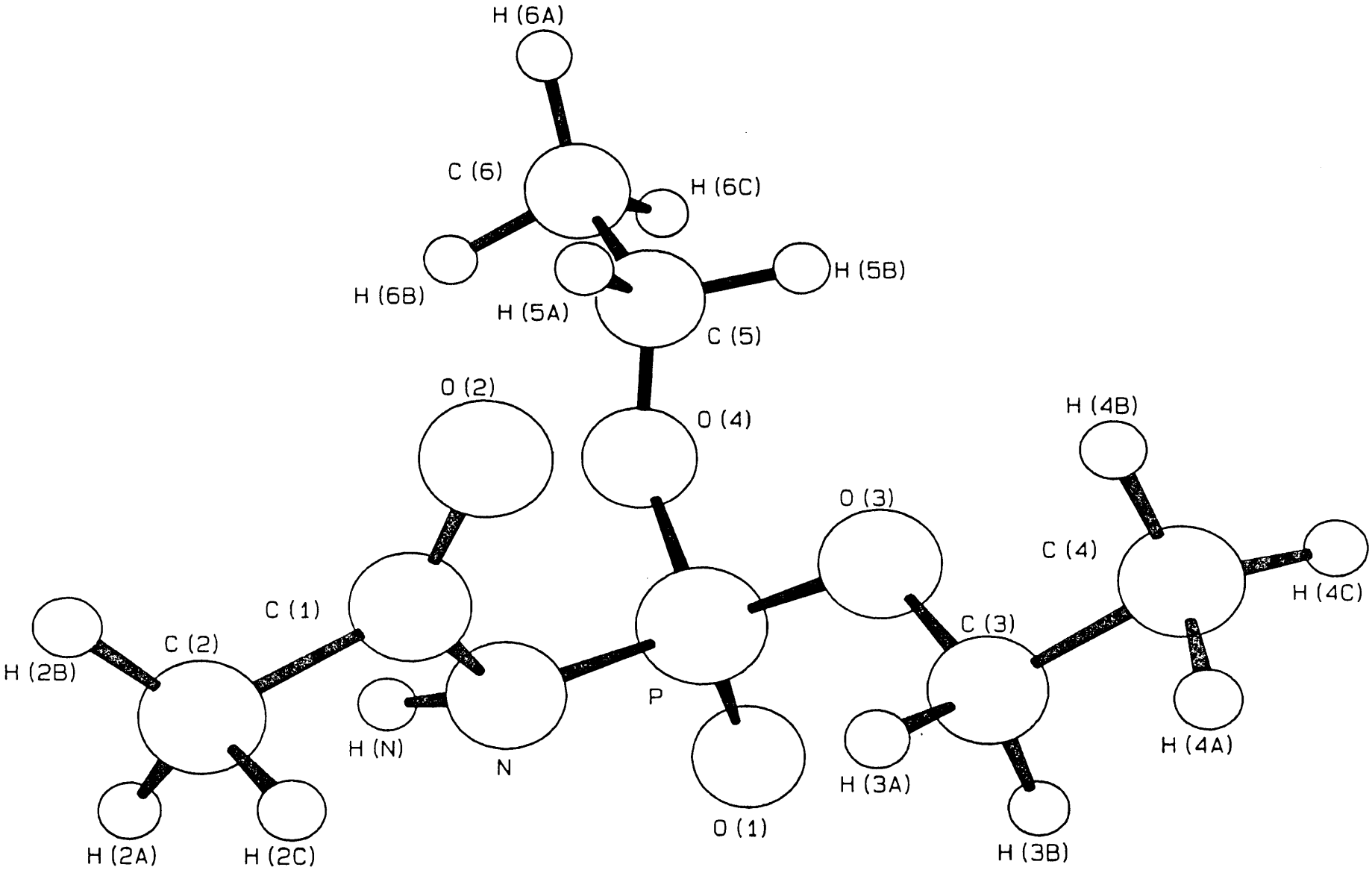
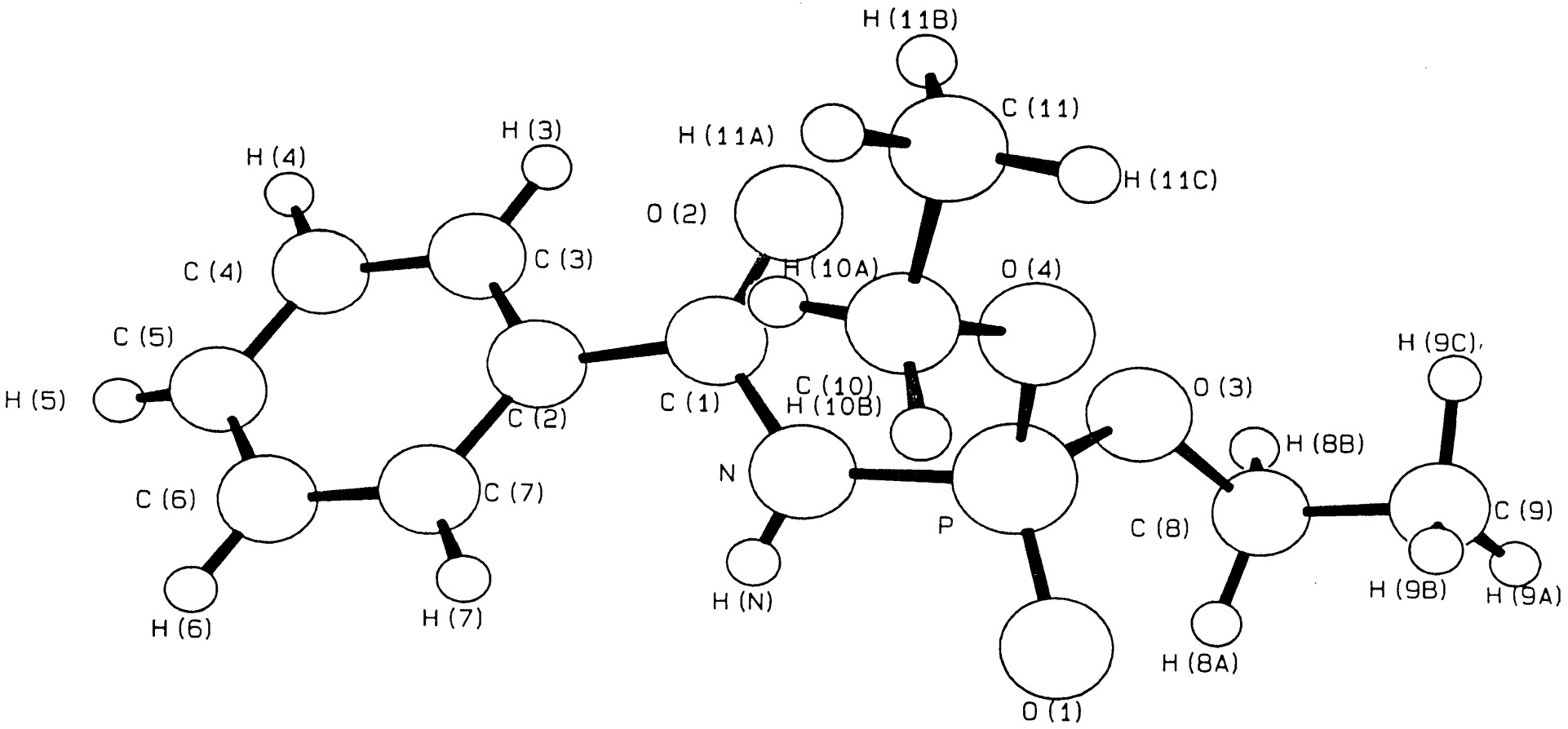


Figure 7: Packing diagram for **21b**; hydrogen bonding indicated by dotted lines

