

**I New Routes to the Generation of Alkyl  
Metaphosphates in Solution**

**and**

**II Synthesis of Novel Phosphorus-containing Scale  
Inhibitors for Use in Oil-field Operations**

**by**

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*To my Parents and to Sarah*

## Abstract

The work described in part I of this thesis is concerned with the development of a number of approaches designed to generate alkyl metaphosphates in solution. In each approach the final reaction step involves the crucial breakdown of a suitable precursor with a  $\sigma$ -bond being both broken and formed at a central phosphorus atom.

Two main routes to alkyl metaphosphates were investigated. The first involved the condensation of a novel disodium pyrocarbonate salt with alkyl dichlorophosphates to form cyclic pyrocarbonate phosphates. These novel cyclic phosphates then underwent chelotropic breakdown with the release of two moles of carbon dioxide to produce alkyl metaphosphates. The second route investigated involved the condensation of potassium hydrogen carbonate with an alkyl dichlorophosphate to form a mixed anhydride. Upon warming breakdown of the mixed anhydride occurred, with the release of one mole each of hydrogen chloride and carbon dioxide to produce alkyl metaphosphates.

In each case when the reactions were repeated in the presence of epoxides, the alkyl metaphosphates were trapped with the formation of 1,3,2-dioxaphospholane-2-oxides. This reaction was valuable in providing evidence for the intermediacy of alkyl metaphosphates and demonstrated unequivocally their high electrophilic character.

$^{31}\text{P}$  NMR spectroscopy was found to be an invaluable tool for following the course of the reactions being investigated. This was demonstrated by the fact that when alkyl metaphosphates were formed in the absence of trapping reagents, self-condensation occurred to give linear and cyclic polyphosphates which were easily identified by  $^{31}\text{P}$  NMR signals in the  $\delta$  -10 and -20 ppm regions. When trapping by epoxides was carried out these signals were replaced by a closely matched pair of peaks in the range  $\delta$  16-18 ppm which were unique to diastereomeric mixtures of cyclic phosphates having five membered rings.

The work described in part II of this thesis is concerned with the synthesis of a variety of polyphosphonic acids and investigations into their properties as scale inhibitors for oil-field water systems. The phosphonic acids concerned were based on the heterocyclic systems 2-imidazolidinone and cyanuric acid. The chemistry involved the initial functionalisation of the acidic *N-H* bonds of the heterocycles followed by conventional methods of phosphonic acid synthesis. The novel phosphonic acids thus prepared were tested for their scale inhibition properties by a technique called the "static precipitation test" developed by British Petroleum.

## Acknowledgements

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Thanks must also be given to the departmental technical staff for their excellent provision of services. In particular, I would like to thank Mr. J. R. Miller for his patience, and his efforts in keeping the  $^{31}\text{P}$  NMR machine operational.

I would also like to mention my colleagues from Lab. 64 and thank them for their friendship, and for making my Ph.D. extremely enjoyable.

Special thanks are due to my parents for their continuous support and encouragement throughout my education.

Finally, I would like to thank Sarah for her love and encouragement. Without her support I am confident this thesis would never have been written.

## Courses Attended

The following is a statement of the courses attended during the period of research:

Organic Research Seminars, various speakers, Department of Chemistry, University of Edinburgh (3 years attendance).

Current Developments in Organic Chemistry, various speakers, Department of Chemistry, University of Edinburgh.

Merck, Sharp and Dohme, Medicinal Chemistry Lectures, Prof. R. Baker *et al*, Department of Chemistry, University of Edinburgh.

Recent advances in the Synthesis and activity of Agrochemicals, Schering Agrochemicals, various speakers, Department of Chemistry, University of Edinburgh, 1992.

Discovery Development and Pharmacology of Zoladex for treatment of Prostate Cancer, I.C.I. Pharmaceuticals, various speakers, Department of Chemistry, University of Edinburgh.

Aspects and Applications of NMR Spectroscopy, Dr. I. Sadler *et al*, Department of Chemistry, University of Edinburgh.

XIIth International Conference of Phosphorus Chemistry, Toulouse,  
France, July 1992.

Royal Society of Chemistry, Perkin Division, Annual Scottish  
Meeting (3 years attendance).

## Symbols and Abbreviations

<b>Ar</b>	aromatic
<b><math>[\alpha]_D</math></b>	specific rotation
<b>Bp</b>	boiling point
<b>b</b>	broad
<b>°C</b>	degrees Celsius
<b>cm</b>	complex multiplet
<b>d</b>	doublet
<b><math>\delta</math></b>	chemical shift
<b>DCM</b>	dichloromethane
<b>DMAP</b>	4-dimethylaminopyridine
<b>DME</b>	dimethoxyethane
<b>eq</b>	equivalents
<b>FAB</b>	fast atom bombardment
<b>IR</b>	infra-red
<b>J</b>	spin-spin coupling constant
<b>lit</b>	literature value
<b>m</b>	multiplet
<b>M</b>	$\text{mol dm}^{-3}$
<b>M<sup>+</sup></b>	molecular ion
<b>mmol</b>	millimoles
<b>mol</b>	moles

<b>Mp</b>	melting point
<b>MS</b>	mass spectrometry
<b>m/z</b>	mass to charge ratio
<b>NMR</b>	nuclear magnetic resonance spectroscopy
<b>ppm</b>	parts per million
<b>s</b>	singlet
<b>symm</b>	symmetrical
<b>THF</b>	tetrahydrofuran
<b>TFA</b>	trifluoroacetic acid
<b>TLC</b>	thin layer chromatography
<b>t</b>	triplet
<b>q</b>	quartet
<b>quat</b>	quaternary
<b><math>\nu_{\max}</math></b>	wave numbers pertaining to maximum absorbance

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**Part 1. New Routes to the**  
**Generation of Alkyl**  
**Metaphosphates in Solution**

# **Chapter One**

## **An Introduction to the Metaphosphate Species**

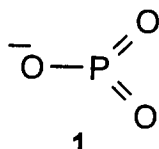
# Chapter One

## Contents

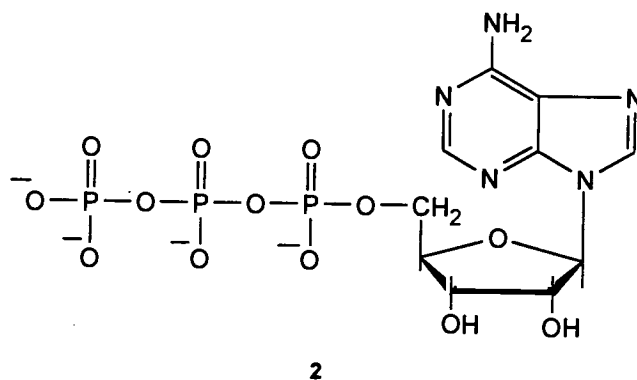
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## 1.1 The Metaphosphate Species

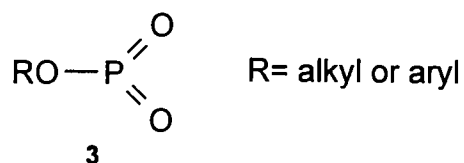
The metaphosphate species was first postulated in 1955 when Westheimer<sup>1</sup> and Bunton<sup>2</sup> independently proposed that the mechanism of hydrolysis of phosphate monoesters involved the intermediacy of the monomeric metaphosphate ion **1**. Since that time a great deal of effort



has been devoted to the study of mechanistic and synthetic aspects of metaphosphate chemistry, mainly due to the fundamental importance of phosphate esters and anhydrides to life itself. For example, DNA and RNA which carry the genetic codes are phosphate diesters, and the principle reservoir of biochemical energy, adenosine triphosphate (ATP) **2** is a phosphoric acid anhydride. Many intermediary metabolites are phosphate esters, phosphates or pyrophosphates and are essential intermediates in biochemical pathways<sup>3</sup>.



As well as the biochemical aspects of metaphosphate chemistry much effort has been made to exploit the electrophilic nature of alkyl or aryl metaphosphates **3** by the synthetic organic chemist, particularly for



the phosphorylation of organic compounds with suitable functional groups. It has been shown that alkyl metaphosphates are powerful electrophiles which can phosphorylate alcohols<sup>4-7</sup>, amines<sup>8-10</sup>, epoxides<sup>11</sup>, and carbonyl<sup>12</sup> compounds. They have been extremely useful with systems which under normal circumstances would prove extremely difficult to phosphorylate such as tertiary alcohols<sup>4-6,13</sup>, *e.g.* *t*-butanol, electron-rich carbons in anilines<sup>8,14</sup> and pyrroles<sup>15</sup>, and aromatic substrates, *e.g.* naphthol<sup>16,17</sup>.

It is therefore clearly crucial to understand the importance of metaphosphates to biochemistry and organic synthesis. Such is the interest in metaphosphates that since 1981 there have been three reviews on the subject<sup>18-20</sup>.

## 1.2. The Metaphosphate Ion

Although the metaphosphate ion **1** was first postulated in 1955 as an intermediate in the hydrolysis of phosphate monoesters<sup>1,2</sup>, it was not observed directly until 1979 when the mass spectrum of certain phosphate pesticides displayed an intense peak at  $m/e = 78.9580$ , which was unequivocally assigned to the metaphosphate ion<sup>21,20</sup>. In the same year its infrared spectrum was also observed in a low-temperature argon matrix as its sodium salt,  $\text{NaPO}_3$ . From analysis of the bands in the infrared spectrum, the species was proven to be a trigonal, planar molecule with  $C_{2v}$  symmetry<sup>23,24</sup>. The fact that it took such a considerable length of time to observe the metaphosphate ion is attributed to the fast reaction of nucleophiles with the phosphorus centre to form derivatives of monomeric metaphosphoric acid,  $\text{HPO}_3$ .

### 1.2.1 Hydrolysis of monoesters of phosphoric acid

Monoesters of phosphoric acid show a characteristic dependence of their rate of hydrolysis upon the pH of the solution<sup>25</sup>. A pH rate profile (Figure 1) shows that the maximum rate of the hydrolysis is around pH 4. This is due to specific reaction of the monoester anion **4**, which exists exclusively under these conditions and leads to the formation of **1**. Three possible mechanisms for the formation of **1** have been postulated as outlined in Scheme 1. The first, proposed by Westheimer<sup>1</sup>, occurs *via* a six-membered anion/water complex **5**, the second<sup>26</sup> is an intramolecular

proton transfer *via* a four-membered ring 6, and the third<sup>27</sup> is *via* the formation of the zwitterion 7. All occur with the loss of one molecule of alcohol.

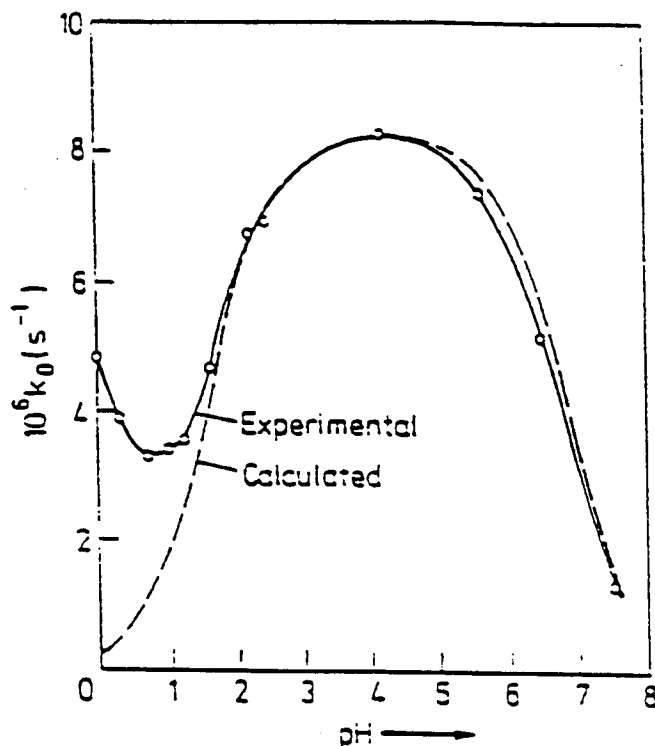
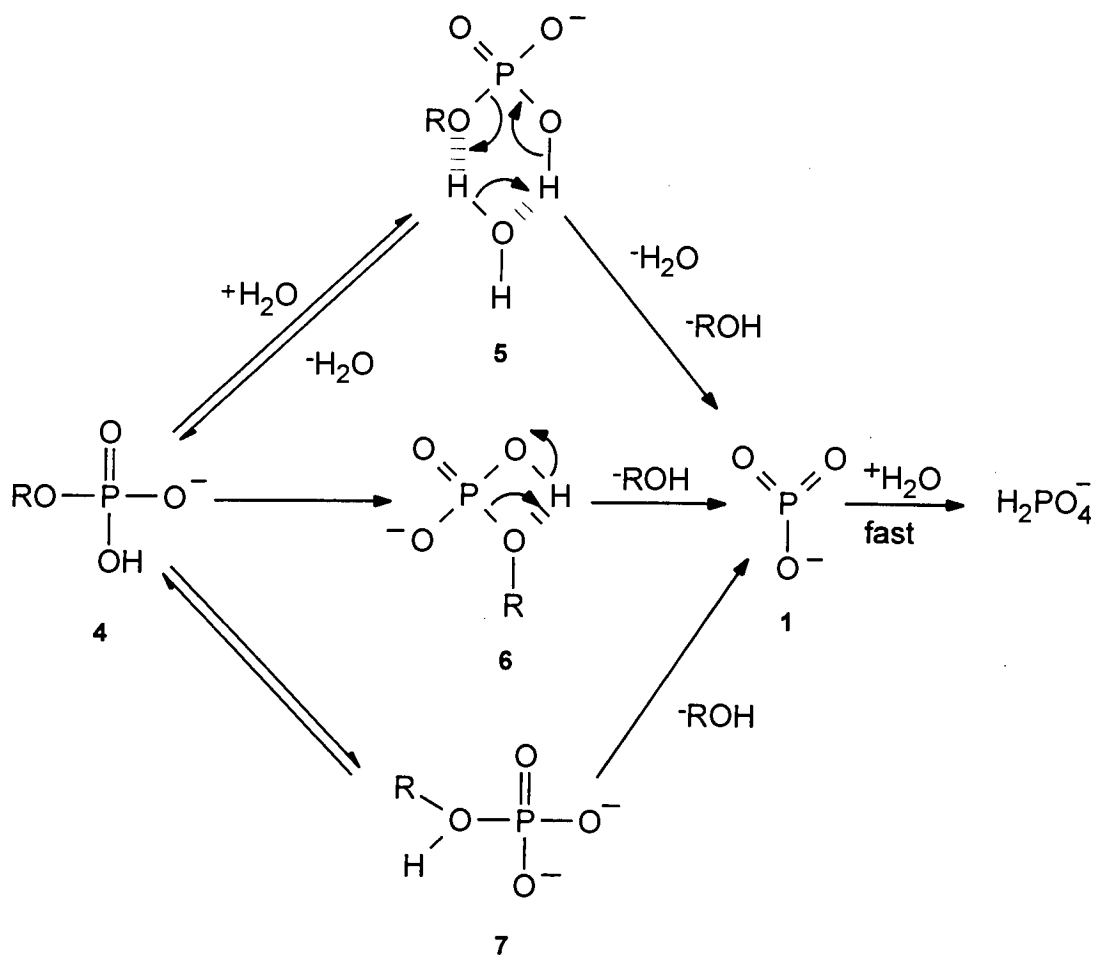


Figure 1. pH-rate profile for the hydrolysis of methyl phosphate at 100°C.

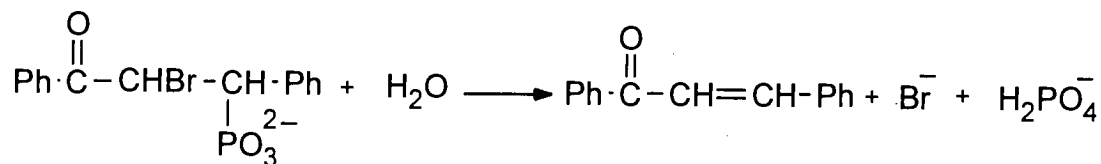
Since the intermediacy of the metaphosphate ion in the hydrolysis of the phosphate esters was first proposed, many detailed kinetic studies have been carried out in support of its intermediacy, and for a detailed discussion of the experimental results, the review article by Regitz and Haas<sup>19</sup> as well as that by Meisel<sup>20</sup> should be consulted.



Scheme 1. Proposed mechanistic pathways for the hydrolysis of monoesters of phosphoric acid.

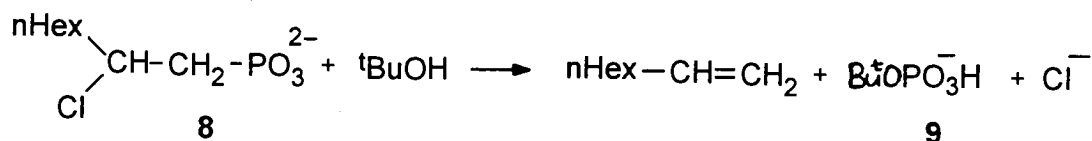
### 1.2.2 Base cleavage of $\beta$ -halophosphonic acids

In the 1920s Conant and co-workers<sup>28-31</sup> synthesised several  $\beta$ -halophosphonates and phosphinates and found that they decomposed in alkaline aqueous solution as shown in Scheme 2. The reaction was later



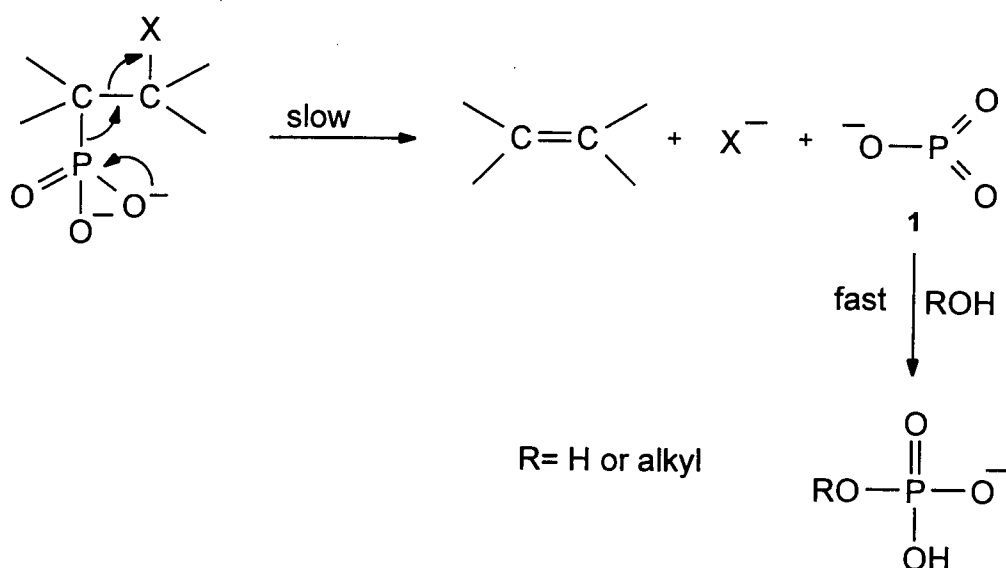
Scheme 2

investigated in 1963 by Maynard and Swan<sup>32,33</sup> who studied the reaction of 2-chlorooctylphosphonate **8** with *tert*-butanol which yielded *tert*-butylphosphate **9** and 1-octene (Scheme 3). Conventional methods to



Scheme 3

prepare phosphate esters of tertiary alcohols are not always simple or successful and the most convincing explanation for the observed reaction products is that the reaction proceeded by way of fragmentation of the  $\beta$ -halophosphonate to olefin, chloride ion and the metaphosphate ion, followed by nucleophilic attack of the alcohol on the metaphosphate ion (Scheme 4).



Scheme 4. Mechanism for the fragmentation of  $\beta$ -halophosphonates

The Conant-Swan fragmentation, as the reaction has now come to be known, occurs stereospecifically *via* a *trans*-elimination<sup>34,35</sup>. Thus, the *erythro* substrate gives the (*E*)-olefin whilst the *threo* isomer forms the (*Z*)-olefin. The fragmentation of  $\beta$ -halophosphonic acids is not limited to aqueous media. It was later shown that the fragmentation of 1-phenyl-1,2-dibromopropylphosphate also takes place in acetonitrile in the presence of amines like cyclohexylamine or triethylamine<sup>34</sup>.

### 1.2.3 Reactivity of the metaphosphate ion

Since the first suggestions for the existence of the metaphosphate ion, only indirect evidence for its existence in solution has been put forward. A simple rationale for this is that the metaphosphate ion is too transient and reacts too rapidly to be detected directly. In many solvolysis reactions, the metaphosphate ion reacts rapidly to phosphorylate water, alcohols, amines or phosphate ions. Since the metaphosphate ion is isostructural with the nitrate ion, this pronounced reactivity needs to be explained. From molecular orbital studies<sup>36,37</sup> it has been shown that the electrophilic reactivity of the metaphosphate ion is orbital-controlled and results from an *anti*-bonding  $\sigma^*$  orbital which has an energy so low that it becomes almost energetically comparable with the *anti*-bonding  $\pi^*$  orbital (Figure 2). This is not the case with the nitrate ion where there is no such similarity of the respective  $\sigma^*$  and  $\pi^*$  *anti*-bonding orbitals. The electrophilic reactivity of the metaphosphate ion can be understood in terms of an interaction between an occupied donor orbital and the unoccupied  $\sigma^*$  and  $\pi^*$  orbitals of the metaphosphate ion in the way of a 3-orbital-2-electron interaction. Attack by the donor orbital allows efficient mixing of energetically similar  $\sigma^*$  and  $\pi^*$  orbitals leading to a new strongly bonding MO of low energy. No such HOMO-LUMO interaction is possible in the nitrate ion due to the high energy of the  $\sigma^*$ . Moreover, in the case of the metaphosphate ion, electron density

at phosphorus will allow better interactions of the metaphosphate ion with nucleophiles than is the case of the nitrate ion.

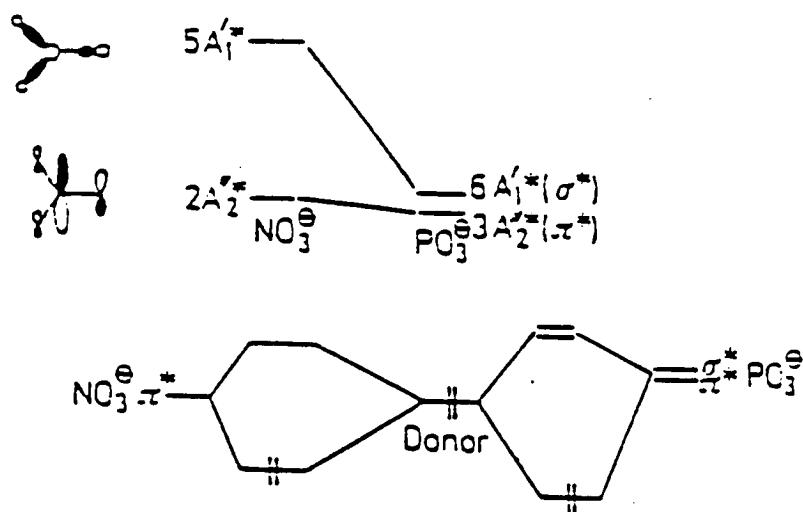
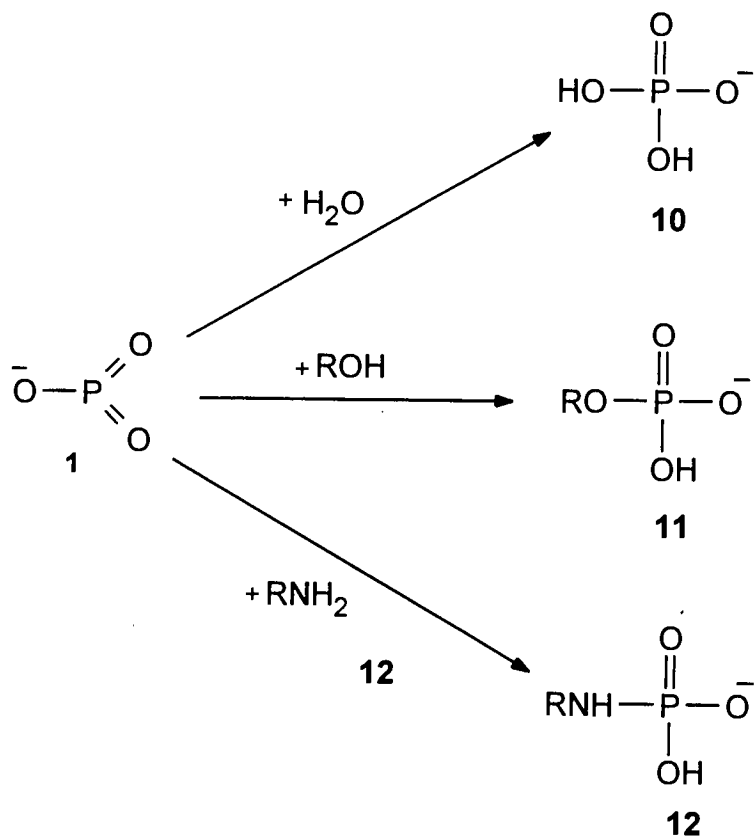


Figure 2. Top:  $\pi^*$  and  $\sigma^*$  orbitals in the nitrate and metaphosphate ions; Bottom: Interaction between occupied donor orbital and unoccupied acceptor orbitals of the nitrate and metaphosphate ions.

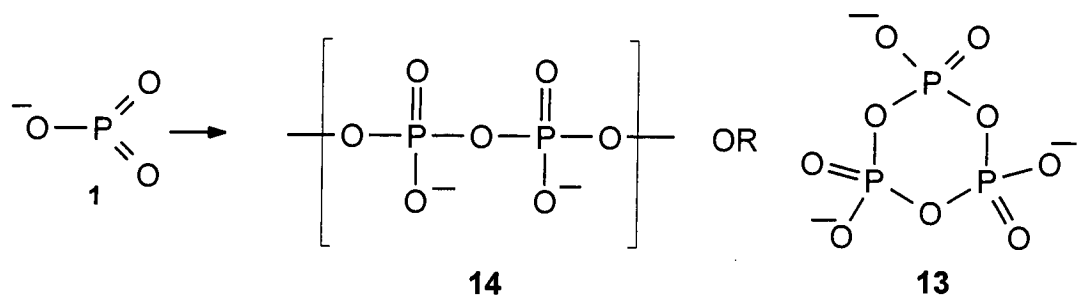
#### 1.2.4 Phosphorylation reactions with the metaphosphate ion

Owing to the high electrophilic character of the metaphosphate ion it will phosphorylate most functional groups containing a lone pair. Typical reactions of the metaphosphate ion are those with water<sup>1,2</sup>, alcohols<sup>38</sup> and amines<sup>39,40</sup>, which yield phosphates 10, alkylphosphates 11 and phosphoramidates 12, respectively (Scheme 5).



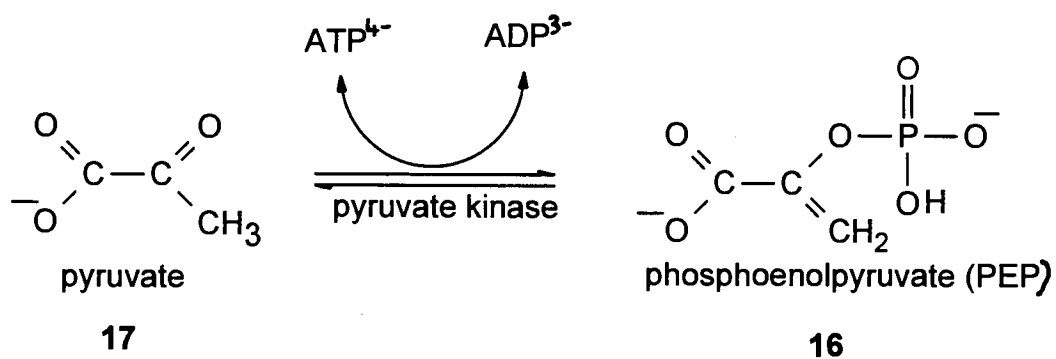
Scheme 5. Some typical reactions of the metaphosphate ion 1.

It is of interest to note that the metaphosphate ion is so reactive that when it is formed in the absence of a substrate it readily undergoes self-condensation to form cyclic oligomers such as 13 or linear polymeric species 14 having *P-O-P* bonds, the nature of the reaction depending on the rate of formation of the metaphosphate ion<sup>4</sup> (Scheme 6). These products can be easily identified by their characteristic chemical shifts in the <sup>31</sup>P NMR spectrum<sup>8</sup>.

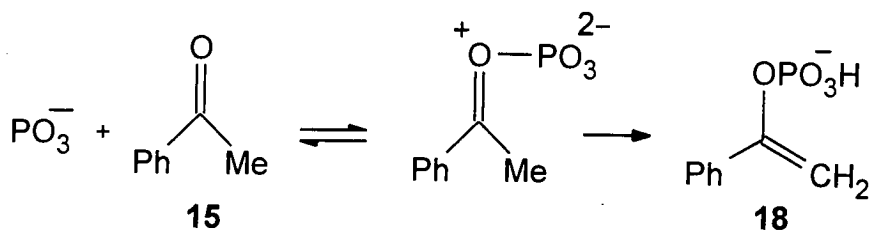


Scheme 6. Self-condensation products of the metaphosphate 1 ion in the absence of a substrate.

The reaction between the metaphosphate ion and acetophenone<sup>41</sup> 15 is formally analogous to the biochemical process involving the formation of phosphoenolpyruvate 16 from ATP and pyruvate<sup>42,43</sup> 17 (Scheme 7). When the metaphosphate ion is generated in the presence of acetophenone, the corresponding enol phosphate 18 is formed (Scheme 8).

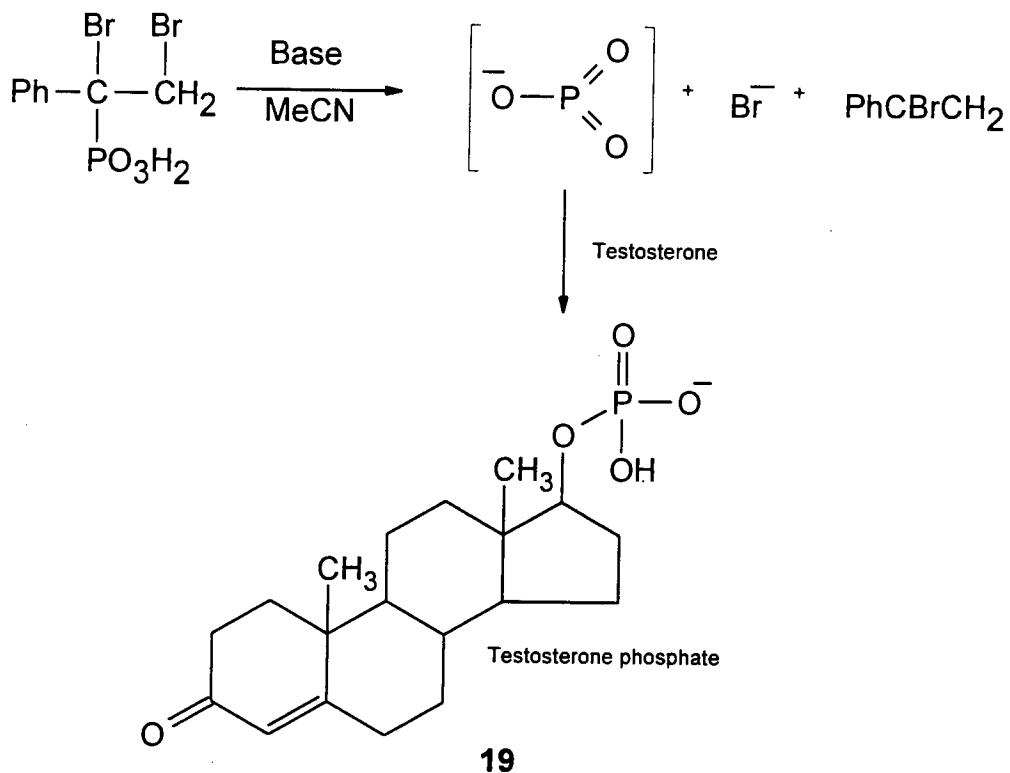


Scheme 7. Formation of phosphoenolpyruvate (PEP) 16 from ATP and Pyruvate 17.



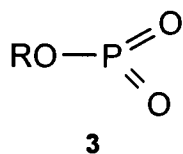
Scheme 8

The synthetic capabilities of the metaphosphate ion have also been illustrated by the phosphorylation of sensitive and valuable alcohols. Ramirez<sup>9</sup> managed to obtain steroidal phosphates from the reaction of steroids with the metaphosphate ion generated by the Conant-Swan method. In this way the phosphates of cholesterol, ergosterol and testosterone have been prepared. Scheme 9 illustrates the synthesis of the phosphate of testosterone **19**.



Scheme 9. Phosphorylation of testosterone by the metaphosphate ion.

### 1.3. Alkyl Metaphosphates



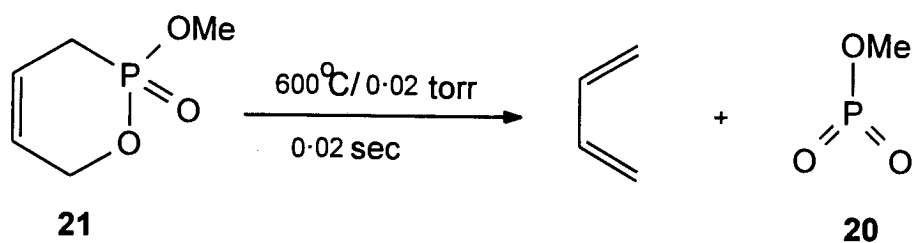
Alkyl metaphosphates **3** (or metaphosphoric esters) are simply esters of metaphosphoric acid,  $\text{HOPO}_2$ . As with the metaphosphate ion

they are non-isolable, and even more electrophilic, making them highly reactive intermediates<sup>20</sup>. They can be generated in the gas phase or in solution by thermal or photochemical fragmentations of suitably activated phosphates.

### 1.3.1 Synthesis

#### 1.3.1.1 Generation of alkyl metaphosphates in the gas phase

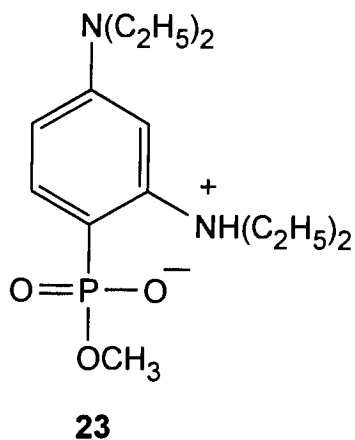
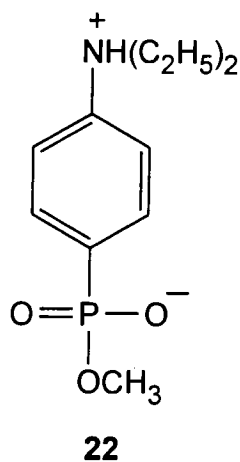
The first example of the generation of an alkyl metaphosphate was that of methyl metaphosphate **20** by Clapp and Westheimer<sup>8</sup> in 1974. They prepared methyl 2-butenylphosphonate **21**, and its subsequent flash vacuum pyrolysis (FVP) in the gas phase at 650°C, led to **20** and butadiene *via* a retro-Diels Alder reaction (Scheme 10).



Scheme 10

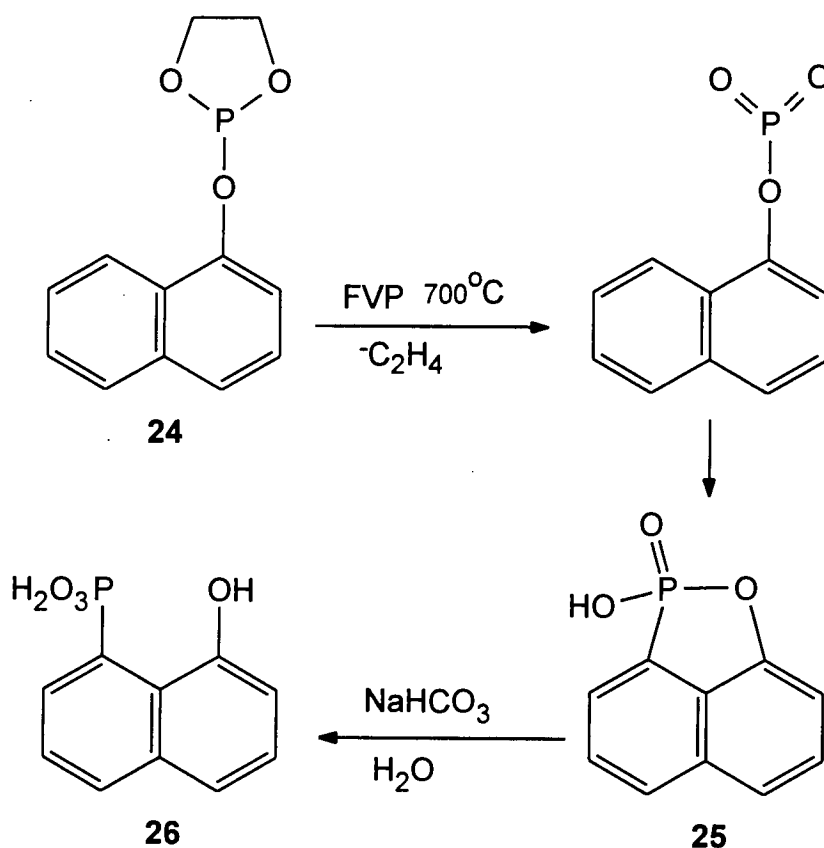
In the absence of a trapping agent most of the phosphorus-containing fragments in the nitrogen-cooled trap appeared as pyrophosphate, cyclic

and linear polymeric phosphates. However, when the gas stream containing the pyrolysis products was introduced into a solution of diethylaniline or *N,N,N',N'*-tetraethyl-*m*-phenylenediamine, compounds **22** and **23** were isolated<sup>8</sup>. These products are those of electrophilic attack of monomeric methyl metaphosphate on the aromatic ring, a prime example of the powerful electrophilicity of monomeric alkyl metaphosphates.



Other starting compounds for the generation of alkyl metaphosphates by pyrolysis are the aryl phosphites<sup>16,17</sup> such as **24**. During pyrolysis of **24**, loss of ethylene occurs and the aryl metaphosphate generated inserts into an aromatic *C-H* bond to form the cyclic phosphonic ester **25** (Scheme 11). Further reaction of **25** with

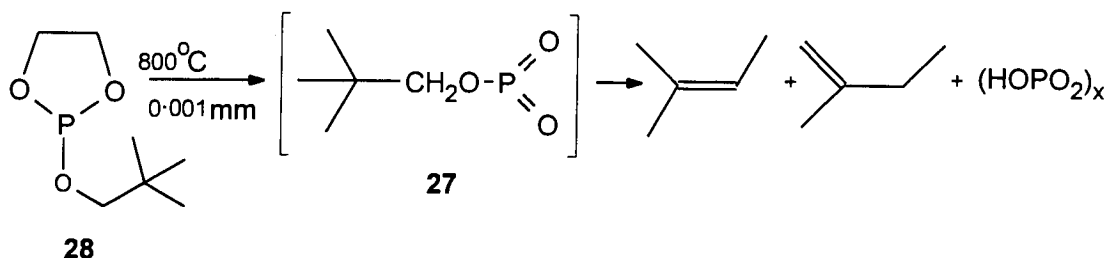
aqueous sodium hydrogen carbonate yielded the phosphorylated naphthol **26**. This is yet another example of the high electrophilicity of alkyl metaphosphates since phosphorylation of aromatics is normally an extremely difficult process.