Figure 8: A perspective view of **21d** with atomic numbering



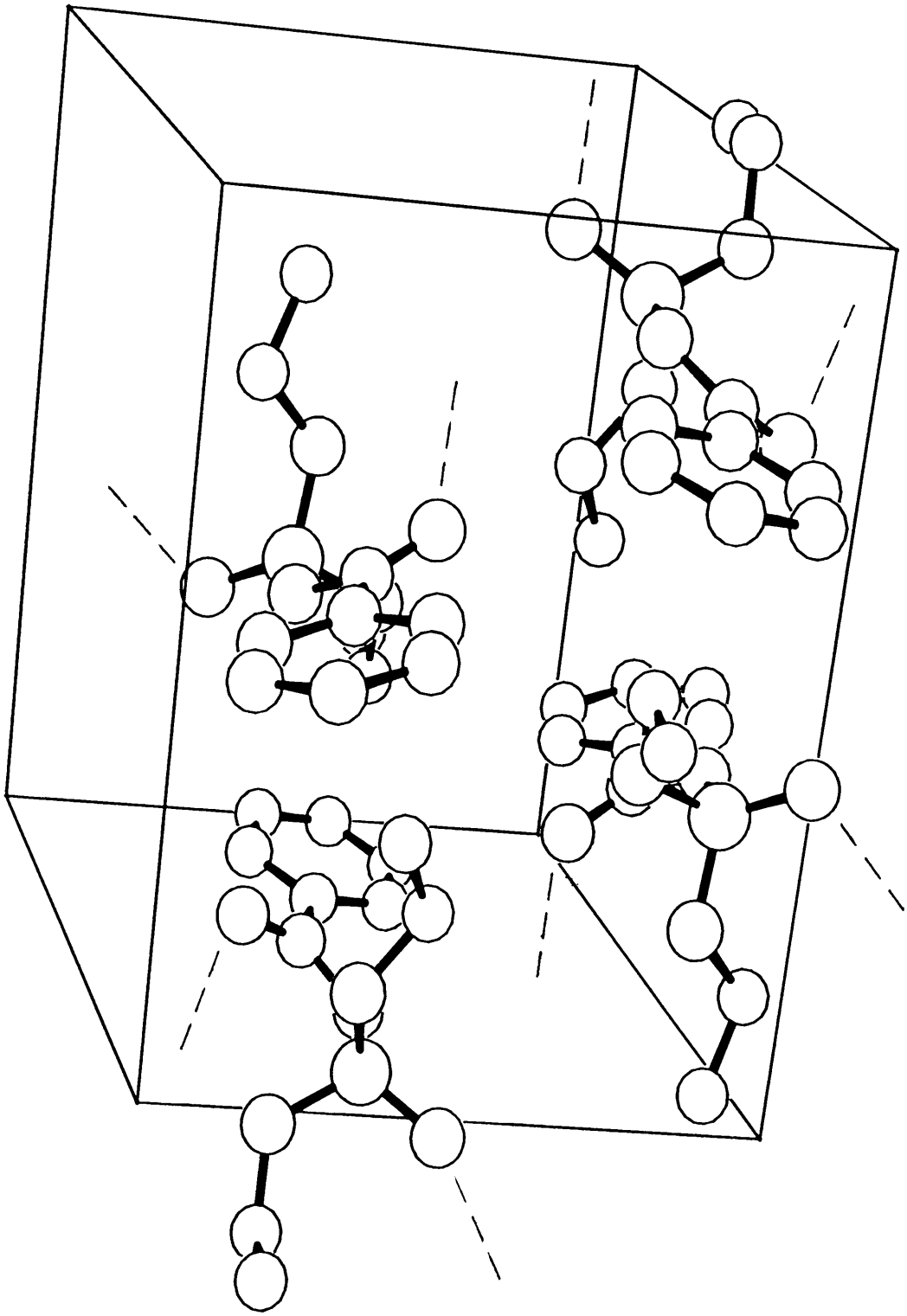


Figure 9: Packing diagram for **21d**; hydrogen bonding indicated by dotted lines

Table 7: Selected molecular parameters for (48) and related systems

Intramolecular bond distances (Å)					
Compound	Ref.	P=O	P-N	N=C (N=S)	C-N
$(EtO)_2P(O)NC(H)NH_2$ **(48)**	a	1.463(2)	1.631(2)	1.296(3)	1.326(4)
$(EtO)_2P(O)NHC(O)Me$ **(21a)**	a	1.449(2)	1.682(3)		1.381(4)
$(EtO)_2P(O)NHC(O)Ph$ **(21b)**	a	1.468(2)	1.662(2)		1.378(3)
$(MeO)_2P(O)NHC(O)Ph$ **(21h)**	117	1.461(4)	1.667(5)		1.393(7)
$(PhO)_2P(O)NHC(O)NMePh$ **(53)**	118	1.462(4)	1.646(5)	1.406(8)	1.358(7)
$(RO)_2P(O)NS(O)Me_2$[b] **(54)**	119	1.463(7)	1.618(8)	(1.526(8))	
(RO)(R'O)P(O)NHR"[b] **(55)**	120	1.464	1.630		1.424

Intramolecular bond angles (°)					
Compound	O=P-N	P-N-C	P-N=S	N=C-N	N-C=O (N=S-O)
(48)	118.4(1)	118.0(2)		123.2(3)	
(21a)	109.2(1)	127.6(3)			121.6(4)
(21b)	108.6(1)	126.3(2)			121.3(3)
(21h)	107.5(2)	124.7(4)			120.0(5)
(53)	109.5(2)	125.6(4)		114.1(5)	122.9(5)
(54)[b]	116.4(5)		126.1(5)		118.8(5)

Intramolecular bond angles (°)					
Compound	O=P-N	P-N-C	P-N=S	N=C-N	N-C=O (N=S-O)
(55)[b]	112.0	127.0			
Torsion angles (°)					
Compound	O=P-N-C	P-N-C-N	P-N-C=O	O=P-N-S	P-N-S-O
(48)	-11.3(3)	-177.7(2)			
(21a)	172.6(7)		-4.06(1.25)		
(21b)	177.0(2)		0.64(0.39)		
(21h)	c		c		
(53)	-179.4(5)	170.1(4)	-10.9(9)		
(54)[b]				33.8	57.0
(55)[b]	4.7				

[a] This work.

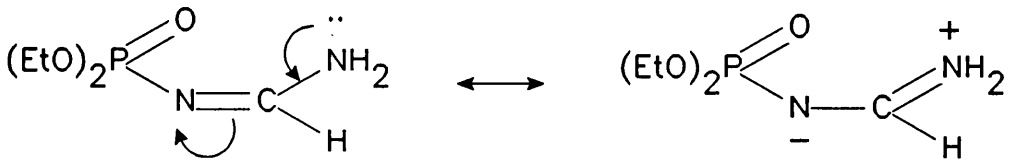
[b] Average value.

[c] No values of the torsion angles given, but for the plane determined by the O=P—N(H)—C=O backbone, the root mean square deviation was found to be only 0.041.

While the distance of the phosphoryl bond, P=O, remains remarkably constant for all structures (**21**, **48**, **53**, **54** and **55**) (1.461(6) Å), the length of the P—N bond is sensitive to the nature of the *N*-substituent. The structures discussed can be divided into three groups, that is those with a long (1.670, 1,646 Å; (**21**), (**53**)), medium (1.630, 1.631 Å; (**48**),(**55**)), and short (1.618 Å; (**54**)) P—N bonds. When the

nitrogen atom is substituted by the electron-withdrawing group (carbonyl, compounds (**21**) and (**53**)), no *N*→*P* back donation is expected, and the P—N bond order is not far from unity. For the compounds in which an electron-rich group is attached to the nitrogen (R in (**55**), amidine function in (**48**)), the back donation results in a serious shortening of the P—N bond. The exceptionally short distance found in (**54**) was interpreted[119] in terms of the heteroallenic system, reported for other sulfur-containing organophosphorus compounds.[121]

As expected, both C—N bonds in (**48**) are considerably shorter than those in (**53**). Although they differ from each other (1.296 *vs.* 1.326 Å), the difference is not large, implying significant contribution of the resonance form (**48a**) to the bonding description of the molecule (**Scheme 20**).



48 **48a**

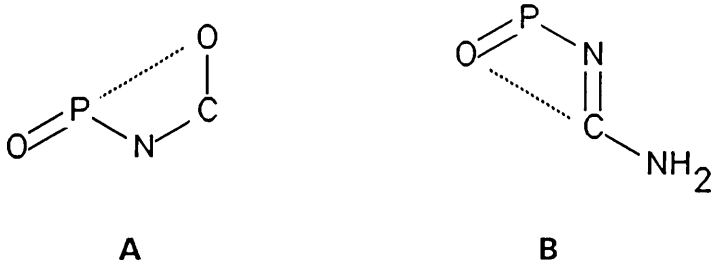
Scheme 20

The C—N bonds in (**53**) are much longer, indicating little resonance with

the carbonyl group because of the presence of two electronegative substituents (phosphoryl and phenyl) at each of the N atoms. Taking the difference in the P—N distances into account (1.406 *vs* 1.358 Å), it follows that the diethoxyphosphoryl substituent has a stronger effect on a nitrogen atom than does the phenyl group.

It is known[122] that multiple-bond orbitals repel other orbitals more strongly than do single bond orbitals, the value of a X—P—Y angle reflects therefore the P—X and/or P—Y bond order. Since the phosphoryl bond order in the series included in **Table 7** is approximately constant (*vide supra*), it can be concluded from the values of the O═P—N bond angles that the P—N bond order decreases in a sequence: (**54**), (**48**) > (**55**) > (**53**), (**21**), in agreement with the observed P—N bond distances. As far as the P—N—C bond angle is concerned, this angle in (**48**) is significantly smaller than that for all N—H containing compounds (**21**),(**53**),(**55**) (118.0° *vs ca* 126°). This difference can be explained as follows. In (**21**),(**53**),(**55**) two big substituents at nitrogen locate as far from each other as possible, bringing the hydrogen atom more close to the lone pair of electrons. In (**48**), short N═C bond implies considerable electron density on nitrogen (see the resonance structure **48a**), hence the electronic repulsion, resulting in the smaller P—N═C angle, just below the value expected for a sp^2 hybrydization. The values of the N—C—N bond angles can be compared for structures (**48**) and (**53**). Large difference between those values (123.2° *vs* 114.1°) reflects the

difference in the bonding situation in those two systems. In (**53**) both C—N bonds are essentially "single" (long), hence causing less repulsion (smaller angle), as compared with the electron-rich "single"/"double" (short) bonding system in (**48**). This is confirmed by the average value of the O═C—N angle for (**53**) = 122.9°, reflecting (like in compounds (**21**)) the "single"/"double" interactions. Analysis of the torsion angles obtained for structures (**21**, **48**, **53** and **54**) offers an insight into the intramolecular interactions operating in those systems. In derivatives (**21**) and (**53**) the O═P—N—C moiety attains an almost ideal antiperiplanar orientation (see **Figures 6** and **8**), with the carbonyl oxygen located not far from that plane, with the geometry shown in **Scheme 21** (structure **A**).