Scheme 11. Generation of aryl metaphosphates by pyrolysis of aryl phosphites.

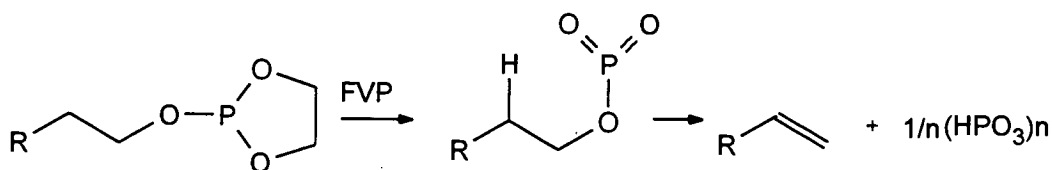
The FVP approach was also used to generate neopentyl metaphosphate **27** from neopentyl phosphite<sup>44</sup> **28**, but under the conditions required, this substance underwent elimination of

metaphosphoric acid with the formation of an isomeric mixture of 2-methylbutenes. As expected the resulting metaphosphoric acid underwent polymerisation (Scheme 12).



Scheme 12

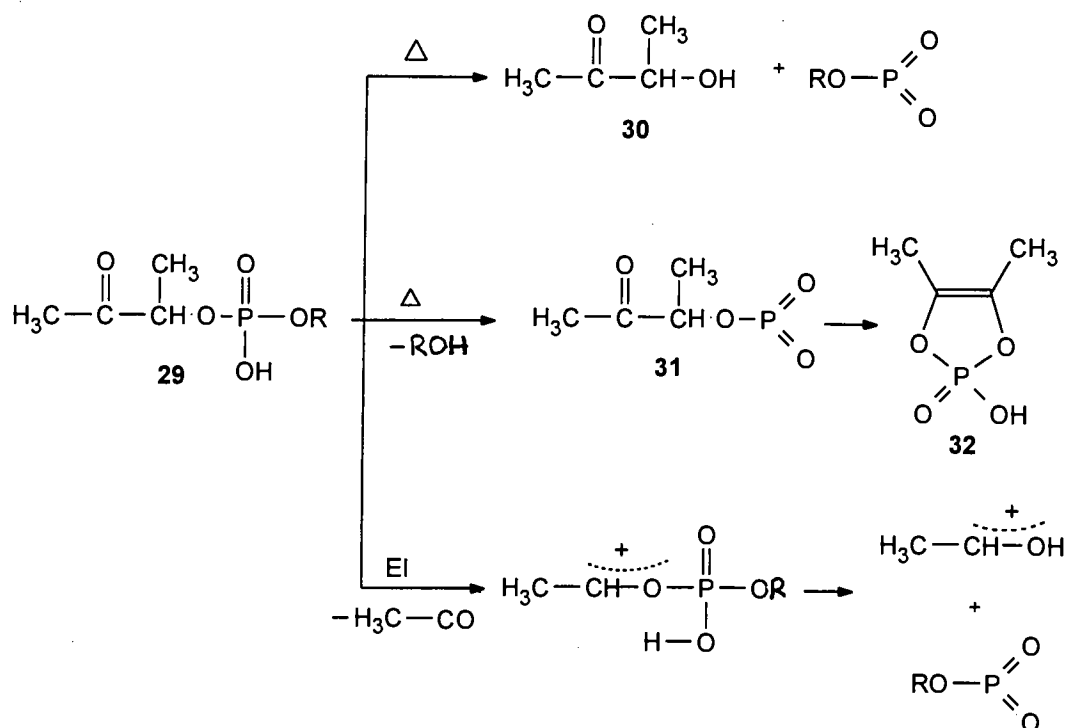
The reaction is typical of the vacuum pyrolysis of alkyl or aryl phosphites when they contain an abstractable  $\beta$ -hydrogen. The initially formed metaphosphate intermediate fragments *via a*  $\beta$ -elimination pathway to give an alkene and monometaphosphoric acid which then polymerises (Scheme 13). However, this rearrangement only occurs in the gas phase since it will be seen later that these metaphosphates are actually trappable in solution.



Scheme 13

The last example of the generation of metaphosphates is that of the gas-phase fragmentation of 3-oxo-2-butyl phosphate **29** in the mass spectrometer<sup>45</sup> (Scheme 14). For example, **29** decomposes thermally ( $\text{ca} \sim 200^\circ\text{C}$ ) into acetoin **30** and alkyl metaphosphate, with both fragments appearing in the mass spectrum. Thermal dehydration of **29** to acetoin metaphosphate **31** and its rapid isomerisation into the cyclic enediol phosphate **32** is also envisaged, although not all the details are confirmed. Under EI conditions **29** yields a fragment  $\text{C}_2\text{H}_6\text{O}_4\text{P}^+$  which decomposes to give  $\text{C}_2\text{H}_5\text{O}^+$  and once again alkyl metaphosphates. Mass spectrum fragmentation patterns suggesting elimination of alkyl metaphosphates have also been observed with other compounds<sup>46-48</sup>.

The intramolecular products described in this section (1.3.1.1) could not have been anticipated from the solution chemistry known for metaphosphates (sections 1.3.1.2 and 1.3.2). It might be expected that other novel intramolecular reactions of metaphosphates in the gas phase will be encountered in the future, adding another dimension to the practical aspects of metaphosphate chemistry.

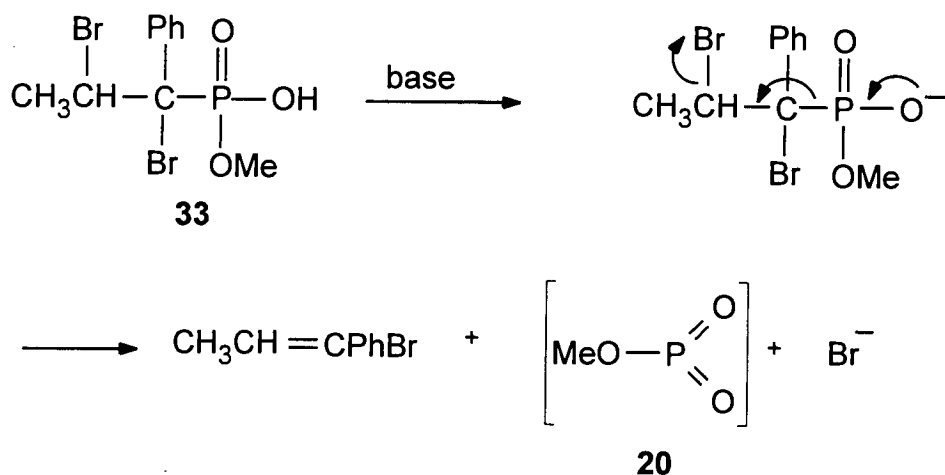


Scheme 14. Gas phase fragmentation of 3-oxo-2-butyl phosphate 28 in the mass spectrometer

### 1.3.1.2 Generation of alkyl metaphosphates in solution

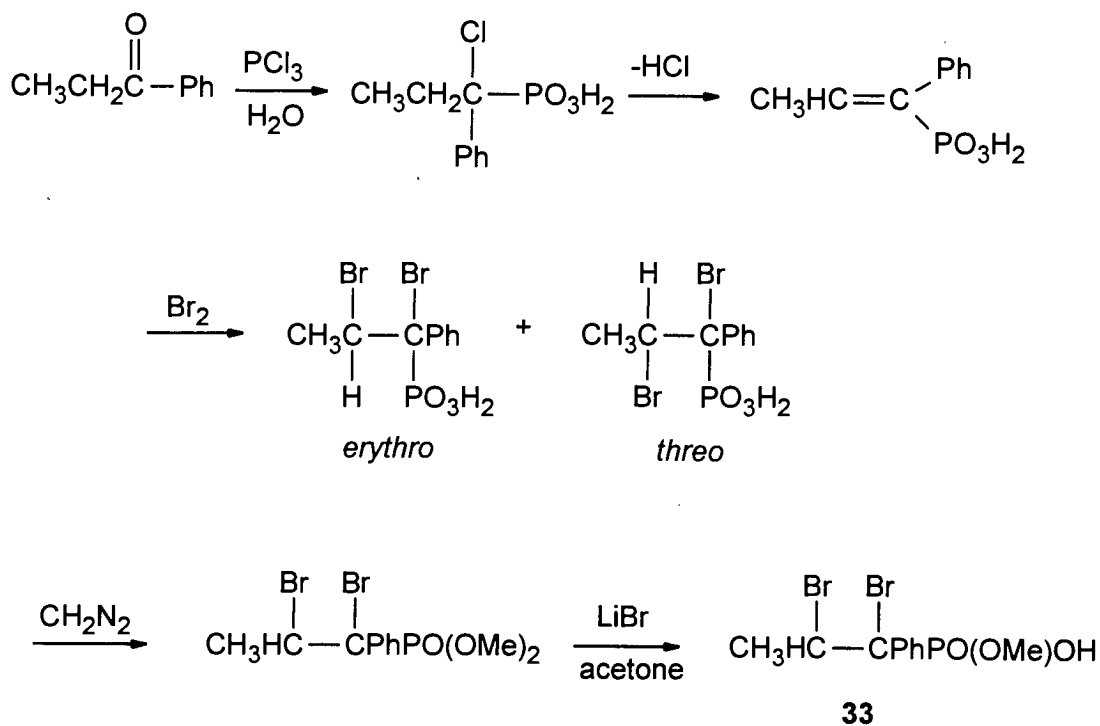
One of the earliest methods for the generation of the metaphosphate ion in solution was the fragmentation of  $\beta$ -haloalkylphosphonate dianions. The reaction was discovered by Conant<sup>28-31</sup>, and later recognised by Swan<sup>32,33</sup>, to proceed through elimination of the metaphosphate ion; since then, it has since become known as the Conant-Swan reaction (Section 1.2.2). In 1978 this reaction was successfully

extended to generate methyl metaphosphate<sup>20</sup> **20** by heating methyl hydrogen 1-phenyl-1,2-dibromopropylphosphonate **33** in acetonitrile at 70°C for 6-10hrs (Scheme15). As in previous studies on the generation of



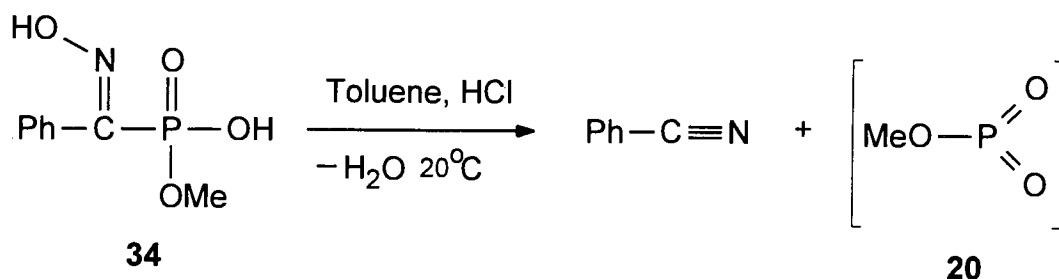
Scheme 15. Conant-Swan generation of methyl metaphosphate **20**.

methyl metaphosphate, aromatic tertiary amines were present as trapping agents, and the reaction yielded phosphorylated aromatic compounds, an indication of a powerful phosphorus electrophile being present, *i.e.* methyl metaphosphate **20**. This method of generation of alkyl metaphosphates is more of historical importance than practical use due to the numerous steps required for the synthesis of the precursor, and also the low to modest yields obtained in each step (Scheme 16).



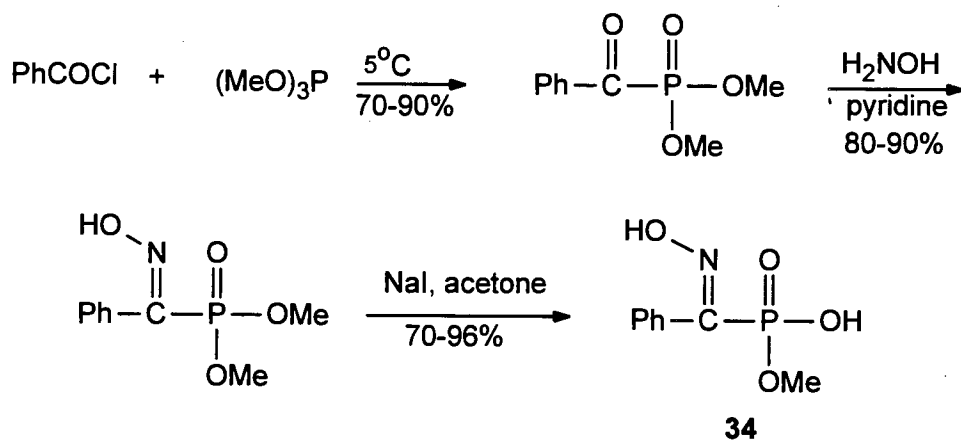
Scheme 16. Synthesis of methyl hydrogen 1-phenyl-1,2,-dibromopropylphosphonate **33**.

Another type of phosphate that undergoes a fragmentation reaction to yield metaphosphates are alkyl-oximinobenzylphosphonates such as **34**. As with the Conant-Swan reaction, these phosphonates undergo cleavage of the *C-P* bond, but as first introduced, this method required the action of hydrochloric acid on an alcoholic solution of the phosphonate<sup>49,50</sup> to protonate the hydroxyl group on nitrogen, thus allowing facile cleavage of the *N-O* bond<sup>13</sup>. In a later development, alcohol was replaced as solvent by inert toluene, (Scheme 17), allowing the metaphosphate formed to act as a phosphorylating agent<sup>7</sup>. It is important to note that when *tert*-butanol was used as solvent, the alcohol



Scheme 17

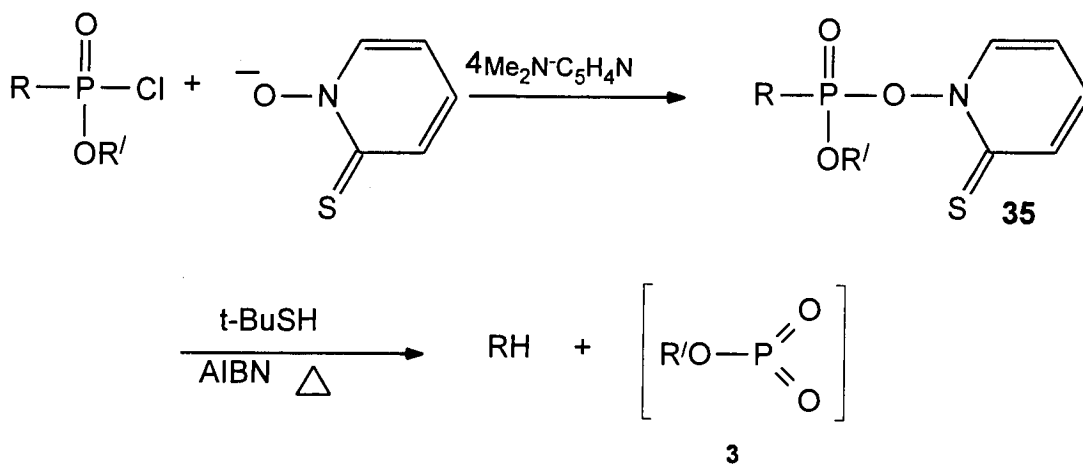
was phosphorylated<sup>13</sup>, which again indicates the presence of an extremely powerful phosphorylating agent. The synthesis of phosphonate **34** is outlined in Scheme 18, which shows that the yields are high and that only three steps are required.



Scheme 18. Synthesis of methyl-oximinobenzylphosphonate **34**.

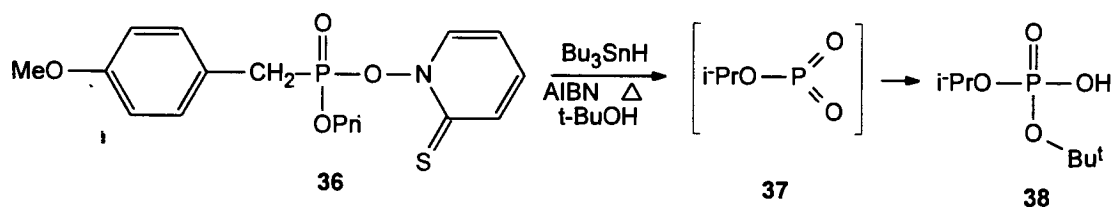
The fragmentation of oximinophosphonates such as **34** is virtually quantitative and the method has considerable practical value as a source of metaphosphates. However, one possible drawback, depending on the character of the substrate to receive the metaphosphate, is the high acidity of the medium required to generate the simple alkyl derivatives. This problem has recently been solved by the introduction of a photochemical method for cleavage of the oximinophosphonate<sup>51</sup>. This approach requires the presence of a photo-cleavable *O*-substituent on phosphorus, and it was found that both *O*-benzyl and *O*-nitrobenzyl groups are suitable. The photolyses were performed at room temperature in dioxane solutions and this method has considerable potential for performing phosphorylations under milder conditions, without the presence of harmful acidic or basic reagents.

A further example of the fragmentation of phosphonates that yields metaphosphate intermediates is one in which the *C-P* cleavage proceeds through a phosphonyl radical intermediate<sup>6</sup>. The phosphonates that have been used in this study include **35**, which contains a relatively weak *N-O* bond. When heated in benzene with AIBN as a radical initiator, together with *tert*-butylmercaptan as a chain propagator/radical quencher, metaphosphates are formed which are intercepted by a suitable trapping agent (Scheme 19).



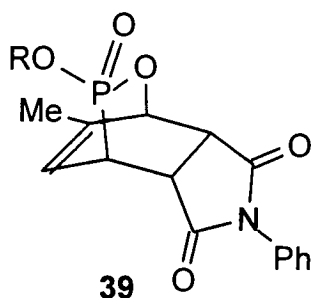
Scheme 19

The most convincing evidence for the intermediacy of metaphosphate in this reaction occurred when the phosphonate **36** was fragmented in the presence of *tert*-butanol (Scheme 20). The subsequent isolation of isopropyl *tert*-butyl phosphate **38** was indicative of the intermediacy of isopropyl metaphosphate **37**, the first instance of the synthesis of this compound, and another example of the practical value of metaphosphates.

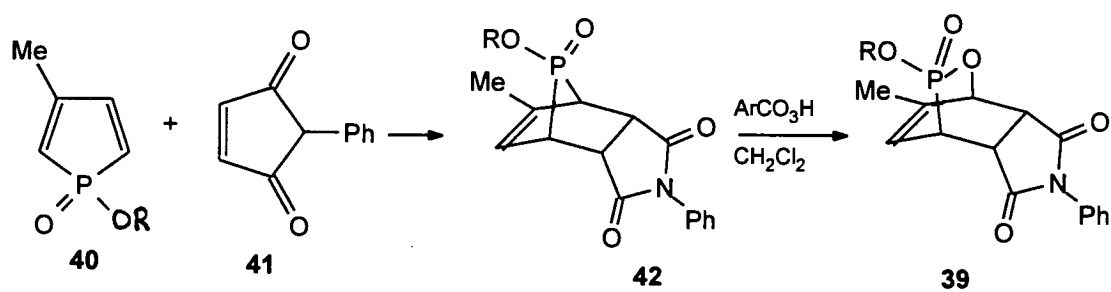


Scheme 20

Over the last decade the leading practitioner of alkyl metaphosphate chemistry has been L.D. Quin. Quin observed that thermal degradation of the 2,3-oxaphosphabicyclo[2,2,2]octene ring system **39** can lead to the

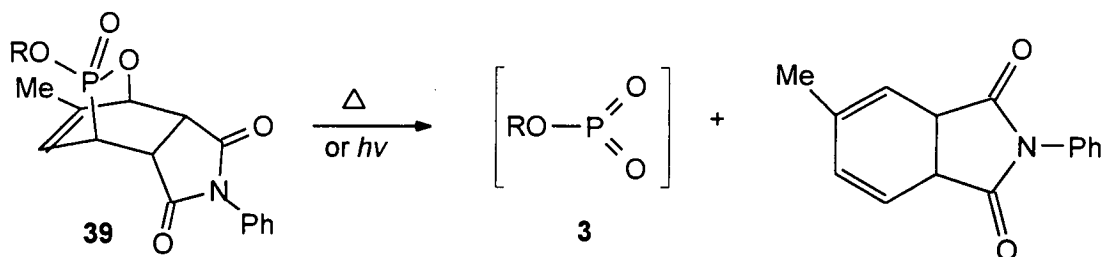


extrusion of alkyl metaphosphates<sup>15</sup>. The ring system is synthesised by a Diels-Alder reaction between phosphole oxide **40** and *N*-phenylmaleimide<sup>15,52</sup> **41** (Scheme 21), followed by an insertion of oxygen into a ring *C-P* bond of the resulting 7-phosphanorbornene system<sup>53</sup> **42**.



Scheme 21. Synthesis of Quin's 2,3-oxaphosphabicyclo[2,2,2]octene ring system **39**.

The system generates alkyl metaphosphates by either thermal<sup>15</sup> or photochemical<sup>5</sup> fragmentation and releases the bridging *P-O* unit as the metaphosphate (Scheme 22).



Scheme 22

There are several reasons as to why this bicyclic system is such a valuable metaphosphate generator. Firstly, the process can easily be used to generate a variety of different metaphosphates (dioxophosphoranes) by simply changing the nature of the substituent on oxygen<sup>52</sup> (Table 1). Secondly, once the bicyclic system is obtained, the generation of the metaphosphate is simple and straightforward and can take place either thermally<sup>15</sup> or photochemically<sup>5</sup> in a variety of solvents. Moreover, there is no requirement for acid or base to be used, thereby avoiding damage to sensitive substrates. When generated photochemically, temperatures as low as  $-78^\circ\text{C}$  can be used in some cases<sup>52</sup>. Finally, the fragmentation of the bicyclic system leads to almost

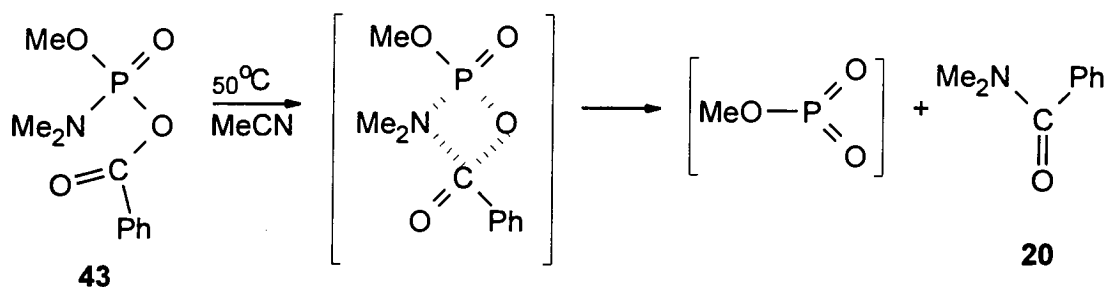
complete metaphosphate formation with no significant side reactions, and when trapped by alcohols, yields of up to 85% have been reported<sup>20</sup>.

Dioxophosphoranes	Alkyl or aryl grouping
$RPO_2$ aryldioxophosphoranes	R = Phenyl
$ROPO_2$ alkoxydioxophosphoranes	R = methyl, ethyl, neopentyl, 1-adamantyl and <i>l</i> -menthyl.
$R_2NPO_2$ aminodioxophosphoranes	$R_2N$ = (Methyl) <sub>2</sub> N-, (Ethyl) <sub>2</sub> N-, PhenylNH-, <i>t</i> -ButylNH-, MesitylNH- and 1-AdamantylNH-

Table 1. Dioxophosphoranes generated by Quin's bicyclic ring system.

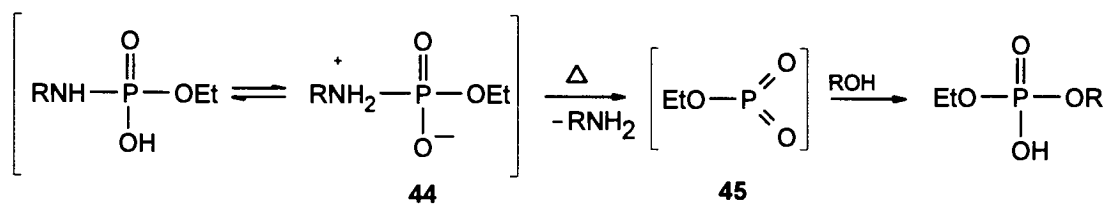
Other methods of metaphosphate synthesis which should be mentioned include the fragmentation of mixed phosphoric-carboxylic anhydrides reported by Symes and Modro<sup>10</sup> and involve the unimolecular fragmentation of anhydrides formed by reacting carboxylic acid chlorides with the anion of *O*-alkyl *N*-substituted phosphoramidic acids. The

fragmentation may be considered as a migration of the amino group from phosphorus to the carbonyl centre (Scheme 23).



Scheme 23

Finally, mention should be made of the fragmentation of *O*-alkyl-*N*-substituted phosphoramidic acids which involve the loss of an amine<sup>54-56</sup>. The fragmentation is envisaged to occur *via* the dipolar form of the phosphoramidic acid 44, and the resulting metaphosphate has been trapped with alcohols (Scheme 24).



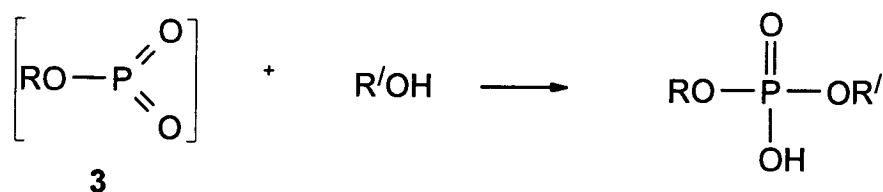
Scheme 24

### 1.3.2 Reactions of alkyl metaphosphates with nucleophiles

The following section will review the types of reactions that alkyl metaphosphates can undergo. Some of the reactions are normally only used for trapping purposes to prove the existence of the transient species in mechanistic studies. However, others can be used to produce novel phosphorylated compounds that are difficult to obtain using conventional methods. It is this group of reactions that will give practicality to metaphosphates as synthetic reagents. In every case the phosphorus atom is an electrophilic centre, being attacked by nucleophiles with a displaceable hydrogen, adding to oxygen atoms, *e.g.* in epoxides or carbonyl compounds or performing electrophilic substitution at electron-rich carbon atoms.

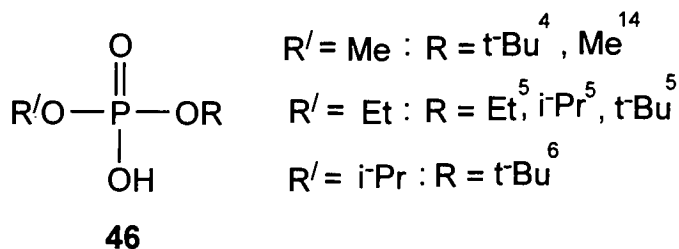
#### 1.3.2.1 With alcohols

The most commonly used trapping agent in metaphosphate chemistry is an alcohol, which adds to the phosphoryl group of the metaphosphate **3** and gives rise to phosphodiester (Scheme 25).

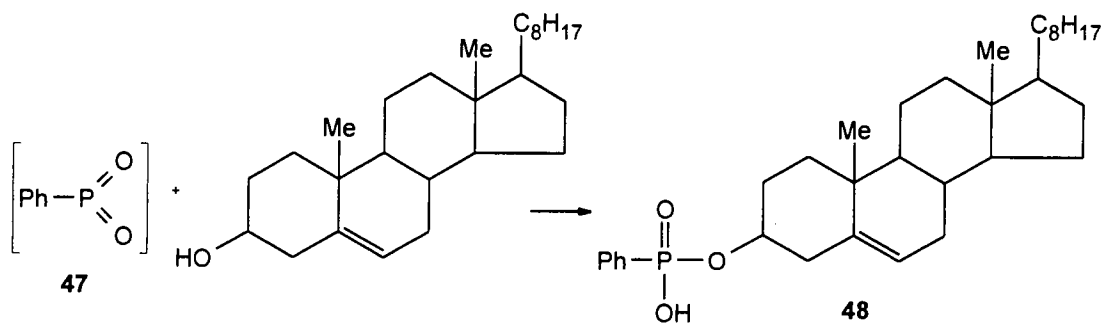


Scheme 25. Reaction of an alcohol with an alkyl metaphosphate.

The phosphodiesters **46** may have two different alkyl groups present. This is particularly useful if one of the alkyl groups has a tertiary structure since it is often extremely difficult to synthesis such phosphodiesters using conventional methods. For example, *tert*-butyl isopropyl phosphate **38** was prepared for the first time by trapping of the appropriate (Pr<sup>i</sup>OPO<sub>2</sub>) metaphosphate with *tert*-butanol<sup>6</sup> (section 1.3.1.2. Scheme 20 ). A summary of the products **46** which have been isolated and identified from this reaction is provided below.

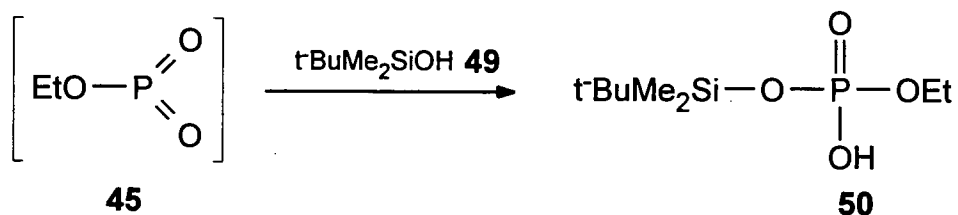


An interesting reaction carried out by Quin was the trapping of phenyldioxophosphorane **47** by cholesterol to afford the phosphorylated sterol<sup>57</sup> **48** (Scheme 26). This followed an earlier example by Ramirez who had shown that the metaphosphate anion gave phosphates with cholesterol and other sterols<sup>9</sup>. It does not require any stretch of the imagination to see that it would be perfectly feasible to extend this reaction to include alkyl metaphosphates as phosphorylating reagents. Hitherto, this has, however, yet to be reported.



Scheme 26. Phosphorylation of cholesterol by phenyldioxophosphorane 47.

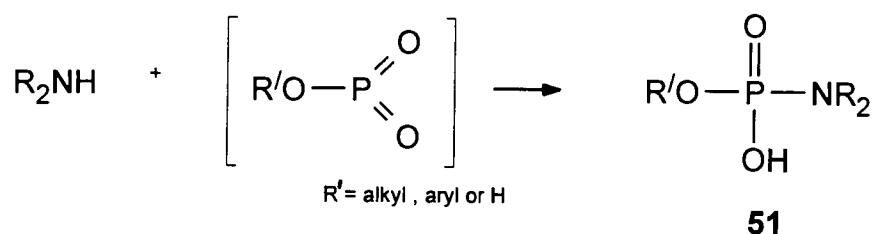
Quin has also phosphorylated the *HO* group of *tert*-butyldimethyl silanol 49 with ethyl metaphosphate<sup>58</sup> 45, which was generated from his bicyclic ring system discussed earlier (Scheme 27). The reaction with silanols has been extended to the silanol groups on the surface of silica gels and zeolites (see section 1.3.2.6).



Scheme 27

### 1.3.2.2 With amino groups

Amines can also be used as trapping agents for metaphosphates as shown in Scheme 28.

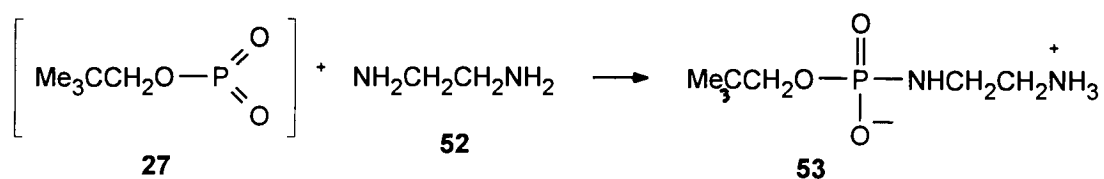


Scheme 28. Reaction of an amine with an alkyl metaphosphate.

An advantage of using metaphosphates to phosphorylate amines is that a mixed *O*-alkyl *N*-substituted phosphoramidic acid **51** results, and while simple compounds of this structure are known, compounds with more complicated amine substituents are rare and could possibly be obtained *via* metaphosphates.

Another advantage of phosphorylation by alkyl metaphosphates was found with the selective mono-phosphorylation of ethylenediamine<sup>57</sup> **52**. Here, attack only occurs at one of the two amino groups; the first phosphoramidic acid moiety formed reacts with the other amino group to form a zwitterionic salt, and this then precipitates from the non-polar

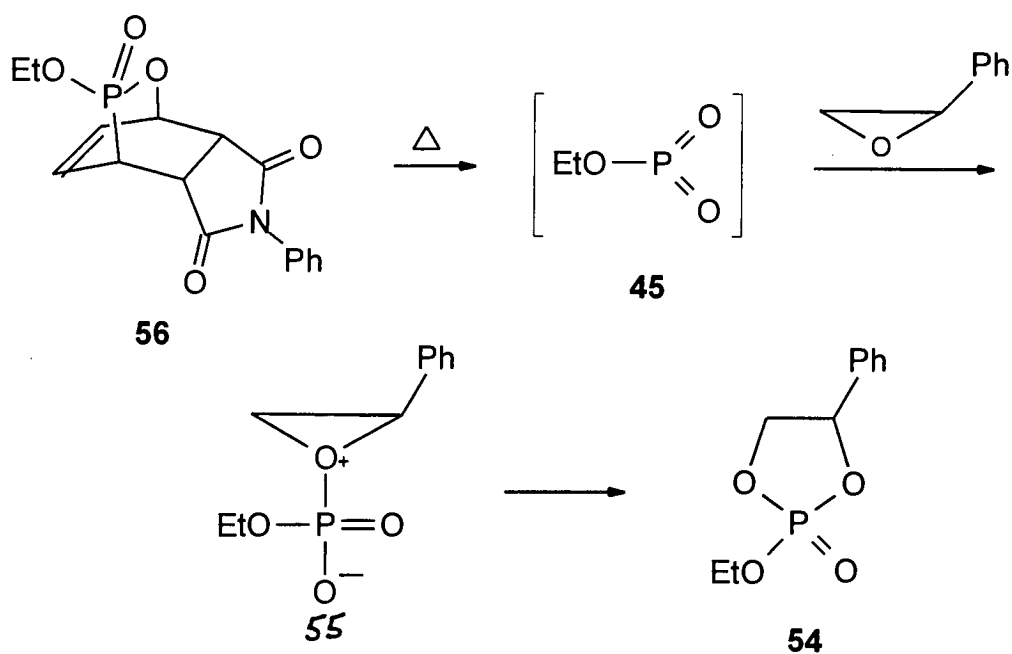
solvent used. This approach, where the metaphosphate was generated by Quin's ring fragmentation method, provided the novel salt **53** in 86% yield (Scheme 29). Presumably this method could be used with other diamines to form further novel salts.



Scheme 29

### 1.3.2.3 With epoxides

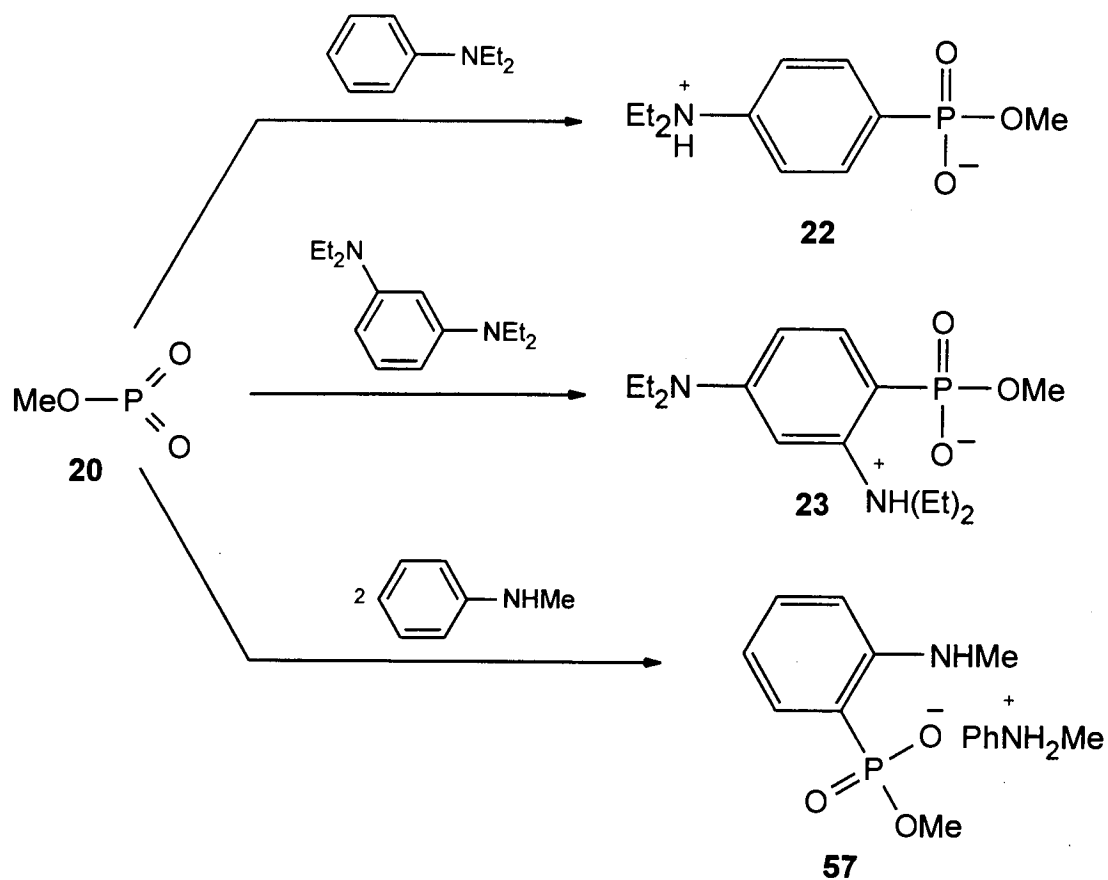
Ethyl metaphosphate **45** generated by the ring fragmentation of Quin's bicyclic ring system, attacks the oxygen of epoxides, *e.g.* styrene oxide to form a 5-membered cyclic phosphate<sup>11</sup> **54**. The initial product is presumably the Lewis salt **55** which undergoes rearrangement, by a pathway not yet fully understood, to the phosphate **54** (Scheme 30). This reaction is of interest in confirming the powerful Lewis acid character of alkyl metaphosphates.



Scheme 30. Reaction of ethyl metaphosphate 45 with styrene oxide.

#### 1.3.2.4 With electron rich carbon in anilines and *N*-methylpyrrole

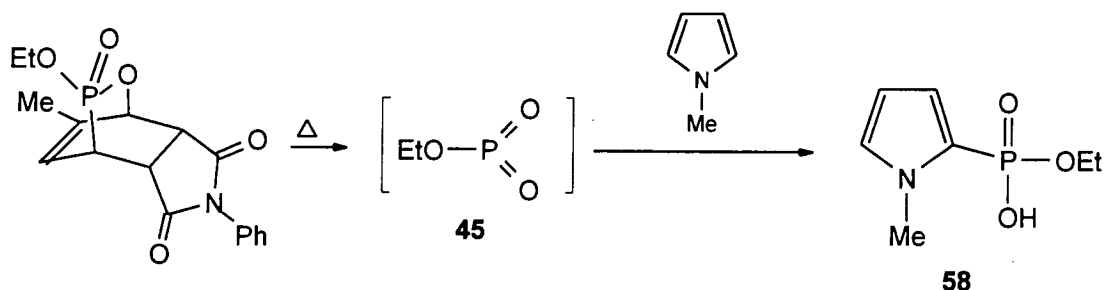
That metaphosphates can function as powerful electrophilic aromatic substitution agents was first observed during the work on the generation of methyl metaphosphate in the gas phase<sup>8</sup>, and later in solution by the Conant-Swan method<sup>14</sup>. It was found that when metaphosphates are formed in the presence of diethylaniline, methylaniline and *N,N,N',N'*-tetraethyl-*m*-phenylenediamine, phosphorylation of the aromatic ring occurs, in the *ortho*- and *para*-positions, as depicted in Scheme 31.