A **B**

Scheme 21: Geometry of the O═P—N—C—X backbone of **21**, **48**, **53**.

Such a geometry allows for the donor-acceptor, non-bonded interactions between carbonyl oxygen and phosphorus atoms, and such an effect should be revealed in the molecular structure of a compound. Examination of the crystal structures shows that this distance (dotted line in **Scheme 21**, **A**) for the three related structures **21b**, **21d**, **21h** is

3.062 Å, 3.010 Å, and 2.97 Å, respectively. Those values are considerably smaller than the sum of the respective van der Waals radii (3.30 Å) and we propose to use them as a measure for the driving force responsible for that particular conformation of the molecules in the solid state. It should be mentioned at this point that the secondary C═O···P interactions shows as system **A** in **Scheme 21** can be considered as an "early stage" of nucleophilic substitution at the phosphoryl center, leading ultimately to a pentacoordinated phosphorus intermediate, a very typical type of structure for organophosphorus compounds.[123] Such an approach of relating the molecular parameters obtained from crystal structures with structural changes occurring along the reaction coordinate was applied successfully to a large number of molecular systems.[124] In (**54**) spatial arrangement of the O═P—N═S═O backbone of the molecule is such that *both*, the (S)O···P, and the (P)O···S non-bonded distances approach the values of the corresponding van der Waals radii. In structure (**48**) the situation is qualitatively different. The O═P—N═C—NH_2 system is again almost planar (the respective two torsion angles are - 11.3 and 177.7°), but the arrangement is quite different from that characteristic of mixed imides, as shown in **Scheme 21**, structure **B**. In the molecule of (**48**) it is the phosphoryl oxygen that is in short contact with the sp^2 carbon atom of the amidine group; the O(1)···C(1) distance is 2.948 Å, while the sum of the van der Walls radii is 3.30 Å. The change of the geometry of the molecule to the type **B** (**Scheme 21**) reflects the change in the relative

nucleophilicity/electrophilicity of the respective centres in the OPNCX system. According to the structure **A** (**Scheme 21**), the phosphorus atom represents the most electrophilic, and the carbonyl oxygen the most nucleophilic centre of the molecule. These conclusions are fully supported by the results of the neutral solvolysis of mixed phosphoric-carboxylic imides,[53,a] and of the trimethylsilylation[95] of these compounds. Strong electron donation from the amidine group to the phosphoryl centre in (**48**) (resonance structure (**48a**)) is also demonstrated by the virtual planarity of the NH_2 group (the deviation of the nitrogen atom from the plane defined by C(1) and two H atoms was found to be only 0.003 (3) Å). The *N*-phosphorylated amidine represents therefore a derivative with a powerfully electron-donating substituent at the phosphoryl centre.

3.2.5 CONCLUSIONS

The first obvious conclusion of the results of this chapter is that the mixed imide system **21** represents indeed a multifunctional molecule. Selectivity in the reactions with such electrophilic reagents as haloalkanes or trimethylsilyl derivatives appears to be a very sensitive

[a] Although in the earlier work on solvolysis[53] the P—N bond cleavage in **21** was interpreted in terms of the direct attack of a nucleophile at phosphorus, Baraniak and Stec demonstrated recently[103] that the reaction involves the initial attack at the carbonyl carbon, followed by the *N*→*O* migration of the phosphoryl moiety in the reaction intermediate. This mechanism is, however, in even better agreement with model **A** (**Scheme 21**), in which a tendency of the phosphorus to migrate from nitrogen to oxygen is clearly evident.

function of the structural and reaction conditions factors. Under conditions tested so far, only selected systems can be recommended as effective synthetic routes to particular types of derivatives of **21**.

More work on the nature of the factors determining reaction yield and selectivity is certainly necessary in order to arrive at more practical applications of those systems. One avenue should involve closer studies on the effect of various Phase Transfer Catalysts on the selectivity of substitution in **21**. In this respect, we are presently discussing collaboration in this field with Professor E. V. Dehmlow (University of Bielefeld), one of the world's greatest authority in the area of Phase Transfer Catalysis.

Another area, which should (and will) be continued, is the reaction of the *conjugate base* of **21** with silylating agents. We have carried out some preliminary experiments in this field, but the results obtained were complex and did not lead to any clear conclusions. For that reason, those results have not been included in this thesis.

We also feel that the discussion of the crystal and molecular structures, carried out in this Chapter (*vide supra*), would be much more complete if we had included a structure of at least one of the alkylated derivatives of **21**. As mentioned before, we were unable to prepare samples of crystals suitable for X-ray diffraction. In order to overcome this problem,

we intend to prepare one of such products *via* a procedure completely different from the direct substitution of **21**. For example, we plan to arrive at (hopefully) pure *N*-alkylated compound **42** (see Eq. ***(18)***) by the condensation of the two, suitably chosen, phosphoryl and carbonyl precursors. Such precursors could include a pair of the corresponding acylating reagent, RC(O)X, and a phosphoramidate, $(R'O)_2P(O)NHR"$, or the substrates with reversed functional groups. Since there is already some literature on this subject available, we hope to parallel our studies on the nucleophilic reactivity of systems of the type of **21**, with the preparation of the analogous products *via* different routes.

3.2.6 EXPERIMENTAL

General information is the same as in Chapter 2.2.6 with only a few changes to note: All reactions were carried out in an atmosphere of dry argon; ^{13}C NMR chemical shifts are given relative to $SiMe_4$; for the silylation reactions the NMR spectra were recorded in C_6D_6, and for the alkylation reactions in $CDCl_3$, unless otherwise stated; IR spectra were recorded as neat liquids with a Bruker IFS 113v FT-IR spectrometer; HMDS (Aldrich) was purified by distillation, b.p. 119 - 120°C; iodomethane and bromoethane were passed through a short column using Al_2O_3 (basic) as a stationary phase, while higher haloalkanes were purified by distillation.

* ***Substrates***

Diethyl-N-formylphosphoramidate (**21a**) (Eq. ***(19)***)

The intermediate ***Ethyl-[N-(di-ethoxyphosphoryl)]-formimidate*** (**41a**) (**41**, R′ = H; R" = Et) was prepared from diethylphoshoramidate and triethyl orthoformate according to the literature procedure.[105]

^{31}P NMR: δ: 3.54;

MS: *m/z* 209 (M^{+}, 14%),
182 (13), 181 (12), 153 (35), 138 (99), 126 (59),
110 (55), 109 (83), 82 (60), 81 (100).
Other data in full agreement with those reported.

Hydrolysis of **41a**. A mixture of **41a** (34.0 g, 0.163 mol), water (5.85 g, 0.325 mol), and trifluoroacetic acid (a few drops) was stirred at room temperature for 3 h. Volatile by-products were removed under reduced pressure and crude **21a** was purified by distillation.

Yield: quantitative;
b.p.: 119°C (0.15 Torr; lit.: b.p. 135°C/0.25 Torr[125]);

^{1}H NMR: δ: 1.33 (6H, t, J_{HH} 7.1 Hz, 2 x Me of POEt),

4.15 (4H, m, 2 x CH_2 of POEt),

8.45 (1H, br s, C(O)H);

^{31}P NMR: δ: - 4.46.

IR: $\nu_{(NH)}$ 3447, 3115,

$\nu_{(C=O)}$ 1718,

$\nu_{(P=O)}$ 1254,

$\nu_{(POC)}$ 1099 cm^{-1};

MS: *m/z* 181 (M^{+}, 0.6%),

153 (22), 126 (77), 98 (100), 81 (92).

Diethyl-N-acetylphosphoramidate (**21b**) (Eq. ***(19)***)

The intermediate ***Methyl-[N-(di-ethoxyphosphoryl)]-acetimidate*** (**41b**) (**41**, R′ = R" = Me) was prepared from diethylphosphoramidate and trimethyl orthoacetate in the presence of catalytic amounts of trifluoroacetic acid.

Yield: 88%;

^{1}H NMR: δ: 1.11 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),

2.10 (3H, s, N=CMe),

3.51 (3H, s, C(O)Me),

3.88 (4H, quin, J_{HH} 7.2 Hz, 2 x CH_2 of POEt);

^{31}P NMR: δ: 0.73;

MS: *m/z* 209 ($M^{\ddagger}$, 4%),

149 (4), 136 (9), 95 (27), 81 (31), 42 (100).

41b was hydrolyzed as described above; **21b**,

Yield: 100%;

m.p.: 49 - 51°C (lit.: m.p. 52 - 53°C[126]);

^{1}H NMR: δ: 1.32 (6H, t, J_{HH} 6.3 Hz, 2 x Me of POEt),

2.09 (3H, s, C(O)Me),

4.15 (4H, m, 2 x CH_2 of POEt),

8.99 (1H, br s, NH);

^{31}P NMR: δ: - 4.50;

MS: *m/z* 195 ($M^{\ddagger}$, 1%),

168 (4), 127 (72), 98 (100), 81 (97), 43 (91).