Scheme 31. Products from the generation of methyl metaphosphate **20** in the presence of selected aromatic amines

This finding was a benchmark experiment in metaphosphate chemistry as it clearly pointed to an intermediate with a powerfully electrophilic phosphorus centre. It was later found that the electron-rich pyrrole ring could also be phosphorylated by ethyl metaphosphate

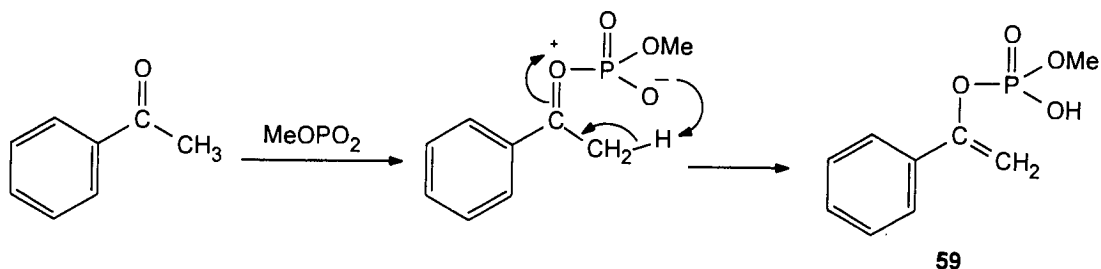
generated by Quin's ring fragmentation approach (Scheme 32). The process led to the novel 2-pyrrolephosphonic acid derivative **58** which was formed in 80% yield. It is clear that these reactions are of important synthetic value in yielding the often difficult to synthesis phosphorylated aromatics.



Scheme 32. Generation of ethyl metaphosphate **45** in the presence of a pyrrole.

### 1.3.2.5 With carbonyl compounds

Enol phosphates are the products from the reaction of methyl metaphosphate with ketones. This reaction was first observed by Westheimer<sup>12</sup> who generated methyl metaphosphate *via* the Conant-Swan method in the presence of acetophenone. Analysis of the products showed that more than 90% of the phosphorus content was present as the enol phosphate **59** (Scheme 33).

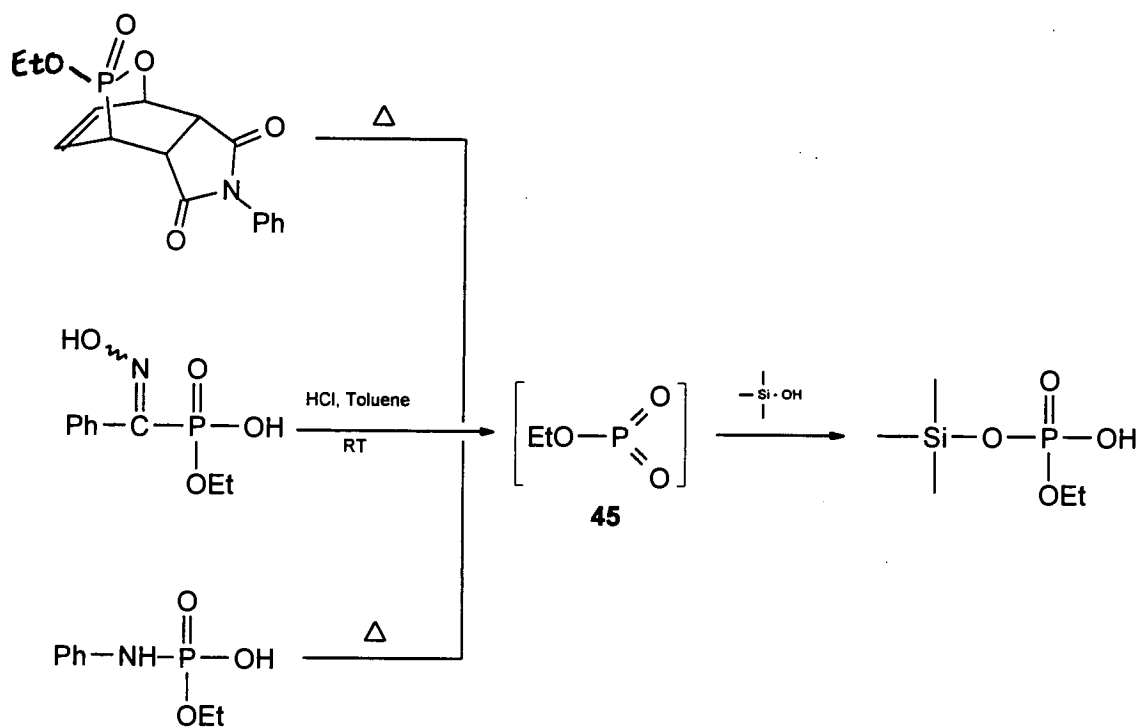


Scheme 33. Reaction of methyl metaphosphate **20** with acetophenone

An alternative pathway that could be considered involves the reaction of methyl metaphosphate **20** with the small amount ( $\sim 0.035\%$ ) of enol present in equilibrium with its keto form. However, the reaction could only occur by this pathway if the metaphosphate were highly selective, which is contrary to its known reactivity. Furthermore, if such were the case, presumably the metaphosphate would also react with alcohols that mimic the enol. However, when 5% (relative to acetophenone) of either phenol or phenethyl alcohol was added to the reaction mixture, the predominant product was still the enolphosphate. Notably, this result was obtained despite the fact that these models for the enol were present in enormous excess over the minute amount of enol in solution and must have swamped the enol itself. The pathway in Scheme 33 is therefore reasonably secure with the metaphosphate being attacked by the lone pair on the oxygen.

### 1.3.2.6 With hydroxy groups on the surfaces of solids

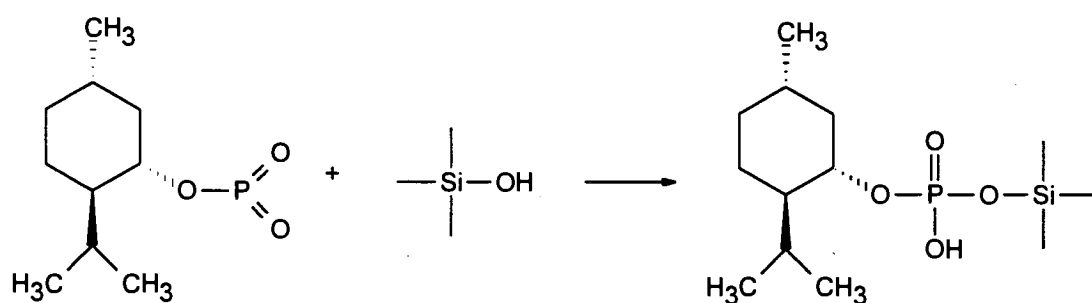
Quin has shown that metaphosphates are sufficiently powerful phosphorylating agents that they are capable of reacting with OH groups on the surfaces of certain solids<sup>59</sup>. The reactions are carried out by generating the metaphosphates by normal methods in an inert solvent in the presence of the suspended solid. A typical reaction is that of ethyl metaphosphate 45 with silica gel, the overall transformation providing a direct route to an ethyl phosphate group bonded directly to the surface silica. Quin has used three different methods to generate the metaphosphate and all give identical products on exposure to silica gel (Scheme 34). In addition to silica gel Quin has also phosphorylated



Scheme 34. Methods used by Quin to generate ethyl metaphosphate 45 for the phosphorylation of silica.

the OH groups on alumina<sup>60</sup> and certain zeolites (silicoaluminates)<sup>57</sup>.

The ability of metaphosphates to phosphorylate the surfaces of solids is possibly one of the most important practical reactions which metaphosphates undergo. To date, it has already been demonstrated that HPLC grade silica gel after phosphorylation with ethyl metaphosphate 45 has improved characteristics in the separation of chemical mixtures, notably of aromatic amines and of petroleum distillates<sup>57</sup>. This is undoubtedly due to loss of Si-OH groups and the formation of the more acidic P-OH groups. A possibility that Quin has already begun to explore is that phosphorylation of silica gel with metaphosphates bearing optically active groups may be of value in the separation of racemic mixtures. For this purpose he has generated (+)-menthyl metaphosphate and reacted it in situ with silica gel to form a chiral stationary phase that is now under investigation<sup>60</sup> (Scheme 35).



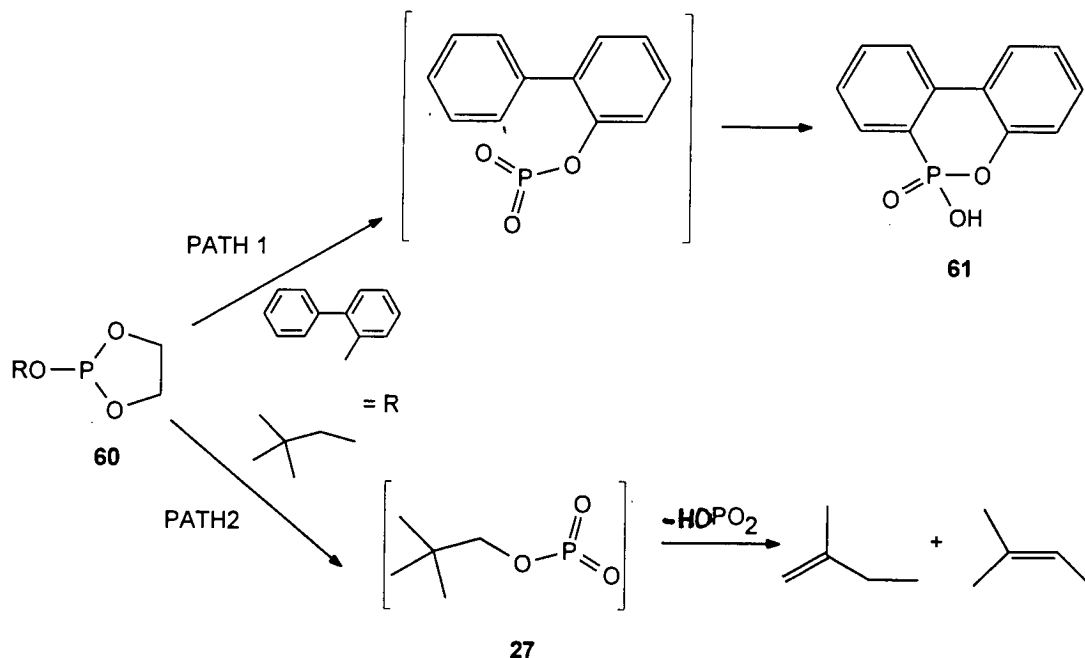
Scheme 35

## 1.4 Programme of Research

Chelotropic reactions are those reactions in which two  $\sigma$ -bonds that terminate at a single atom are made or broken in concert<sup>61</sup>. Such reactions can be exploited in the synthesis and study of reactive intermediates *via* the pyrolysis of a suitable precursor that fragments with the elimination of gaseous side-products such as sulphur dioxide, nitrogen, ethene or carbon dioxide.

At the University of Edinburgh, previous studies<sup>16,17,44</sup> have utilised such reactions to generate both alkyl- and aryl-metaphosphates. This method involves the gas-phase pyrolysis of 2-substituted 1,3,2-dioxaphospholanes **60**, which fragment under thermal conditions with chelotropic extrusion of ethene to produce metaphosphates that are utilised in synthetic procedures (Scheme 36).

Depending upon the nature of the 2-substituent, the metaphosphate formed reacts by different reaction pathways. Aryl metaphosphates cyclise spontaneously by intramolecular insertion (phosphonylation) into a *C-H* bond of the adjacent aromatic ring system to produce cyclic phosphoric esters such as **61**. (Scheme 36, path 1) On the other hand, non-aromatic alkyl metaphosphates undergo fragmentation by a process that involves the elimination of metaphosphoric acid with the formation of alkenes (Scheme 36, path 2).



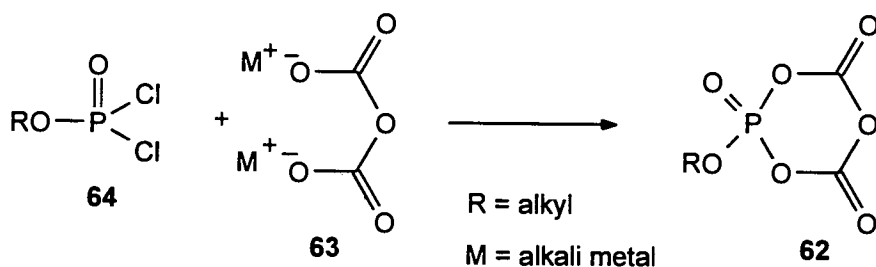
Scheme 36. Gas phase pyrolysis of 1,3,2-dioxaphospholanes **60**.

Whereas the generation of aryl metaphosphates by pyrolysis of 1,3,2-dioxaphospholanes has practical value due to the formation of phosphorylated aromatic ring systems, the generation of alkyl metaphosphates by this method does not possess the same practical value due to the fragmentation of the resultant metaphosphate. The conditions used to generate the metaphosphates also require temperatures of up to  $800^\circ\text{C}$  and pressures as low as  $0.001\text{mm Hg}$ .

The present programme of research is aimed at developing a new approach to the generation of metaphosphates in solution. Such an

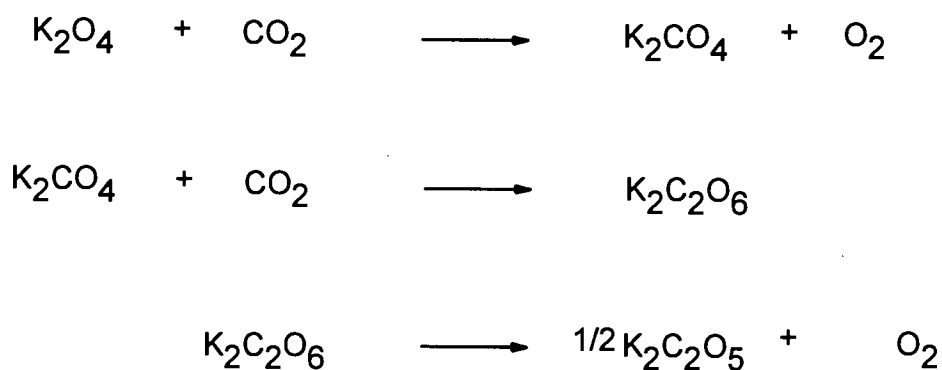
approach has important practical implications since it is known that alkyl metaphosphates produced in solution do not fragment unlike when generated in the gas-phase by pyrolysis of 1,3,2-dioxaphospholanes. In consequence they are free to phosphorylate nucleophiles that may be present in the reaction mixture such as alcohols<sup>4-7</sup>, amines<sup>8-10</sup>, and also compounds containing functional groups with lone pairs such as epoxides<sup>11</sup> and carbonyls<sup>12</sup>. The practical aspects of generating metaphosphates in solution are also made easier by the fact that the reactions can be carried out at either room temperature or by heating under reflux in a suitable solvent and at atmospheric pressure.

The starting point for the generation of alkyl metaphosphates in the present study involves the attempted preparation of novel cyclic pyrocarbonates such as **62**. It is envisaged that the synthesis of such cyclic pyrocarbonates can be accomplished by the condensation of pyrocarbonate salts such as **63** with alkyl phosphorodichloridates **64** (Scheme 37).



Scheme 37

From a preliminary literature search only one reference to dialkali pyrocarbonates was found. This was by a group of Russian workers<sup>62</sup> in 1951 who produced dipotassium pyrocarbonate **65** by passing carbon dioxide over granulated potassium peroxide at 0°C, the proposed reaction mechanism is shown in Scheme 38, but this method is limited since the

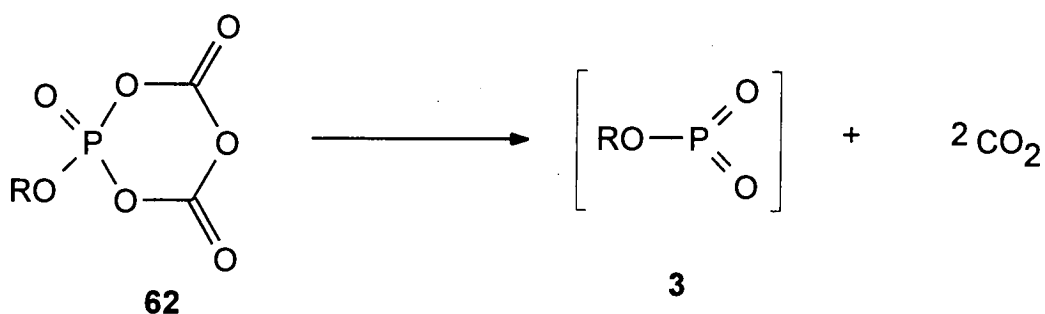


Scheme 38

reaction time is quoted as being 1300 hours (54 days)! Nonetheless, encouragement was taken from this report which provided evidence for the existence of such pyrocarbonates and their stability, albeit below 25°C.

By using these pyrocarbonate salts, it is intended to synthesis the cyclic pyrocarbonates **62** which will then be investigated as possible precursors to alkyl metaphosphates. It is envisaged that these cyclic

pyrocarbonates will undergo a chelotropic breakdown with the release of two moles of carbon dioxide to produce alkyl metaphosphates **3** (Scheme 39). If the generation of alkyl metaphosphates by this method is confirmed then investigations will begin into their trapping by suitable reagents.



Scheme 39

The discussion chapters will also detail investigations into other systems that are thought to undergo fragmentations to produce alkyl metaphosphates. These systems were not part of the original programme of research but came about either as a result of the initial attempts to synthesis cyclic pyrocarbonates **62** or from discussions within the research group.

## **Chapter Two**

### **Generation of Alkyl Metaphosphates by Reaction of Alkyl Phosphorodichloridates with Potassium Hydrogen carbonate**

# Chapter Two

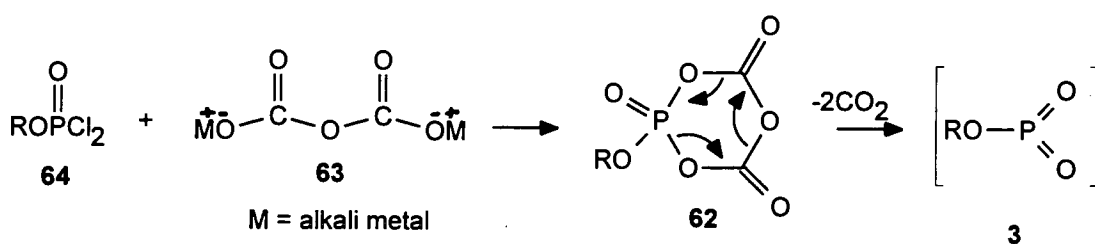
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## 2.1 Introduction

The discovery that alkyl metaphosphates could be generated by reaction of alkyl phosphorodichloridates with potassium hydrogen carbonate was an entirely serendipitous finding. To understand how this finding first came about it is necessary to return to the aims set out in the programme of research in section 1.4, and to describe the initial experiments employed to synthesise dipotassium pyrocarbonate **65** and its subsequent use in the proposed generation of alkyl metaphosphates.

The starting point for the present study was to synthesise novel pyrocarbonate salts **63**, and to react them with alkyl phosphorodichloridates **64** to produce novel cyclic pyrocarbonate phosphates such as **62**. It is envisaged that these cyclic pyrocarbonates would then undergo chelotropic breakdown to produce alkyl metaphosphates **3** as shown in Scheme 40.