Diethyl-N-propionylphosphoramidate (21c) (Eq. ***(19)***)

The intermediate ***Ethyl-[N-(di-ethoxyphosphoryl)]-propionimidate*** (**41c**) (**41**, R′ = R" = Et) was prepared as **41b**,

Yield: 94%;

b.p.: 92 - 94°C/0.8 Torr;

^{1}H NMR: δ: 1.06 (3H, t, J_{HH} 7.7 Hz, Me of CEt),
1.16 (3H, t, J_{HH} 7.2 Hz, Me of COEt),
1.02 (6H, t, J_{HH} 7.0 Hz, 2 x Me of POEt),
2.57 (2H, q, J_{HH} 7.7 Hz, CH_2 of CEt),
3.96 (4H, quin, J_{HH} 7.0 Hz, 2 x CH_2 of POEt),
4.08 (2H, q, J_{HH} 7.2 Hz, CH_2 of COEt);

^{31}P NMR: δ: 0.56;

MS: *m/z* 238 ($M+1^{\ddagger}$, 80%),
237 ($M^{\ddagger}$, 42%),
208 (9), 192 (26), 164 (100), 155 (68), 138 (79),
124 (48), 109 (56), 81 (39), 56 (72).

41c was hydrolyzed as described above; **21c**,

Yield: 98% (viscous liquid);

^{1}H NMR: δ: 0.95 (3H, t, J_{HH} 7.5 Hz, Me of CEt),
1.78 (6H, t, J_{HH} 6.5 Hz, 2 x Me of POEt),
2.21 (2H, q, J_{HH} 7.5 Hz, CH_2 of CEt),

4.03 (4H, m, 2 x CH_2 of POEt),

9.05 (1H, d, J_{HH} 10.5 Hz, NH);

^{13}C NMR: δ: 9.0 (Me of CEt),

16.0 (d, J_{CP} 6.8 Hz, Me of POEt),

30.1 (d, J_{CP} 9.7 Hz, CH_2 of CEt),

63.9 (d, J_{CP} 5.6 Hz, CH_2 of POEt),

175.6(d, J_{CP} 8.2 Hz, CO);

^{31}P NMR: δ: - 4.90;

MS: *m/z* 210 ($M+1^{\ddagger}$, 100%),

209 ($M^{\ddagger}$, 6%),

155 (94), 137 (48), 127 (72), 109 (70), 99 (63),

81 (48), 57 (28).

Diethyl-N-benzoylphosphoramidate (21d) (Eq. ***(20)***)

The intermediate ***N-benzoyl-O,O,O-triethylphosphorimidate*** 43d was prepared as follows. A solution of sodium azide (15.6 g, 0.24 mol) in water (50 mL) was added dropwise with stirring and cooling at - 5° - 0°C to the mixture of benzoyl chloride (27.5 g, 0.196 mol), dichloromethane (300 mL), and tetrabutylammonium bromide (TBAB, 0.2 g). The two-phase system was stirred vigorously at - 5° - + 5°C for 2.5 h, separated, the organic layer was washed with water (2 x

50 mL) and dried over anhydrous $MgSO_4$. This solution was added dropwise with stirring at room temperature to the solution of triethyl phosphite (33.2 g, 0.20 mol) in benzene (500 mL). After the addition the solution was stirred for additional 5 h at room temperature, and evaporated under reduced pressure. Crude **43d** was purified by distillation.

Yield: 50.6 g, 91%;

b.p.: 110 - 115°C/0.05 Torr;

^{1}H NMR: δ: 1.28 (9H, t, J_{HH} 6.9 Hz, 3 x Me of POEt),
4.19 (6H, quin, J_{HH} 7.2 Hz, 3 x CH_2 of POEt),
7.26 (3H, m, H_{meta}, H_{para}),
8.12 (2H, d, J_{HH} 6.6 Hz, H_{ortho});

^{31}P NMR: δ: 11.50 (lit.: δ 10.66[90]);

The product **43d** (50.0 g, 0.17 mol) was dissolved in benzene (80 mL) and dry HCl was passed through the solution at 15 - 20°C for 1.5 h. The solution was washed with aq. Na_2CO_3 until neutral, and then with water, and dried. The solvent was evaporated under reduced pressure yielding crude **21d** as a pale yellow solid. The product was purified by crystallization from cyclohexane.

Yield: 29.3 g, 67%;

m.p.: 72.6 - 75.6°C;

^{1}H NMR: δ: 1.06 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),
(C_6D_6) 4.13 (4H, m, 2 x CH_2 of POEt),
7.17 (3H, m, H_{meta}, H_{para}),
8.54 (2H, d, J_{HH} 8.2 Hz, H_{ortho}),
10.61(1H, d, J_{HH} 8.3 Hz, NH);

^{13}C NMR: δ: 16.1 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),
64.2 (d, J_{CP} 5.8 Hz, 2 x CH_2 of POEt),
128.7, 129.1 (C_{ortho}, C_{meta}),
132.6 (C_{para}),
133.5 (C_{ipso}),
168.0 (CO);

^{31}P NMR: δ: - 4.50;

MS: *m/z* 257 ($M^{\ddagger}$, 7%),
180 (4), 154 (22), 127 (38), 105 (93), 81 (17),
77 (100), 51 (28).

Diethyl-N-(ethoxycarbonyl)phosphoramidate (**21**e) (Eq. ***(21)***)

The intermediate diethyl phosphorisocyanatidate **47** was prepared as

described[106]; Yield: 72%; ^{31}P NMR δ: - 15.5 (lit., δ: - 17.6[106]). This product was treated with anhydrous ethanol in tetrachloromethane in a manner analogous to that given for the preparation of the t-butoxy-carbonyl derivative, **21e**.[106]

Yield: 94% (colourless, viscous liquid);

b.p.: 90 - 96°C/0.5 Torr;

^{1}H NMR: δ: 1.18 (3H, t, J_{HH} 7.1 Hz, Me of COEt),
1.26 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),
4.11 (6H, m, 3 x CH_2 of COEt and POEt),
7.79 (1H, br s, NH);

^{13}C NMR: δ: 14.3 (Me of COEt),
(C_6D_6) 16.0 (d, J_{CP} 6.7 Hz, 2 x Me of POEt),
61.3 (CH_2 of COEt),
63.7 (d, J_{CP} 5.1 Hz, 2 x CH_2 of POEt),
154.0(d, J_{CP} 3.9 Hz, CO);

^{31}P NMR: δ: - 4.50;
(C_6D_6)

MS: *m/z* 226 ($M+1^{+}$, 100%),
225 (M^{+}, 34%),

198 (93), 180 (41), 170 (26), 154 (36), 124 (70), 109 (62), 98 (56), 81 (65).

N-(Diethoxyphosphoryl)-N′,N′-diethylurea (21f) (Eq. ***(21)***)

A solution of diethylamine (10.4 g, 0.14 mol) in tetrachloromethane (15 mL) was added dropwise with cooling to a solution of freshly distilled **47** (25.2 g, 0.14 mol) in CCl_4 (30 mL) at such a rate as to maintain the temperature of the mixture below 5°C. The mixture was then stirred at 5°C for 45 min, warmed up to the room temperature and stirred for further 3 h. The solvent was removed under reduced pressure yielding crude **21f** as a pale yellow liquid, which was purified by bulb to bulb distillation (oven temperature 150°C/0.4 Torr). Pure **21f** crystallized upon standing.

Yield: 30.0 g, 84%;

m.p.: 37.8 - 41.5°C;

^{1}H NMR: δ: 0.97 (6H, t, J_{HH} 7.0 Hz, 2 x Me of NEt),
1.17 (6H, t, J_{HH} 7.3 Hz, 2 x Me of POEt),
3.18 (4H, q, J_{HH} 7.0 Hz, 2 x CH_2 of NEt),
4.04 (4H, m, 2 x CH_2 of POEt),
7.79 (1H, br s, NH);

^{13}C NMR: δ: 13.8 (2 x Me of PNEt),

(C_6D_6) 15.9 (d, J_{CP} 7.0 Hz, 2 x Me of POEt),
41.4 (2 x CH_2 of NEt),
63.5 (d, J_{CP} 6.2 Hz, 2 x CH_2 of POEt),
154.0(CO);

^{31}P NMR: δ: - 3.00;

MS: *m/z* 253 ($M+1^{\ddagger}$, 81%),
252 ($M^{\ddagger}$, 16%),
180 (32), 152 (36), 124 (52), 81 (17), 72 (100),
58 (84), 44 (52).

* ***Reactions of phosphoramidates* 21 *with silylating reagents***

(i) Reactions of* 21a *with trimethylsilyl chloride (TMSCl)

Reactions of **21a** *with TMSCl* (**Scheme 11**)

(a) To the solution of **21a** (1.03 g, 5.66 mmol) in benzene (4 mL) the solution of TMSCl (1.23 g, 11.35 mmol) in benzene (3 mL), followed by the solution of Et_3N (1.15 g, 11.33 mmol) in benzene (3 mL) were added with stirring at room temperature. The mixture was stirred for 21 h, the amine salt was filtered off, washed with benzene, and the

solvent was evaporated under reduced pressure. The crude product **44** was obtained as a viscous, pale-yellow oil.