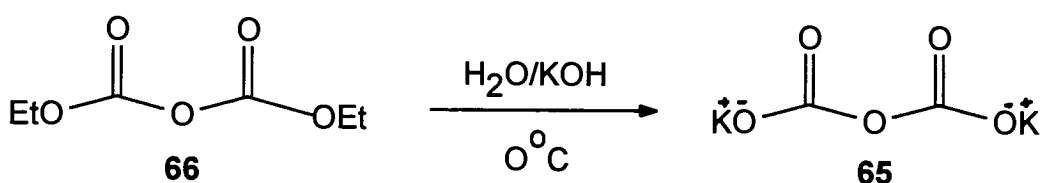


Scheme 40. Proposed generation of alkyl metaphosphates **3** via novel cyclic pyrocarbonate phosphates **62**

As mentioned previously (section 1.4), a literature search for dialkali pyrocarbonates found only one reference<sup>62</sup>, which was for dipotassium pyrocarbonate, but it was of no practical value since the reaction time was too long.

## 2.2 Attempted synthesis of dipotassium pyrocarbonate 65

Initial and tentative attempts to prepare dipotassium pyrocarbonate **65** concentrated upon the careful base hydrolysis of commercially available diethyl pyrocarbonate **66**. The method involved the stirring of diethyl pyrocarbonate with potassium hydroxide in distilled water at 0°C (Scheme 41) until all the diethyl pyrocarbonate had dissolved. The reaction mixture was then kept at 0°C, and subsequently freeze-dried to yield a colourless solid, which was tentatively assigned the structure of dipotassium pyrocarbonate **65**.

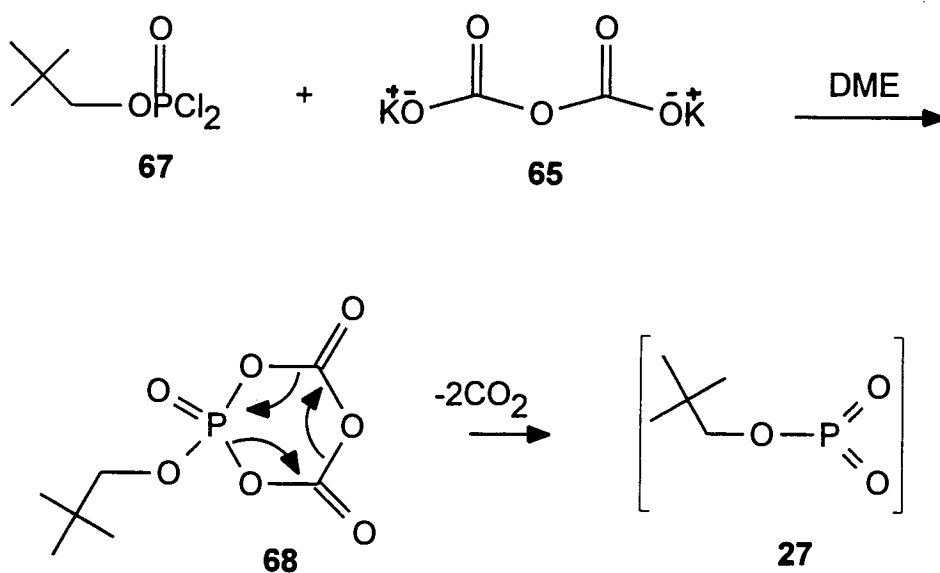


Scheme 41. Base hydrolysis of diethylpyrocarbonate **66**



## 2.3 Condensation of dipotassium pyrocarbonate 65 with neopentyl phosphorodichloridate 67

The pyrocarbonate salt 65 was immediately used for the next step in the generation of alkyl metaphosphates. This step involved the condensation of the pyrocarbonate salt with neopentyl phosphorodichloridate 67 at room temperature in anhydrous dimethoxyethane (DME) to produce the novel cyclic pyrocarbonate phosphate (2-neopentyl-1,3,5,2-trioxaphosphorinane-4,6-dione-2-oxide 68, Scheme 42), which subsequently fragmented to generate neopentyl metaphosphate 27.



Scheme 42. Generation of neopentyl metaphosphate 27 *via* the cyclic pyrocarbonate phosphate 68.

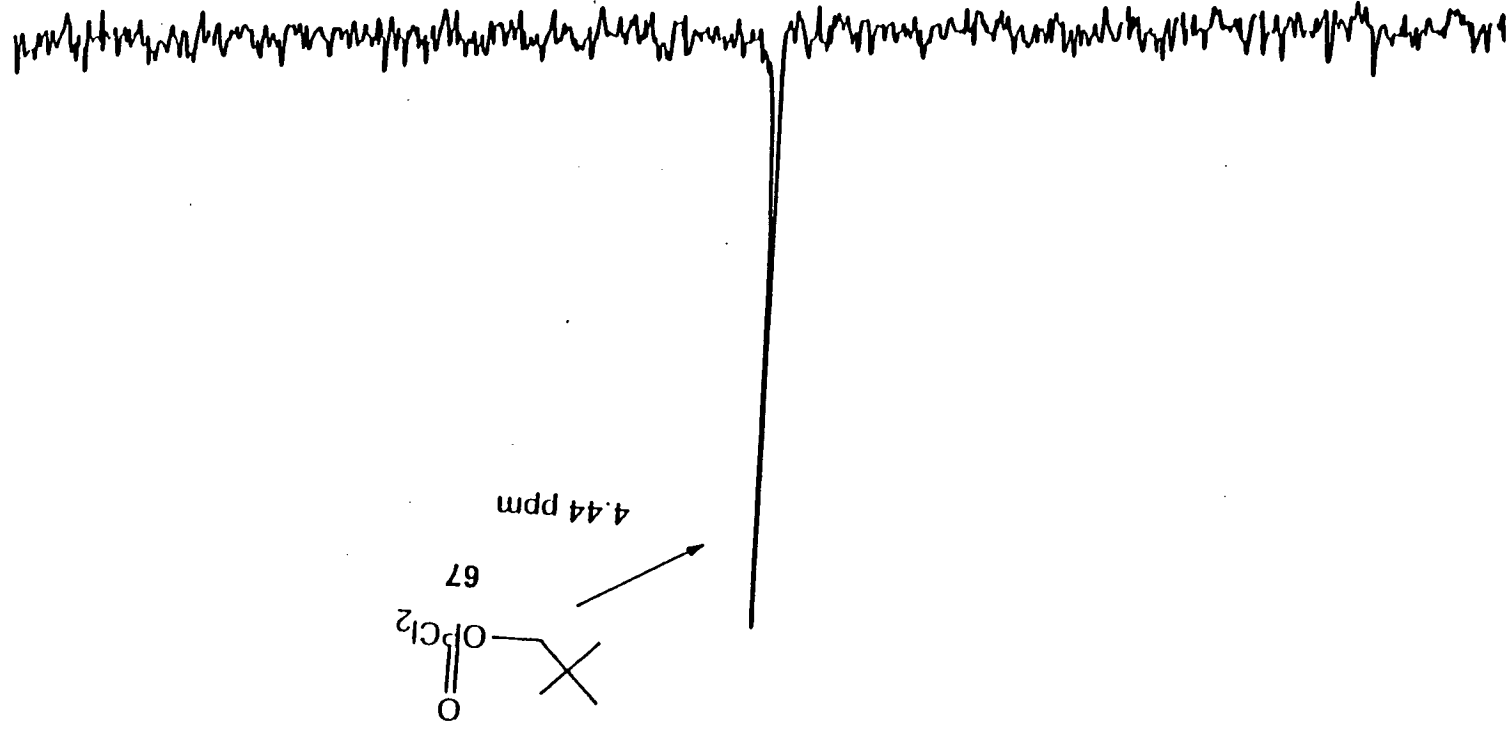
In order to follow the course of the reaction and understand the events that were occurring, the reaction was monitored by  $^{31}\text{P}$  NMR spectroscopy. The  $^{31}\text{P}$  NMR spectra illustrating the course of the reaction can be seen in Figure 3.

The spectrum shown in Figure 3b provides strong evidence to support the formation of neopentyl metaphosphate. This is due to the presence of signals in the characteristic regions associated with polymeric products formed from the self-condensation reactions of monomeric alkyl metaphosphates<sup>8,18</sup>. These signals appear in the  $\delta$  -12 to -14 ppm region, due to terminal phosphate groups, and in the  $\delta$  -23 to -26 ppm region due to internal and cyclic phosphate groups. Also present was a major signal at 0.26 ppm, which at this stage of the study was an unidentified phosphate (but was later found to be neopentyl phosphonic acid).

It is also of interest to note at this point that when the starting neopentyl phosphorodichloridate **67** (Figure 3a, 4.44 ppm) began to be consumed, the immediate products from  $^{31}\text{P}$  NMR observations, were those polymeric products mentioned previously. This implies that the intermediate cyclic pyrocarbonate phosphate **68** had such a short lifetime that it immediately fragmented to form neopentyl metaphosphate **27**, and consequently, could not be observed in the  $^{31}\text{P}$  NMR spectrum.

Further evidence to support the formation of the cyclic polymers of neopentyl metaphosphate ( $\delta$  -23 to -26 ppm regions, Figure 3b) was attained by FAB mass spectroscopy of samples taken from the reaction

Figure 3a. <sup>31</sup>P NMR spectrum from the reaction of neopentyl phosphorodichloridate 67 with dipotassium pyrocarbonate 65 after 10 minutes at room temperature.



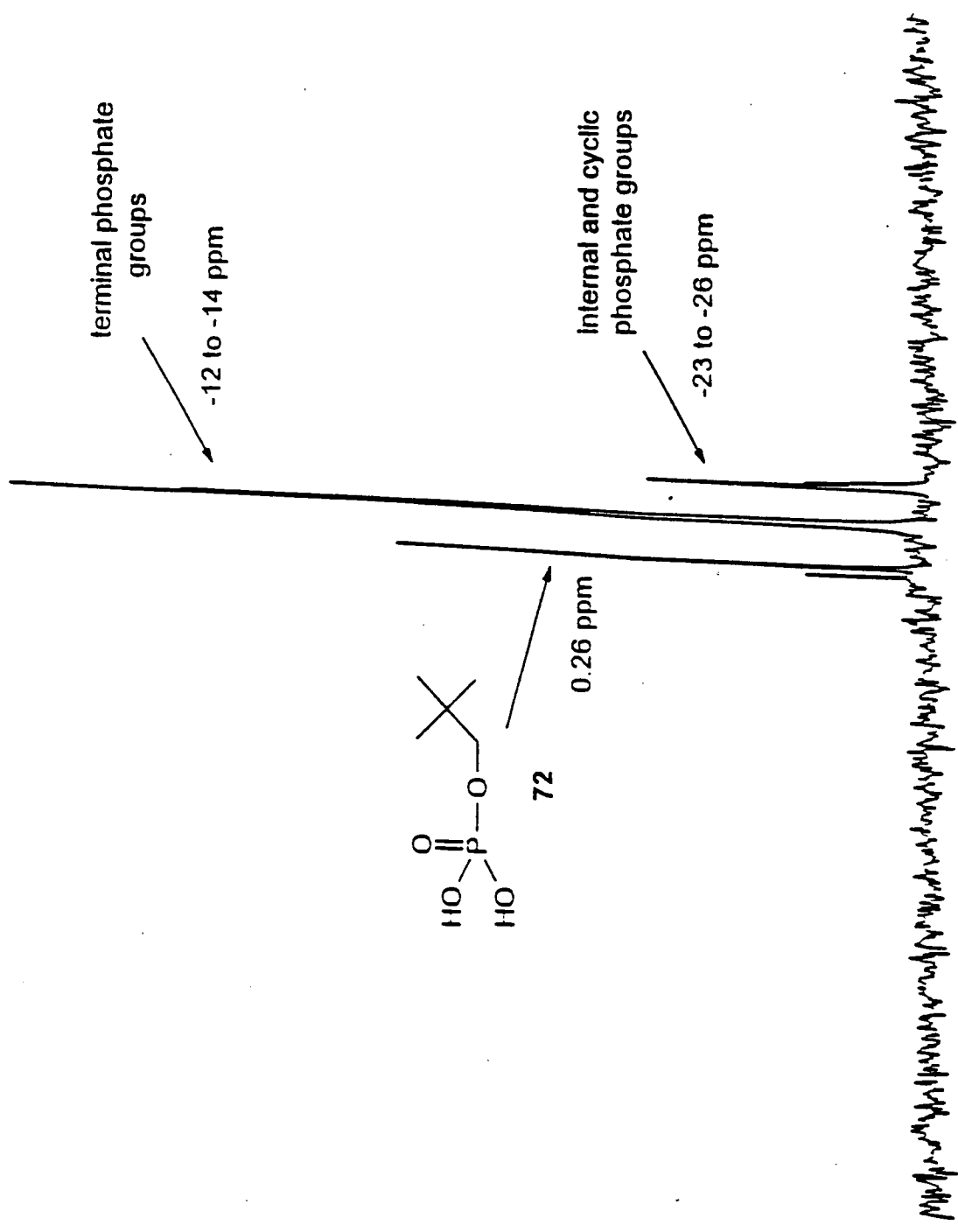


Figure 3b.  $^{31}\text{P}$  NMR spectrum from the reaction of neopentyl phosphorodichloridate 67 with dipotassium pyrocarbonate 65 after two and a half hours at room temperature.

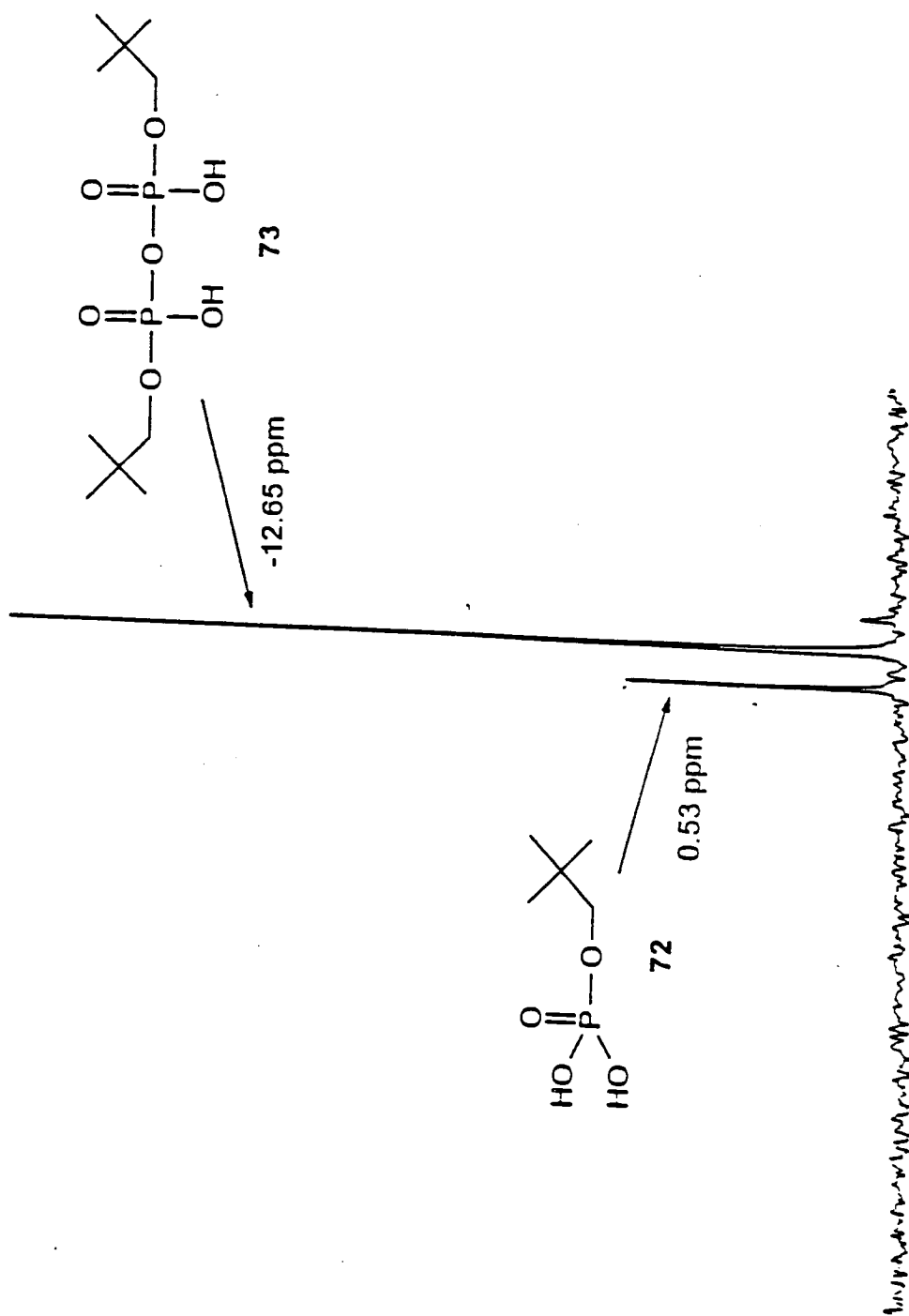


Figure 3c.  $^{31}\text{P}$  NMR spectrum from the reaction of neopentyl phosphorodichloride 67 with dipotassium pyrocarbonate 65 after twenty four hours at room temperature.

mixture after 2.5 hours, as illustrated in Figure 4. The spectrum clearly shows trimeric (69,  $[M+1]^+ = 451$ ), tetrameric (70,  $[M+1]^+ = 601$ ) and pentameric (71,  $[M+1]^+ = 751$ ) neopentyl metaphosphate.

Additional evidence to support the proposed mechanism for the generation of neopentyl metaphosphate (Scheme 42) was the detection of carbon dioxide being expelled from the reaction mixture. This was detected by the classic "turning of lime water chalky" by the gasses being driven from the reaction by the constant stream of argon. A gas being released from the reaction was also noted when an NMR sample of the reaction mixture, after standing for two hours, had its cap removed. The removal of the cap resulted in a "popping" sound and the release of pressure was accompanied by a stream of bubbles being released from the sample. These observations are in agreement with the proposed reaction pathway as shown in Scheme 42.