Yield: 1.24 g, 87%;

^{1}H NMR: δ: 0.11 (9H, s, Me_3Si),
1.12 (6H, t, J_{HH} 6.8 Hz, 2 x Me of POEt),
3.96 (4H, quin, J_{HH}, J_{HP} 6.8 Hz, 2 x CH_2 of POEt),
8.27 (1H, d, J_{HP} 13.9 Hz, N=CH);

^{31}P NMR: δ: 3.23;

When a sample of the product was exposed to the atmosphere, or when the compound was treated with a small amount of water, its NMR spectra (^{1}H and ^{31}P) showed rapid hydrolysis to the starting material (**21a**). Similarly, attempts to record the IR spectrum of **2**, resulted in the complex spectrum, corresponding mostly to that of **21a**. The instability of **44** also prevented us to obtain an unambiguous ^{13}C NMR and mass spectra of the product.

Reaction of **44** *with HCl* (**Scheme 12**)

Dry HCl was passed through a solution of **44** (1.20 g, 4.74 mmol) in benzene (10 mL) at room temperature for 30 min. The slightly turbid mixture was filtered through a layer of Celite and $MgSO_4$, the layer

was washed with benzene, and the solvent and volatile products were evaporated on a rotary evaporator, followed by high vacuum. The residue was examined by NMR spectroscopy which indicated the complete disappearance of the substrate and the formation of two products: **21a** and the new product **45** in a ratio 1.4 : 1, as determined by ^{31}P NMR spectroscopy.

45: (Scheme 13)

^{1}H NMR: δ: 1.07 (6H, t, J_{HH} 7.1 Hz, 2 x Me of POEt, overlapping with the corresponding signal of **21a**),
3.94 (4H, quin, J_{HH}, J_{HP} 7.1 Hz, 2 x CH_2 of POEt),
8.60 (1H, br s, C(sp^2)H);

^{31}P NMR: δ: - 15.6;

Attempts to separate the mixture of **21a** and **45** by column chromatography led to extensive decomposition.

(b) The solution of **21a** (4.0 g, 22.08 mmol) and TMSCl (2.40 g, 22.08 mmol) in benzene (14 mL) was stirred at room temperature for 3 days. Solvent and volatile products were removed under reduced pressure and the residue was examined by NMR (^{1}H and ^{31}P) spectroscopy. ^{31}P NMR spectrum showed the presence of three components: **45** (δ_P -

15.6), **21a** (δ_P -3.9), and **46** (δ_P 8.5). The proportion of these products varied with the reaction time; for example, after 4.5 h, the ratio **21a** : **45** : **46** was 15 : 2.3 : 1, while after 2.5 days this ratio changed to 7.2 : 0.7 : 1 (as determined by ^{31}P NMR spectroscopy). The ^{1}H NMR spectrum showed only the presence of the POEt groups (overlapping for all three compounds), the C(sp^2)H groups (br s, δ_H 8.16 for **46**, 8.5 - 8.6 for **21a** and **45**), and the NH functions (δ_H 9.55, br s, overlapping for compounds **21a** and **45**).

Reaction of **21a** *with HCl*

21a (1.03 g, 5.69 mmol) was dissolved in benzene (10 mL) and the excess of dry HCl was passed through this solution at room temperature for 30 min. The solution was filtered through a layer of Celite and $MgSO_4$, and after washing the layer with benzene, the combined benzene solutions were evaporated under reduced pressure. The NMR (^{1}H and ^{31}P) spectra of the product demonstrated that it consisted of two compounds, **45** and **21a** in a ratio of 1.2 : 1.

(ii) Reactions with hexamethyldisilazane (HMDS)

General procedure.

A solution of HMDS (0.6 - 1.1 mol-equivalent) in benzene or dimethoxyethane (0.3 mL/mmol) was added to a solution of **21** (1 mol-equivalent) in the same solvent (0.2 mL/mmol), and the solution

was heated under reflux for 3 - 6 h. After cooling to room temperature the solvent was evaporated under reduced pressure, and the product was identified as given below. The following results were obtained (for ^{31}P chemical shifts, yields and other details, see **Table 3** and **5**).

Silylation of **21a** (**Scheme 14**)

N-(Diethoxyphosphoryl)-formamidine

Hexamethyldisilazane (310 mg, 1.9 mmol) in the appropriate solvent (0.6 mL) was added slowly to a solution of phosphoramidate **21a** in the same solvent (0.5 mL). The reaction mixture was heated under reflux for 3.5 h, cooled to room temperature and the solvent was evaporated under reduced pressure, yielding the product as a viscous liquid which crystallized on standing in a cold room.

Yield: 80 - 90% (colourless cubic crystals);

m.p.: 68 - 69°C (from benzene); lit.: m.p. 76 - 78°C[111]

^1H NMR: δ: 1.19 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),

4.01 (4H, quin, J_{HH}, J_{HP} 7.2 Hz, 2 x CH_2 of POEt),

8.26 (2H, br s, 2 x NH),

8.41 (1H, d, J_{HP} 22.2 Hz, N=CH);

^{13}C NMR: δ: 16.1 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),
61.9 (d, J_{CP} 5.8 Hz, 2 x CH_2 of POEt),
161.9 (d, J_{CP} 5.5 Hz, N=C);

^{31}P NMR: δ: 8.2;

MS: *m/z* 180 (M^+, 26%),
153 (38), 152 (12), 136 (41), 126 (79), 108 (70),
98 (98), 81 (100), 80 (90), 43 (52);

IR: $\nu_{(NH)}$ 3279, 3150,
$\nu_{(C=N)}$ 1668,
$\nu_{(P=O)}$ 1223,
$\nu_{(POC)}$ 1098 cm^{-1};

Anal. calcd. for $C_5H_{13}N_2O_3P$: C 33.3, H 7.3, N 15.5;
found: C 32.8, H 7.3, N 15.4%.

Silylation of **21b**

Oil. ***O,O-Diethyl-N-acetyl-N-trimethylsilylphosphoramidate*** (major),

^{1}H NMR: δ: 0.17 (9H, s, Me_3SiN),
1.07 (6H, t, J_{HH} 6.5 Hz, 2 x Me of POEt),

2.22 (3H, s, C(O)Me),

3.92 (4H, quin, J_{HH}, J_{HP} 6.1 Hz, 2 x CH_2 of POEt);

^{13}C NMR: δ: -0.2 (Me_3Si),

16.2 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),

23.9 (d, J_{CP} 9.7 Hz, Me of C(O)Me),

62.2 (d, J_{CP} 5.6 Hz, 2 x CH_2 of POEt),

171.7(CO);

MS: *m/z* 268 ($M+1^{\ddagger}$, 0.3%),

267 ($M^{\ddagger}$, 0.1%),

241 (0.1), 211 (0.6), 195 (43), 168 (7), 155 (43),

137 (12), 127 (95), 109 (55), 98 (100), 81 (80),

43 (78).

Trimethylsilyl-[N-(diethoxyphosphoryl)]-acetimidate (minor),

^{1}H NMR: δ: 0.30 (9H, s, Me_3SiO),

2.51 (3H, s, N=CMe),

signals of the POEt groups overlapping with those of the major product.

Silylation of **21d**

Oil. ***O,O-Diethyl-N-benzoyl-N-trimethylsilylphosphoramidate***,

^{1}H NMR: δ: 0.21 (9H, s, Me_3SiN),
1.06 (6H, t, J_{HH} 7.1.5 Hz, 2 x Me of POEt),
4.06 (4H, dq, J_{HH} 7.1 Hz, J_{HP} 8.4 Hz, 2 x CH_2 of POEt),
7.24 (3H, m, H_{meta}, H_{para}),
8.54 (2H, dd, J_{HH} 3.4, 7.7 Hz, H_{ortho});

^{13}C NMR: δ: 0.7 (Me_3Si),
16.2 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),
64.5 (d, J_{CP} 5.3 Hz, 2 x CH_2 of POEt),
128.0, 130.1 (C_{meta}, C_{ortho}),
131.1 (C_{para}),
132.7 (C_{ipso}),
174.2 (CO).

Silylation of **21e**

Oil. ***O,O-Diethyl-N-(ethoxycarbonyl)-N-trimethylsilylphosphoramidate*** (major),

^{1}H NMR: δ: 0.04 (9H, s, Me_3SiN),

1.04 (3H, t, J_{HH} 7.7 Hz, Me of COEt),

1.08 (6H, t, J_{HH} 6.5 Hz, 2 x Me of POEt),

3.94 (4H, dq, J_{HH} 7.2 Hz, J_{HP} 11.1 Hz, 2 x CH_2 of POEt);

^{13}C NMR: δ: -0.6 (Me_3Si),

16.0 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),

16.3 (Me of COEt),

61.6 (d, J_{CP} 6.0 Hz, 2 x CH_2 of POEt),

63.4 (CH_2 of COEt),

158.9 (CO);

O-Ethyl-O′-trimethylsilyl-N-(diethoxyphosphoryl)-carbimidate (minor),

^{1}H NMR: δ: 0.24 (9H, s, Me_3SiO),

signals of the COEt and POEt groups overlapping with those of the major product;

^{13}C NMR: δ: -0.5 (Me_3Si),

16.3 (d, J_{CP} 5.3 Hz, 2 x Me of POEt),

16.4 (Me of COEt),

61.7 (d, J_{CP} 6.3 Hz, 2 x CH_2 of POEt),

63.3 (CH_2 of COEt),

162.0 (CO);

O,O-Diethyl-O-trimethylsilyl-N-(carboethoxy)phosphorimidate (minor),

^{1}H NMR: δ: 0.20 (9H, s, Me_3SiO),
signals of the COEt and POEt groups overlapping with those of other isomers;

^{13}C NMR: δ: 0.1 (Me_3Si),
162.1 (CO),
signals of the COEt and POEt groups overlapping with those of other isomers.