## 2.4 The role of water

Perhaps the most important observation made, however, with regards to the present chapter, was the  $^{31}\text{P}$  NMR spectrum shown in Figure 3c. This was taken from the reaction mixture after 24 hours at room temperature and consisted almost entirely of two major signals at 0.53 and -12.65 ppm. The relevance of this observation is that these values corresponded to the literature report by Satterthwait and Westheimer<sup>14</sup> for the phosphorus signals found in the thermal

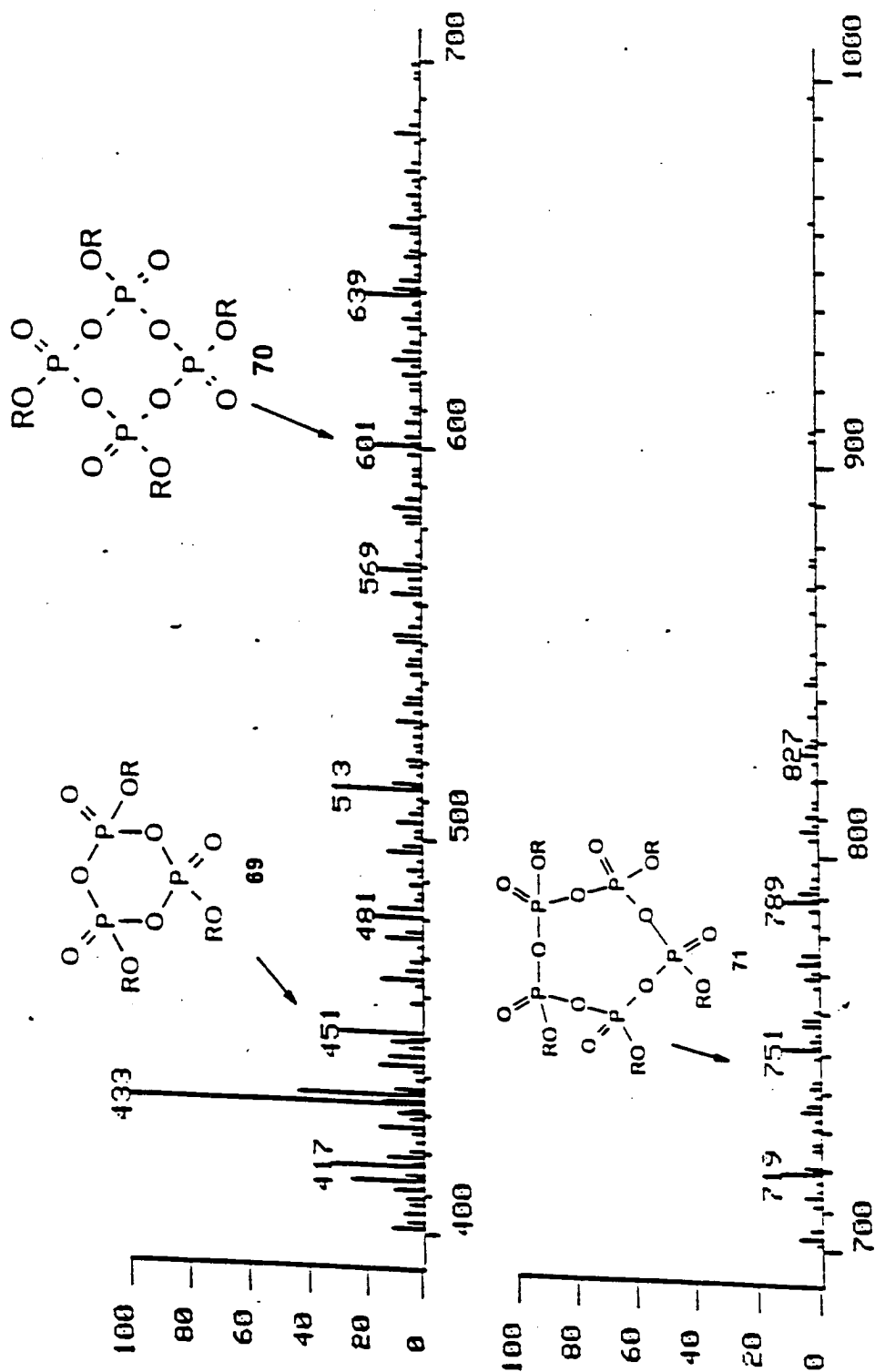


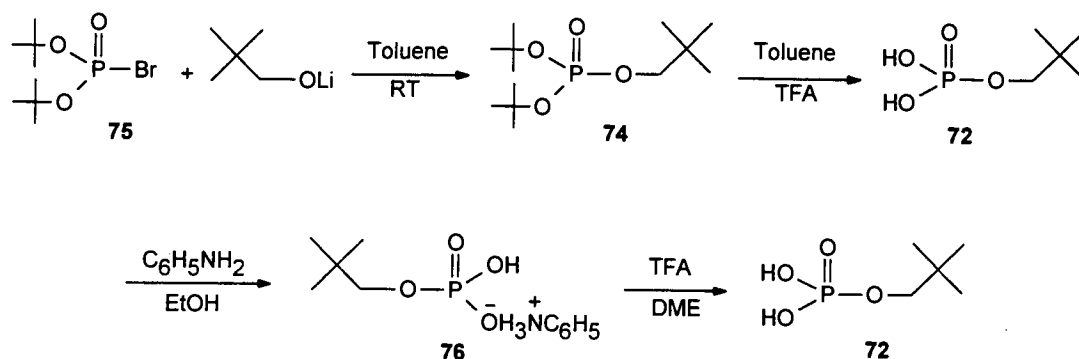
Figure 4. FAB-MS of the crude products after two and a half hours from the reaction of neopentyl phosphorodichloridate 67 with dipotassium pyrocarbonate 65.

decomposition on methyl-2-butenylphosphonate which extruded butadiene to form *sym*-di-methylpyrophosphate (-12.02 ppm) and methyl phosphonic acid (0.73 ppm), apparently *via* the intermediacy of methyl metaphosphate. The origin of these products clearly requires the involvement of water, and provided the products in the spectrum shown in Figure 3c are in fact neopentyl phosphonic acid (0.53 ppm) **72** and neopentyl pyrophosphate (-12.65 ppm) **73**, then our proposed reaction pathway (Scheme 42) and the experimental techniques used needed to be re-examined, since they failed to account for water being available in the reaction.

#### 2.4.1 Neopentyl phosphonic acid **72** and neopentyl pyrophosphate **73**

The initial steps to shed some light on this problem would be to identify whether or not the two signals in the spectrum shown in Figure 3c were in fact due to neopentyl phosphonic acid **72** and neopentyl pyrophosphate **73**. The simplest way to achieve this would be to synthesize the two compounds independently, and then carry out <sup>31</sup>P NMR peak enhancement experiments. The peak enhancement experiment involves taking part of the reaction mixture with the unidentified signal present and adding it to a solution of the independently synthesised compound. If the signal to be identified grows in intensity, with reference to the original spectrum from the reaction mixture, then the signal can be positively identified as being due to the independently synthesised

compound. On the other hand, if a new signal appears, with reference to the spectrum of the reaction mixture, then the signal to be identified is not the same as the compound which has been independently synthesised.



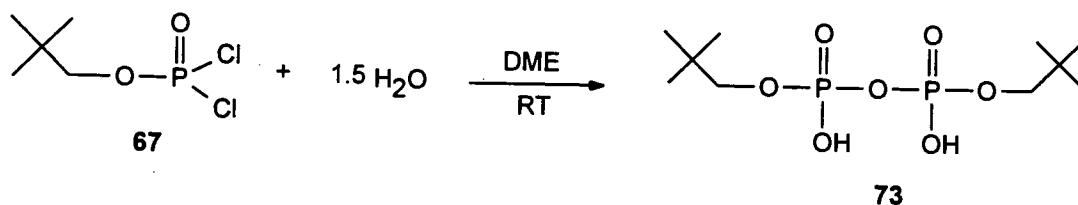
Scheme 43. Synthesis of neopentyl phosphonic acid 72

The route used to synthesise neopentyl phosphonic acid is shown in Scheme 43. The method is adapted from the literature report by Gajda and Zwierzak<sup>63,64</sup>. Thus, phosphorylation of neopentyl alcohol to form the corresponding phosphotriester 74 was carried out by adding di-*t*-butyl phosphorobromide 75 to a toluene suspension of the corresponding alkoxide (prepared from neopentyl alcohol and butyllithium) at room temperature. The resultant phosphotriester 74 was treated with a slight excess of trifluoroacetic acid, which removed the acid-labile *t*-butyl

groups, to yield crude neopentyl phosphonic acid **72**. The crude acid was then purified by converting it into the anilinium salt **76**, recrystallisation of which from ethanol and by treatment with trifluoroacetic acid, provided a sample of pure neopentyl phosphonic acid **72**.

The  $^{31}\text{P}$  NMR spectrum of the synthesised neopentyl phosphonic acid is shown in Figure 5. It can be seen that the shift of the acid differs by 1.5 ppm from that of the signal suspected to be neopentyl phosphonic acid in Figure 3c. However, when a sample of each were mixed and the  $^{31}\text{P}$  NMR spectrum taken, no new signals appeared, with reference to the spectrum in Figure 3c, and therefore the signal at 0.53 ppm in Figure 3c can in fact be identified as neopentyl phosphonic acid **72**. To support the synthesis of an authentic sample of neopentyl phosphonic acid an accurate FAB mass spectrum of the product was obtained (FAB-MS  $[\text{M}+1]^+ = 169.062964$ ,  $\text{C}_5\text{H}_{14}\text{O}_4\text{P}$   $[\text{M}+\text{H}]^+$  requires 169.06296).

The synthesis of neopentyl pyrophosphate **73** was much simpler as is shown in Scheme 44, and only required the stirring of neopentyl



Scheme 44. Synthesis of neopentyl pyrophosphate **73**

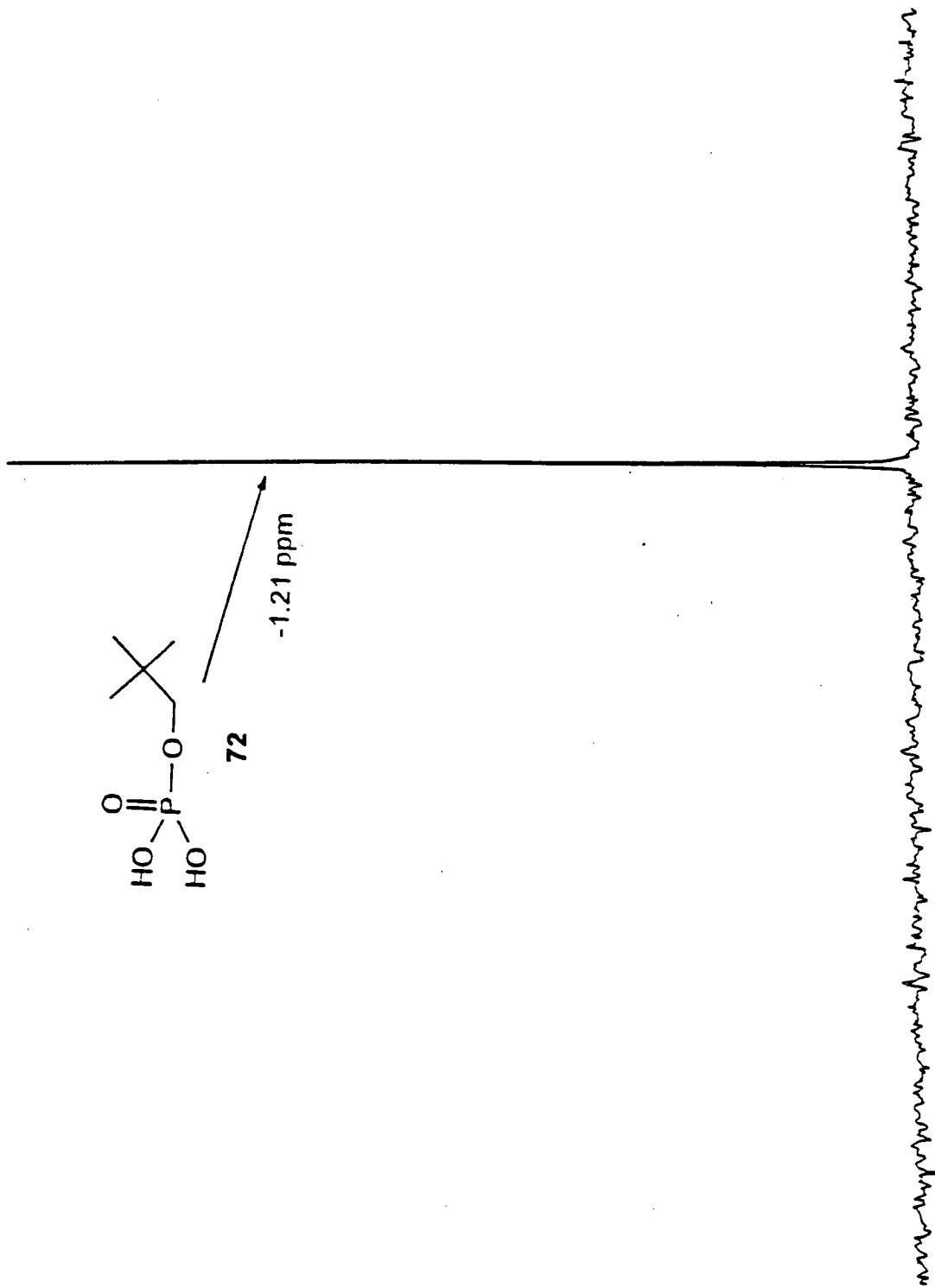


Figure 5.  $^{31}\text{P}$  NMR spectrum of neopentyl phosphonic acid 72 synthesised from a route independent of neopentyl metaphosphate.

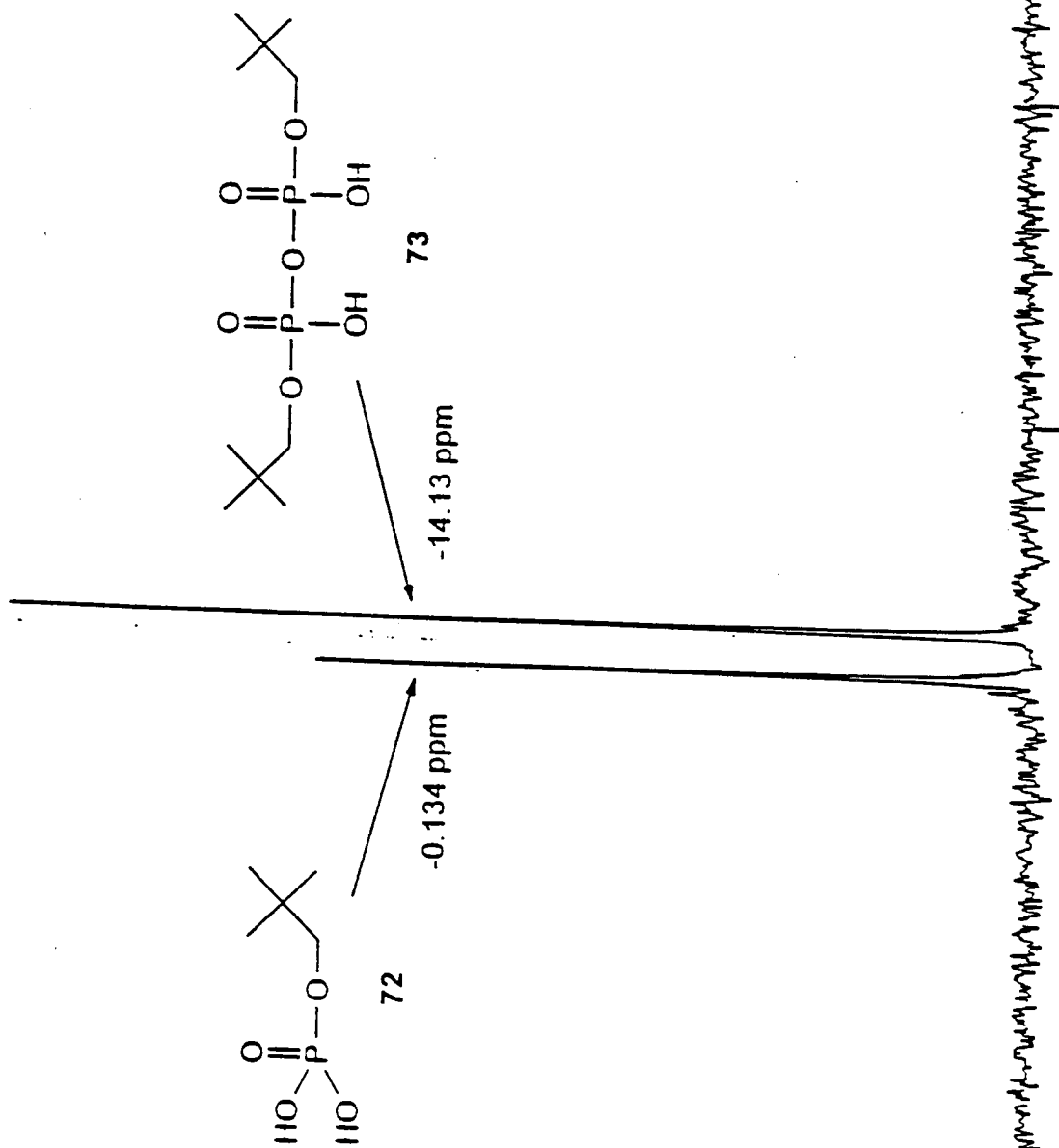


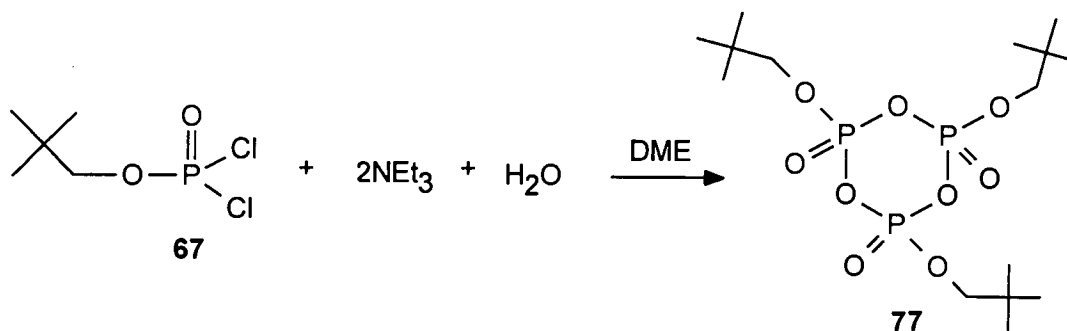
Figure 6.  $^{31}\text{P}$  NMR spectrum of neopentyl pyrophosphate 73 and neopentyl phosphonic acid 72 synthesised from a route independent from neopentyl metaphosphate

phosphorodichloridate **67** with 1.5 equivalents of water<sup>65</sup> to produce the pyrophosphate **73**, which was as might have been expected, accompanied by the formation of a significant amount of neopentyl phosphonic acid **72**. The <sup>31</sup>P NMR spectrum of the product mixture is shown in Figure 6. The formation of neopentyl phosphonic acid along with neopentyl pyrophosphate is, however, not a problem since these are the two products we suspected as being present in Figure 3c. Indeed, when the peak enhancement experiment was carried out there were still only two signals present in the <sup>31</sup>P NMR spectrum, thus proving unequivocally that the two signals in Figure 3c are indeed neopentyl phosphonic acid **72** and neopentyl pyrophosphate **73**. Additional evidence to prove that the two compounds synthesised independently are in fact neopentyl phosphonic acid and neopentyl pyrophosphate, was obtained from accurate FAB mass spectrometry measurements (for **72** FAB-MS [M+1]<sup>+</sup> = 169.062964, C<sub>5</sub>H<sub>14</sub>O<sub>4</sub>P [M+H]<sup>+</sup> requires 169.06296; for **73** FAB-MS [M+1]<sup>+</sup> = 319.10753, C<sub>10</sub>H<sub>25</sub>O<sub>7</sub>P<sub>2</sub> [M+H]<sup>+</sup> requires 319.10754).

#### 2.4.1.1 Trimeric neopentyl metaphosphate **77**

During the synthesis of neopentyl pyrophosphate **73**, we also carried out an experiment designed to show that the signals occurring in the  $\delta$  -23 to -26 ppm region in Figure 3b could be partly accounted for by cyclic polymers of neopentyl metaphosphate. The experiment involved the synthesis of trimeric neopentyl metaphosphate **77** by a method

adapted from a literature report by Chasar<sup>66</sup>. The procedure is shown in Scheme 45, and involved the partial hydrolysis of neopentyl phosphorodichloridate **67** in the presence of two moles of triethylamine.