Silylation of **1f**

Oil. ***O-Trimethylsilyl-N-(diethoxyphosphoryl)-N′,N′-diethylisourea*** (major),

^{1}H NMR: δ: 0.24 (9H, s, Me_3SiO),
other signals overlapping with those of other isomers and unreacted **21f**;

^{13}C NMR: δ: 0.7 (Me_3Si),
61.5 (d, J_{CP} 4.6 Hz, 2 x CH_2 of POEt),

other signals overlapping with those of other products;

N,N-Diethyl-N′-(diethoxyphosphoryl)-N′-trimethylsilylurea (minor),

^{1}H NMR: δ: 0.02 (9H, s, Me_3SiN),

other signals overlapping with those of other products;

^{13}C NMR: δ: -0.6 (Me_3Si),

63.3 (d, J_{CP} 5.6 Hz, 2 x CH_2 of POEt),

other signals overlapping with those of other products;

O,O-Diethyl-O-trimethylsilyl-N-[(N′,N′-diethyl)carboxyamido]phosphorimidate (minor),

^{1}H NMR: δ: 0.20 (9H, s, Me_3SiO),

other signals overlapping with those of other products;

^{13}C NMR: δ: 0.1 (Me_3Si),

61.3 (d, J_{CP} 5.6 Hz, 2 x CH_2 of POEt),

other signals overlapping with those of other products.

* ***Reactions of phosphoramidates* 21 *with haloalkanes*** (Eq. ***(18)***)

General procedure

Sodium hydride (washed several times with petroleum ether) was added to DME (*ca* 2.5 mL/mmol), and to this suspension substrate **21** dissolved in DME (*ca* 1.5 mL/mmol; molar ratio NaH : **21** = 1.1) was added with stirring at room temperature. After the evolution of hydrogen has ceased the solution of the haloalkane (R"X : **21** = 1.5 for MeI and EtBr, and 1.0 for other haloalkanes) in DME (*ca* 0.8 mL/mmol) was added and the mixture was either stirred overnight at room temperature (for MeI), or heated under reflux for 2 - 24 h. For reactions carried out in the presence of TBAB, 5 mol% of the catalyst was added before the haloalkane was introduced to the mixture. Small volume of water was added, the mixture was evaporated under reduced pressure, ether or benzene (2 mL/mmol of **21**) was added, and the solution was washed with water or dil. aq. NH_4Cl (for reactions with MeI some $Na_2S_2O_3$ was also added) until neutral. After drying and evaporating the solvent under reduced pressure, the alkylation product was identified. The following results were obtained (for ^{31}P chemical shifts, yields, and other details, see **Tables 3**, **5**, and **6**).

Alkylation of **21a**

(a) *Methylation.* ***O,O-Diethyl-N-formyl-N-methylphosphoramidate.*** Purified by bulb to bulb distillation; oven temperature 112°C/1.8 Torr.

^{1}H NMR: δ: 1.21 (6H, t, J_{HH} 6.5 Hz, 2 x Me of POEt),
2.72 (3H, d, J_{HP} 8.1 Hz, NMe),
3.99 (4H, m, 2 x CH_2 of POEt),
8.62 (1H, s, C(O)H);

MS: *m/z* 195 ($M^{\ddagger}$, 3%),
167 (21), 139 (35), 112 (43), 110 (80), 81 (60),
65 (42), 29 (100);

Anal. calcd. for $C_6H_{14}NO_4P$: C 36.9, H 7.2, N 7.2;
found: C 36.4, H 6.8, N 6.4%.

(b) *Ethylation.* ***O,O-Diethyl-N-formyl-N-ethylphosphoramidate***. Purified by bulb to bulb distillation; oven temperature 115°C/2.5 Torr.

^{1}H NMR: δ: 0.97 (3H, t, J_{HH} 7.1 Hz, Me of NEt),
1.16 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),
3.23 (2H, 2q, J_{HH} 7.1 Hz, J_{HP} 7.4 Hz, CH_2 of NEt),
3.96 (4H, m, 2 x CH_2 of POEt),
8.54 (1H, s, C(O)H);

MS: *m/z* 209 ($M^{\ddagger}$, 0.2%),
181 (22), 166 (72), 138 (5), 124 (52), 110 (100),
81 (51), 56 (15), 29 (36);

Anal. calcd. for $C_7H_{16}NO_4P$: C 40.2, H 7.7, N 6.7;

found: C 38.8, H 7.8, N 6.0%.

(c) *Propylation.* ***O,O-Diethyl-N-formyl-N-propylphosphoramidate.*** Colourless oil.

^{1}H NMR: δ: 0.79 (3H, t, J_{HH} 7.5 Hz, Me of NPr),
1.25 (6H, t, J_{HH} 7.4 Hz, 2 x Me of POEt),
1.49 (2H, m, β-CH_2 of NPr),
3.22 (2H, m, NCH_2 of NPr),
4.06 (4H, m, 2 x CH_2 of POEt),
8.65 (1H, s, C(O)H).

(d) *Butylation.* Colourless oil; mixture: ***O,O-diethyl-N-formyl-N-butyl-phosphoramidate*** (major),

^{1}H NMR: δ: 0.81 (3H, t, J_{HH} 7.3 Hz, Me of NBu),
1.21 (2H, m, γ-CH_2 of NBu),
1.25 (6H, t, J_{HH} 7.4 Hz, 2 x Me of POEt),
1.46 (2H, m, β-CH_2 of NBu),
3.26 (2H, m, NCH_2 of NBu),
4.07 (4H, m, 2 x CH_2 of POEt),
8.65 (1H, s, C(O)H);

Butyl-[N-(diethoxyphosphoryl)]-formimidate (minor),

^{1}H NMR: δ: 1.04 (3H, t, J_{HH} 7.1 Hz, Me of COBu),
1.58 (2H, m, β-CH_2 of COBu),
8.11 (1H, d, J_{HP} 15.3 Hz, N=CH);
other signals of the minor product overlapping with those of the major.

(e) *Hexylation.* Colourless oil, purified by distillation (*vide supra*); mixture:

O,O-diethyl-N-formyl-N-hexyl-phosphoramidate (major),

^{1}H NMR: δ: 0.68 (3H, t, J_{HH} 6.9 Hz, Me of NHex),
0.94 - 1.28 (12H, m, 2 x Me of POEt, 3 x CH_2 of NHex),
1.37 (2H, m, β-CH_2 of NHex),
3.14 (2H, m, NCH_2 of NHex),
3.85 - 4.05 (4H, m, 2 x CH_2 of POEt),
8.55 (1H, s, C(O)H);

Hexyl-[N-(diethoxyphosphoryl)]-formimidate (minor),

^{1}H NMR: δ: 0.80 (3H, t, J_{HH} 7.2 Hz, Me of COHex),
1.47 (2H, m, β-CH_2 of COHex),
8.00 (1H, d, J_{HP} 15.2 Hz, N=CH);

other signals of this product overlapping with those of the major;

8.54 (1H, s, C(O)H);

MS: *m/z* 266 ($M+1^{\ddagger}$, 1.3%),

265 ($M^{\ddagger}$, 0.1%),

237 (1), 208 (1), 182 (9), 155 (13), 126 (12),

110 (31), 99 (20), 81 (33), 43 (57), 29 (100).

(f) *Isopropylation.* (i) No TBAB: crude product, glassy liquid, decomposing upon heating or exposure to moisture; ***O,O-diethyl-O-^{i}propyl-N-formyl-phosphorimidate***,

^{1}H NMR: δ: 1.06 - 1.36 (12H, overlapping d and t, 2 x Me of POEt, 2 x Me of PO^{i}Pr),

3.91 (4H, q, J_{HH} 7.0 Hz, 2 x CH_2 of POEt),

4.02 (1H, d of sept, J_{HH} 7.2 Hz, J_{HP} 8.7 Hz, CH of PO^{i}Pr),

8.45 (1H, d, J_{HP} 21.1 Hz, C(O)H);

No ^{13}C NMR spectrum was obtained, since the product was not stable over the period of data acquisition.

(ii) With TBAB: colourless oil, purified by washing with water; ***^{i}propyl-[N-(diethoxyphosphoryl)]-formimidate (E/Z)***,

^{1}H NMR: δ: 1.08 (d, J_{HH} 6.2 Hz, 2 x Me of CO^{i}Pr of one stereoisomer),

1.11 (t, J_{HH} 7.1 Hz, 2 x Me of POEt),

1.16 (d, J_{HH} 6.9 Hz, 2 x Me of CO^{i}Pr of another stereoisomer) (all signals integrating for 12H),

3.80 - 3.94 (6H, m, overlapping CH of CO^{i}Pr; both stereoisomers, 2 x CH_2 of POEt),

7.93 (1H, d, J_{HP} 15.5 Hz, N=CH of one stereoisomer),

7.96 (1H, d, J_{HP} 15.3 Hz, N=CH of another steroisomer);

IR: $\nu_{(vinylic\ CH)}$ 2983,

$\nu_{(C=N)}$ 1635,[127]

$\nu_{(P=O)}$ 1244,

$\nu_{(POC)}$ 1103 cm^{-1}.

Alkylations of lithium salts of **21** were carried out as follows. Isopropylamine (1.1 mol-equivalent) was dissolved in THF (2 mL/mmol), the solution was cooled to - 75°C and BuLi (15% solution in hexane, 1.1 mol-equivalent) was added. After 10 min a solution of **21** (1 mol-equivalent) in THF (2 ml/mmol) was added at -

75°C, and the solution was stirred at this temperature for 45 min. Haloalkane (2 mol-equivalent) in THF (1 mL/mmol) was added to the solution and the temperature was allowed to rise to - 5°C. After stirring for 30 min the mixture was warmed up to room temperature and left overnight. Aqueous NH_4Cl was added, THF was removed under reduced pressure, and the neutral solution was extracted with ether. After drying and evaporating the solvent, crude product was identified as described above.

Alkylation of **21b**.

(a) *Methylation.* Colourless oil. ***O,O-Diethyl-N-methyl-N-acetylphosphoramidate*** (major),

^{1}H NMR: δ: 1.22 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),
2.23 (3H, s, C(O)Me),
2.88 (3H, d, J_{HP} 7.5 Hz, NMe),
4.02 (4H, m, 2 x CH_2 of POEt);

^{13}C NMR: δ: 15.6 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),
24.2 (Me of C(O)Me),
29.3 (d, J_{CP} 25.3 Hz, NMe),
63.2 (d, J_{CP} 5.1 Hz, 2 x CH_2 of POEt),
172.7 (CO);

O,O-Diethyl-N-methylphosphoramidate (minor),

^{1}H NMR: δ: 1.17 (6H, t, overlapping with that of the other phosphoramidate, 2 x Me of POEt),
2.43 (3H, dd, J_{HH} 5.0 Hz, J_{HP} 12.1 Hz, Me of PNHMe),
3.90 (4H, m, overlapping that of the other phosphoramidate, 2 x CH_2 of POEt);

O,O-Diethyl-N,N-dimethylphosphoramidate (minor),

^{1}H NMR: δ: 2.52 (6H, d, J_{HP} 10.2 Hz, 2 x Me of $PNMe_2$); other signals overlapping with those of the first phosphoramidate.

(b) *Ethylation.* Oil. ***O,O-Diethyl-N-ethyl-N-acetylphosphoramidate*** (major),

^{1}H NMR: δ: 0.85 (3H, t, J_{HH} 7.0 Hz, Me of NEt),
1.06 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),
2.02 (3H, s, C(O)Me),
3.32 (2H, 2q, J_{HH} 7.2 Hz, J_{HP} 10.9 Hz, CH_2 of NEt),
3.71 - 3.93 (4H, m, 2 x CH_2 of POEt, overlapping with those of the minor product);

Ethyl-[N-(diethoxyphosphoryl)]-acetimidate (minor),

^{1}H NMR: δ: 0.95 (3H, t, J_{HH} 7.0 Hz, Me of COEt),
2.08 (3H, s, Me of N=CMe),
3.54 (2H, q, J_{HH} 7.1 Hz, CH_2 of COEt); other signals overlapping with those of the major product.

(c) *Hexylation.* Oil. ***O,O-Diethyl-N-hexyl-N-acetylphosphoramidate***,

^{1}H NMR: δ: 0.72 (3H, Me of NHex, overlapping with corresponding signals of other isomers),
1.23 (6H, 2 x Me of POEt, overlapping),
1.98 (3H, s, C(O)Me),
1.30, 1.51, 2.75 (6H, m, β-CH_2, γ-CH_2, δ-CH_2 of Hexyl, overlapping),
3.11 (2H, m, α-CH_2 of NHex),
3.85 - 4.10 (4H, m, 2 x CH_2 of POEt, overlapping);

Hexyl-[N-(diethoxyphosphoryl)]-acetimidate,

^{1}H NMR: δ: 1.87 (3H, s, C(O)Me),
3.32 (2H, m, CH_2 of COHex); other signals overlapping with those of other isomers);

O,O-Diethyl-O-hexyl-N-acetylphosphorimidate,

^{1}H NMR: δ: 1.83 (3H, s, C(O)Me),
other signals overlapping with those of other components).

Alkylation of **21c**

(a) *Methylation.* Oil. ***O,O-Diethyl-N-methyl-N-propionylphosphoramidate,***

^{1}H NMR: δ: 0.94 (3H, t, J_{HH} 7.5 Hz, Me of C(O)Et),
1.17 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),
2.54 (2H, q, J_{HH} 7.3 Hz, CH_2 of C(O)Et),
2.85 (3H, d, J_{HP} 7.5 Hz, NMe),
3.92 - 3.99 (4H, m, 2 x CH_2 of POEt);

^{13}C NMR: δ: 9.0 (Me of C(O)Et),
15.6 (d, J_{CP} 6.7 Hz, 2 x Me of POEt),
29.0 (d, J_{CP} 19.6 Hz, NMe),
31.7 (CH_2 of C(O)Et),
63.1 (d, J_{CP} 5.4 Hz, 2 x CH_2 of POEt),
176.3(d, J_{CP} 9.6 Hz, CO).

(b) *Ethylation.* Oil. ***O,O-Diethyl-N-ethyl-N-propionylphosphoramidate*** (major),

^{1}H NMR: δ: 0.86 (3H, t, J_{HH} 7.3 Hz, Me of NEt),
0.91 (3H, t, J_{HH} 6.9 Hz, Me of C(O)Et),
1.10 (6H, 2 x Me of POEt, overlapping with signals of another isomer),
2.41 (2H, q, J_{HH} 7.3 Hz, CH_2 of C(O)Et),
3.38 (2H, dq, J_{HH} 7.0 Hz, J_{HP} 11.1 Hz, CH_2 of NEt),
3.80 - 3.99 (4H, m, 2 CH_2 of POEt, overlapping with signals of another isomer);

^{13}C NMR: δ: 8.8 (Me of C(O)Et),
14.3 (Me of NEt),
15.5 (d, J_{CP} 6.7 Hz, 2 x Me of POEt),
29.2 (d, J_{CP} 9.3 Hz, CH_2 of NEt),
40.1 (CH_2 of C(O)Et),
63.0 (d, J_{CP} 5.5 Hz, 2 x CH_2 of POEt),
175.4(CO);

O,O,O-Triethyl-N-propionylphosphorimidate (minor),

^{1}H NMR: δ: 1.00 (3H, t, J_{HH} 8.0 Hz, Me of C(O)Et),
2.43 (2H, q, J_{HH} 8.0 Hz, CH_2 of C(O)Et),

Other signals overlapping with those of the major product;

^{13}C NMR: δ: 8.3 (Me of C(O)Et),
13.5 (3 x Me of POEt),
36.9 (CH_2 of C(O)Et),
61.9 (d, J_{CP} 6.3 Hz, 3 x CH_2 of POEt),
176.5(CO);

(c) *Hexylation.* Oil. ***Hexyl-[N-(diethoxyphosphoryl)]-propionimidate*** and ***O,O-diethyl-O-hexyl-N-propionylphosphorimidate***,

^{1}H NMR: δ: The following signals of both compounds overlapped:
1.03 (3H, t, J_{HH} 7.4 Hz, Me of Hex),
1.10 - 1.27 (14H, m, 2 x Me of POEt, β-, γ-, δ-, ϵ-CH_2 of Hex),
3.90 - 4.15 (4H, m, 2 x CH_2 of POEt),
the following signals could be observed for individual products:
2.55 (2H, q, J_{HH} 7.6 Hz, CH_2 of C(O)Et of compound **43c**),
2.74, 2.77 (2H, 2q, J_{HH} 7.1 Hz, CH_2 of N=CEt of two stereoisomers of **41c**),
3.12 (2H, m, CH_2 of POHex of **43c**),

3.43, 3.45 (2H, 2q, J_{HH} 7.1 Hz, CH_2 of COHex of two stereoisomers of **43c**).

Alkylation of **21d**

(a) *Methylation.* Colourless solid, unstable when exposed to air. ***O,O-Diethyl-N-methyl-N-benzoylphosphoramidate***,

^{1}H NMR: δ: 1.89 (6H, t, J_{HH} 6.4 Hz, 2 x Me of POEt),
3.11 (3H, d, J_{HP} 7.7 Hz, NMe),
3.98 (4H, dq, J_{HH} 6.4 Hz, J_{HP} 7.1 Hz, 2 x CH_2 of POEt), 7.31 - 7.41 (3H, m, H_{meta}, H_{para}),
7.51 (2H, dd, J_{HH} 1.3, 7.9 Hz, H_{ortho});

^{13}C NMR: δ: 15.6 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),
29.7 (d, J_{CP} 25.1 Hz, NMe),
63.5 (d, J_{CP} 5.7 Hz, 2 x CH_2 of POEt),
128.3, 129.1 (C_{ortho}, C_{meta}),
132.1 (C_{para}),
136.2 (C_{ipso}),
173.1 (CO).

Alkylation of **21e**

(a) *Methylation.* Colourless oil. ***O,O-Diethyl-N-(ethoxycarbonyl)-N-methyl-phosphoramidate***,

^{1}H NMR: δ: 1.18 (3H, t, J_{HH} 7.1 Hz, Me of COEt),
1.22 (6H, t, J_{HH} 7.2 Hz, 2 x Me of POEt),
2.90 (3H, d, J_{HP} 7.9 Hz, NMe),
3.91 (4H, dq, J_{HH} 7.0 Hz, J_{HP} 8.3 Hz, 2 x CH_2 of POEt),
3.99 (2H, q, J_{HH} 7.1 Hz, CH_2 of COEt);

^{13}C NMR: δ: 13.8 (Me of COEt),
15.5 (d, J_{CP} 6.9 Hz, 2 x Me of POEt),
29.2 (d, J_{CP} 25.1 Hz, NMe),
62.1 (CH_2 of COEt),
63.2 (d, J_{CP} 5.7 Hz, 2 x CH_2 of POEt),
154.7(d, J_{CP} 6.6 Hz, CO).

(b) *Ethylation.* Colourless oil. ***O,O-Diethyl-N-(ethoxycarbonyl)-N-ethyl-phosphoramidate***,

^{1}H NMR: δ: 0.73 (3H, t, J_{HH} 6.9 Hz, Me of NEt),
0.83 (3H, t, J_{HH} 7.1 Hz, Me of COEt),

0.87 (6H, t, J_{HP} 7.1 Hz, 2 x Me of POEt),

3.15 (2H, dq, J_{HH} 6.9 Hz, J_{HP} 11.6 Hz, CH_2 of NEt),

3.66 (4H, dq, J_{HH} 7.1 Hz, J_{HP} 8.3 Hz, CH_2 of POEt);

3.75 (2H, q, J_{HH} 7.1 Hz, CH_2 of COEt);

^{13}C NMR: δ: 13.3 (Me of NEt),

14.4 (Me of COEt),

15.1 (d, J_{CP} 6.8 Hz, 2 x Me of POEt),

40.9 (CH_2 of NEt),

61.3 (CH_2 of COEt),

62.4 (d, J_{CP} 5.7 Hz, 2 x CH_2 of POEt),

153.6(d, J_{CP} 6.3 Hz, CO).

(c) *Hexylation.* Colourless oil. ***O,O-Diethyl-N-(ethoxycarbonyl)-N-hexyl-phosphoramidate***,

^{1}H NMR: δ: 0.62 (3H, t, J_{HH} 6.7 Hz, Me of NHex),

0.96 - 1.11 (17H, m, Me of COEt, 2 x Me of POEt, 4 x CH_2 of NHex),

3.27 (2H, dt, J_{HH} 7.8 Hz, J_{HP} 11.5 Hz, NCH_2 of NHex), 3.89 (4H, dq, J_{HH} 7.0 Hz, J_{HP} 10.7 Hz, 2 x CH_2 of POEt),

3.96 (2H, q, J_{HH} 7.0 Hz, CH_2 of COEt);

^{13}C NMR: δ: 13.4 (Me of NHex),

13.8 (ϵ-CH_2 of NHex),

15.5 (d, J_{CP} 6.9 Hz, Me of POEt),

22.0 (Me of COEt),

25.7 (δ-CH_2 of NHex),

29.6 (γ-CH_2 of NHex),

30.9 (β-CH_2 of NHex),

46.4 (d, J_{CP} 1.9 Hz, NCH_2 of NHex),

61.8 (CH_2 of COEt),

63.0 (d, J_{CP} 5.7 Hz, 2 x CH_2 of POEt),

154.3(d, J_{CP} 6.7 Hz, CO).

Alkylation of **21f**

(a) *Methylation.* Colourless oil. ***N-(Diethoxyphosphoryl)-N-methyl-N′,N′-di-ethylurea***,

^{1}H NMR: δ: 0.95 (6H, t, J_{HH} 7.1 Hz, 2 x Me of NEt),

1.13 (6H, t, J_{HH} 6.9 Hz, 2 x Me of POEt),

2.63 (3H, d, J_{HP} 9.7 Hz, NMe),

3.20 (4H, q, J_{HH} 7.1 Hz, 2 x CH_2 of NEt),

3.92 (4H, quint, J_{HH} 6.9 Hz, 2 x CH_2 of POEt);

^{13}C NMR: δ: 12.7 (2 x Me of NEt),

15.6 (d, J_{CP} 6.8 Hz, 2 x Me of POEt),

29.1 (d, J_{CP} 25.3 Hz, NMe),

41.8 (2 x CH_2 of NEt),

62.5 (d, J_{CP} 5.2 Hz, 2 x CH_2 of POEt),

157.9(J_{CP} 6.5 Hz, CO).

(b) *Ethylation.* Oil. ***N-(Diethoxyphosphoryl)-N-ethyl-N′,N′-diethylurea,***

^{1}H NMR: δ: 0.80 (3H, t, J_{HH} 7.0 Hz, Me of PNEt),

1.05 (6H, t, J_{HH} 7.1 Hz, 2 x Me of CNEt),

1.20 (6H, t, J_{HP} 7.0 Hz, 2 x Me of POEt),

3.28 (2H, m, CH_2 of PNEt),

3.41 (4H, q, J_{HH} 7.2 Hz, 2 x CH_2 of CNEt);

4.06 (4H, quin, J_{HH} 7.6 Hz, 2 x CH_2 of POEt).

(c) *Hexylation.* Oil. ***N-(Diethoxyphosphoryl)-N-hexyl-N′,N′-diethylurea,***

^{1}H NMR: δ: 0.80 (3H, t, J_{HH} 6.9 Hz, Me of NHex),

1.00 - 1.29 (20H, m, 2 x Me of NEt, 2 x Me of POEt,

4 x CH_2 of NHex),

3.27 (2H, m, NCH_2 of NHex),

3.37 (4H, q, J_{HH} 7.4 Hz, 2 x CH_2 of CNEt),

4.02 (4H, quin, J_{HH} 7.4 Hz, 2 x CH_2 of POEt).

* ***Crystal and Molecular Structure***

Data Collection and Processing

CAD4 diffractometer, $\omega/2\theta$ mode with ω scan width = 0.500 + 0.14 tanθ, variable but maximum ω scan speed 5.49 deg min^{-1}, graphite monochromated Cu-Kα radiation.

Structure Analysis and Refinement

Direct methods (SHELX86)[128] followed by standard difference Fourier and refinement methods using SHELX76.[129] Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and all hydrogen atoms included with a common isotropic thermal parameter that refined to the U_{iso} value (see **Table 8**). The hydrogen atoms of the NH_2 moiety of **48** were located experimentally, and were also refined without any restriction in these positions. Other hydrogens of **48** and **21b** were located in expected positions, and constrained to ride upon the associated heavy atoms during refinement. The hydrogens of **21d** were refined in experimentally located positions. Convergence was reached using $\sigma^{-2}(F_o)$ weights.

Atomic scattering factors were taken from SHELX. Fractional atomic coordinates, bond lengths, bond angles and anisotropic thermal parameters have been submitted to the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

Table 8: Crystallographic data acquisition and refinement details of compounds 21b, 21d, 48

Compound	21b	21d	48
Empirical formula	$C_6H_{14}NO_4P$	$C_{11}H_{16}NO_4P$	$C_5H_{13}N_2O_3P$
Molecular weight	195.2	257.2	180.1
Crystal dimension, mm	0.27 X 0.30 X 0.32	0.20 X 0.20 X 0.30	0.24 X 0.28 X 0.38
Space group (no.)	$P2_1/n$ (14)	$P2_1/c$ (14)	$P2_1/n$ (14)
Cell dimensions			
a, Å	8.040(1)	9.789(1)	8.343(1)
b, Å	15.430(1)	13.083(1)	9.249(1)
c, Å	8.683(1)	10.535(1)	12.413(1)
β, °	110.38(1)	102.30(1)	102.06(1)
Z	4	4	4
Volume, $Å^3$	1009(1)	1318(1)	937(1)
D(calc), $g \cdot cm^{-3}$	1.28	1.29	1.28
μ, cm^{-1}	21.8	17.9	22.6
Radiation (λ, Å)	CuK_α, 1.5418	CuK_α, 1.5418	CuK_α, 1.5418
T, °C	24	24	23
F(000)	416.0	544.0	384.0

Cell dimensions			
Scan type (ω:2θ)	1 : 1	1 : 1	1 : 1
Scan Range ,θ°	5<θ<76	5<θ<76	5<θ<76
Zone collected:			
h	0, 10	-12.12	0, 10
k	0, 19	0, 16	0, 11
l	-10, 10	0, 13	-15, 15
Maximum scan speed (variable, deg.min^{-1})	5.49	5.49	5.49
Maximum scan time, sec.	60	60	60
Scan angle (ω + domb tan θ)°	0.51, 0.14	0.43, 0.14	0.50, 0.14
Aperture size ,mm	1.3 X 4.0	1.3 X 4.0	1.3 X 4.0
Reflections collected	2345	3027	2228
Decay, %	10.4 corrected	3.1	4.3
Unique reflections used (F>)	1612, 3 σ(I)	2339, 3 σ(I)	1705, 3 σ(I)
R_{int}	0.192	0.019	0.020[130]
Parameters refined	119	203	113
Max. positional shift/esd	2.01	0.26	0.27
Residual electron density ,eÅ^{-3}:			
Maximum	0.64	0.21	0.42
Minimum	-0.97	-0.28	-0.31
U_{iso}(H), Å^2	0.228(17)	0.129(4)	0.200(7)
R	0.123	0.050	0.061
R_w	0.106	0.044	0.052

CHAPTER 4

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