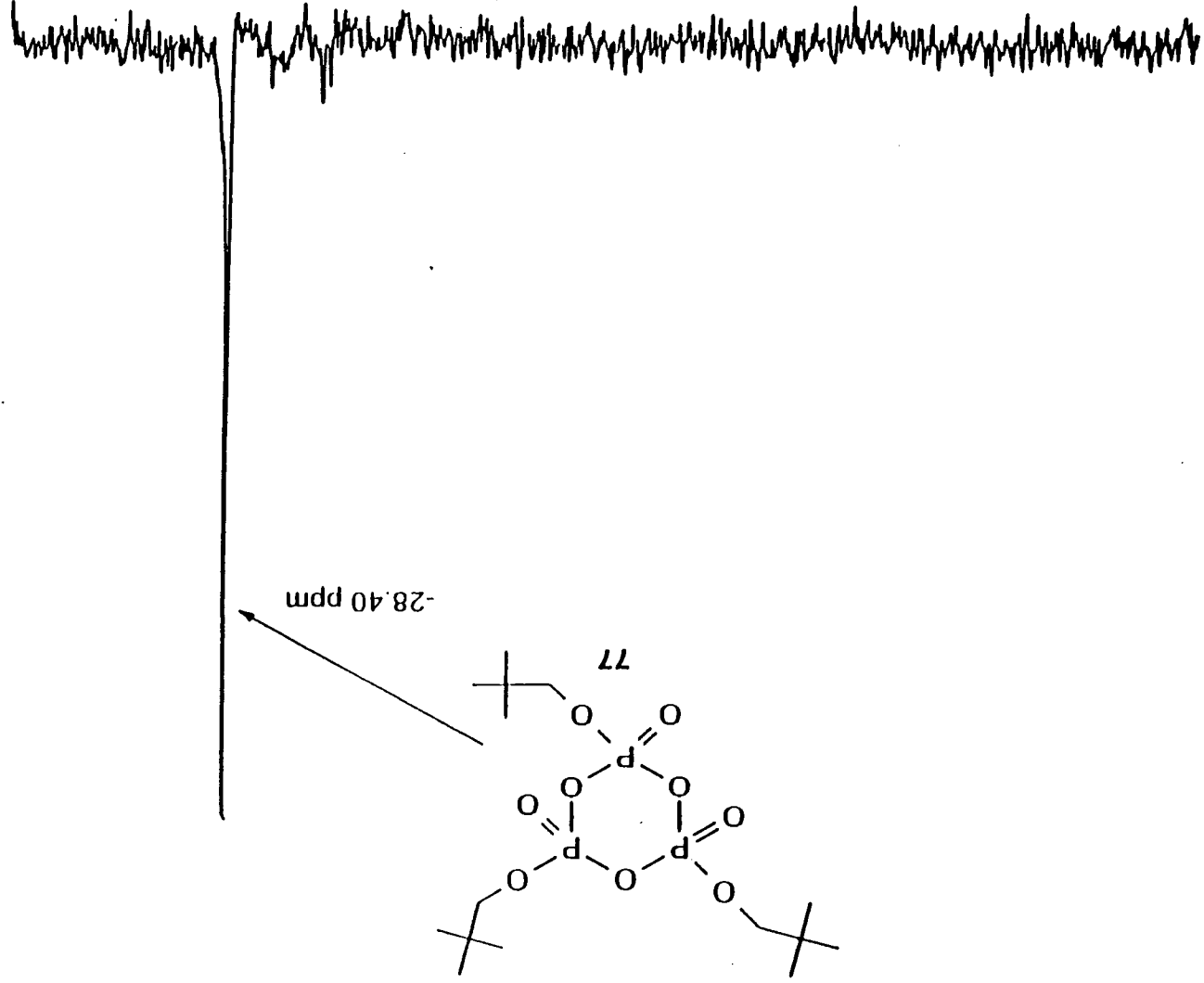
Scheme 45. Synthesis of trimeric neopentyl metaphosphate **77**

Figure 7 shows the  $^{31}\text{P}$  NMR spectrum of the final reaction mixture, and considering the different solvent system used, it is effective in proving that cyclic polymers of neopentyl metaphosphate such as **77** do in fact appear in the  $\delta$  -23 to -26 ppm region of the  $^{31}\text{P}$  NMR spectrum as mentioned earlier.

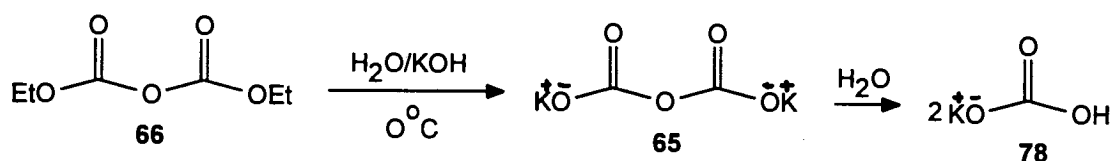
## 2.5 Re-investigation of the proposed pyrocarbonate salt

On the basis that the two signals in the spectrum shown in Figure 3c are in fact due to neopentyl phosphonic acid **72** and neopentyl pyrophosphate **73** it was deemed necessary to re-examine our proposed

Figure 7.  $^{31}\text{P}$  NMR spectrum showing the reaction products from the synthesis of trimeric neopentyl metaphosphate 77.



reaction pathway and the experimental techniques used to generate neopentyl metaphosphate. This arose from the knowledge that the fragmentation of 72 and 73 clearly required the involvement of water, although from the reaction pathway and the reagents used (Scheme 42), its origin was not evident. In particular each chemical used had been thoroughly dried *under vacuo*, or in the case of DME as solvent, over calcium hydride. The experimental conditions and apparatus used had been designed specifically to exclude the presence of water to avoid reaction with the starting neopentyl phosphorodichloridate 67, *i.e.* the glassware was scrupulously dried by heating with a strong bunsen flame whilst flushing with a strong pulse of dry argon; in addition, the reaction was also carried out under an argon atmosphere. These considerations ultimately led us to re-examine in detail the nature of our supposed dipotassium pyrocarbonate precursor 65. These studies established that during its attempted preparation, decomposition of the dipotassium salt had occurred *in-situ*, despite careful precautions, to afford potassium hydrogen carbonate 78; the overall pathway is shown in Scheme 46.



Scheme 46. Formation of potassium hydrogen carbonate 78 from the base hydrolysis of diethyl pyrocarbonate 66

Evidence to support this finding is illustrated in Figure 8, which shows the FT-IR spectrum of the supposed dipotassium pyrocarbonate **65** (Figure 8a) and of authentic potassium hydrogen carbonate **78** (Figure 8b). As expected from two different samples, the intensities of the same peaks in each spectrum vary, however, but basically both spectra are identical with exactly the same peaks occurring in each spectrum. The conclusion drawn from the two spectra is that the two compounds are both identical *i.e.* they are both potassium hydrogen carbonate.

Indeed, the most convincing evidence to support the fact that our precursor was potassium hydrogen carbonate, was when the latter was condensed with neopentyl phosphorodichloridate **67**. The results and spectra obtained were identical to those shown in Figure 3, arising from the use of the supposed dipotassium pyrocarbonate, a clear result again that our precursor is in fact potassium hydrogen carbonate!

## **2.6 Condensation of potassium hydrogen carbonate **78** with neopentyl phosphorodichloridate **67****

In view of the evidence obtained that the supposed dipotassium pyrocarbonate is in fact potassium hydrogen carbonate, the mechanism for the generation of neopentyl metaphosphate **27** shown in Scheme 42 and proceeding *via* a cyclic pyrocarbonate phosphate, is now redundant. The new mechanism which is now proposed is shown in Scheme 47.

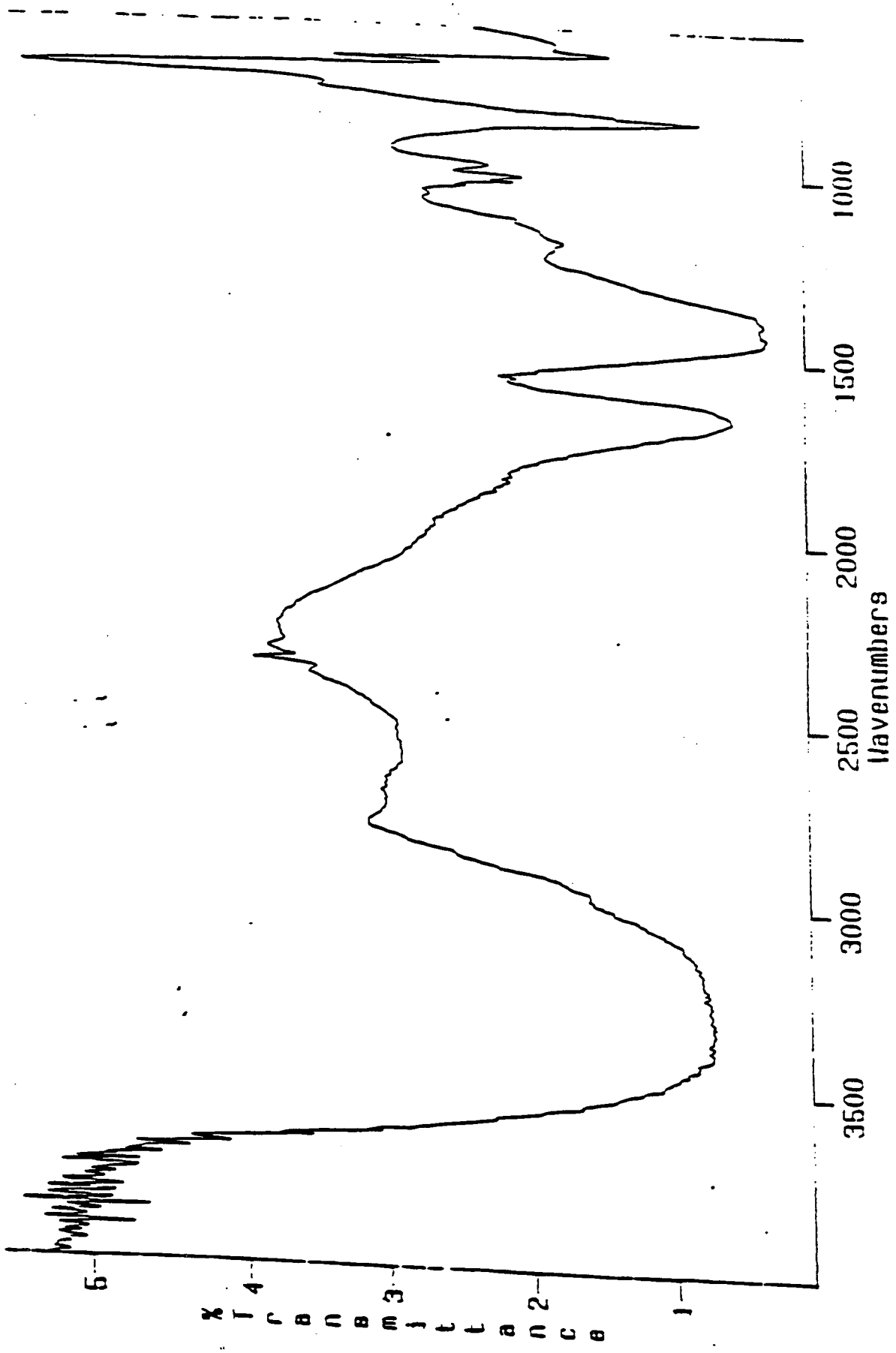


Figure 8a. FTIR spectrum of the product, expected to be dipotassium pyrocarbonate 65, from the base hydrolysis of diethyl pyrocarbonate 66.

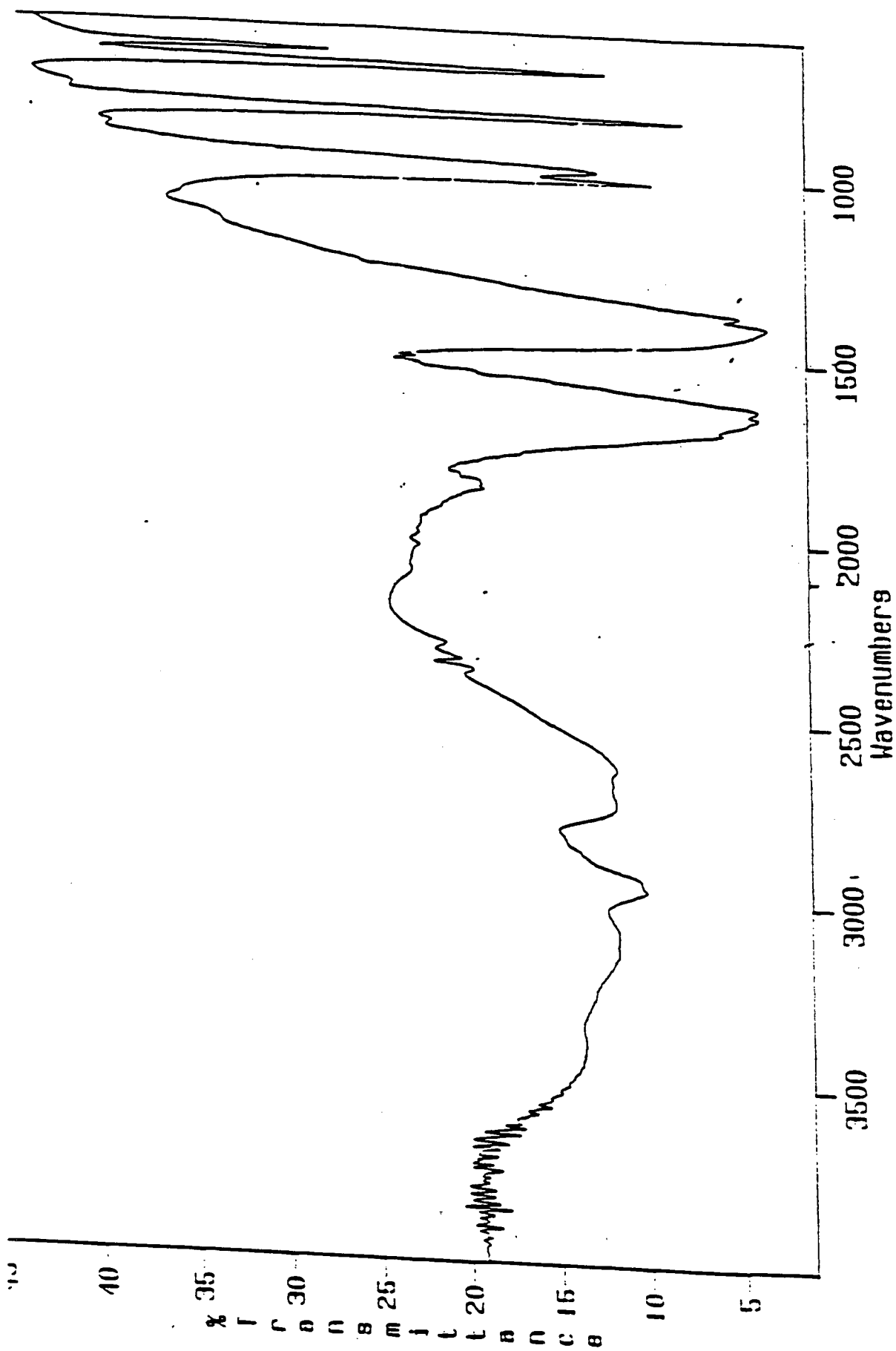
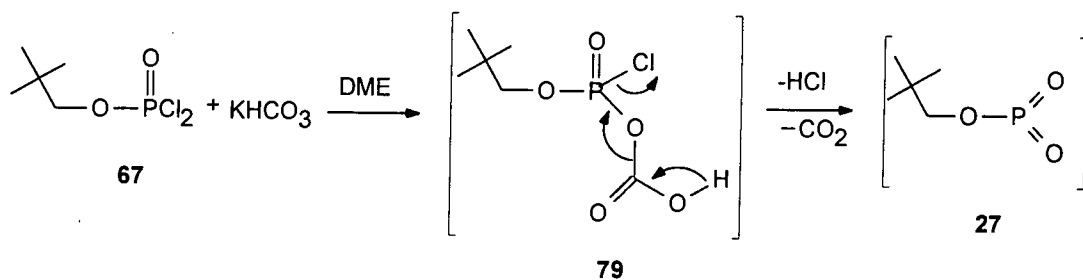


Figure 8b. FTIR spectrum of an authentic sample of potassium hydrogen carbonate 78.



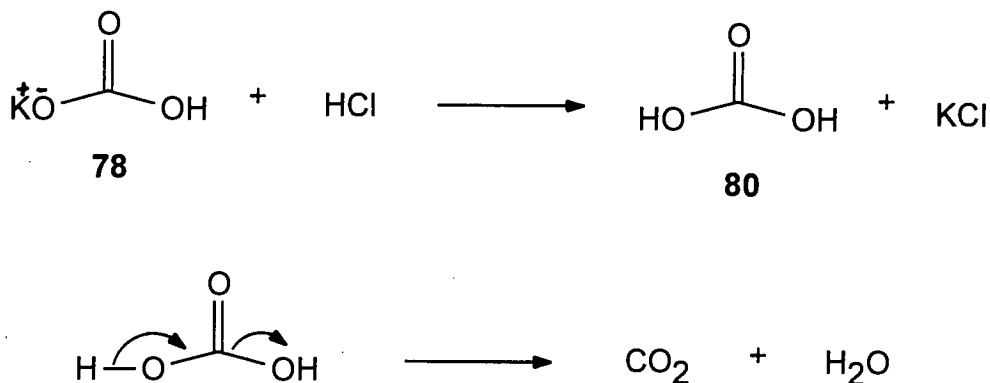
Scheme 47. Proposed mechanism for the generation of neopentyl metaphosphate **27** starting from potassium hydrogen carbonate **78**

The proposed reaction pathway involves two steps, the first being the reaction of potassium hydrogen carbonate with neopentyl phosphorodichloridate **67** to produce the transient mixed carbonic-phosphoric anhydride **79**. The second step involves the fragmentation of the unstable anhydride, by loss of one mole each of hydrochloric acid and carbon dioxide, to produce neopentyl metaphosphate **27**.

## 2.7 The origin of water

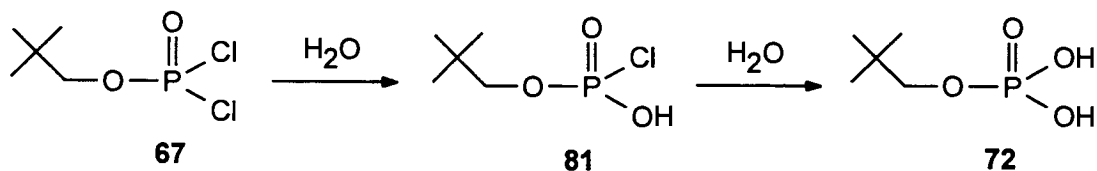
From the proposed reaction pathway and mechanism shown in Scheme 47, the origin of the water to form neopentyl phosphonic acid and neopentyl pyrophosphate (see Figure 3c) is still not apparent, but can be explained on the basis of the evolution of hydrochloric acid, which proceeds to attack unreacted potassium hydrogen carbonate as shown in Scheme 48, to produce dihydrogen carbonate **80**. It seems that the latter

is unstable, and under the conditions employed, fragments to evolve carbon dioxide, and form the essential water.



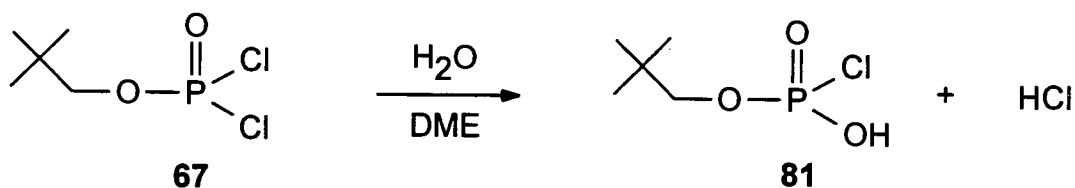
Scheme 48. The origin of water from the condensation of neopentyl phosphorodichloridate **67** with potassium hydrogen carbonate **78**

With reference to the involvement of water in the reaction, one would expect that its presence might also cause the hydrolysis, or part hydrolysis, of the starting neopentyl phosphorodichloridate as shown in Scheme 49. Of course, complete hydrolysis would produce neopentyl



Scheme 49. Hydrolysis of neopentyl phosphorodichloridate **67**

phosphonic acid **72**, which is also a product of the reaction of neopentyl metaphosphate with water, as well as the hydrolysis of polymeric phosphates formed by the polymerisation of neopentyl metaphosphate. Partial hydrolysis of neopentyl phosphorodichloridate **67** is expected to produce neopentyl phosphorochloridic acid **81**, which should be observed in the  $^{31}\text{P}$  NMR spectrum of the reaction mixture. Referring to Figure 3b, there is an unidentified minor signal at 2.82 ppm, which can be assigned to **81** due to its  $^{31}\text{P}$  chemical shift lying midway between **67** and **72**. To try to prove this, and thus account for all of the signals in Figure 3, formation of **81** was attempted by the partial hydrolysis shown in Scheme 50. The  $^{31}\text{P}$  NMR spectrum of the reaction mixture was taken after one hour and is shown in Figure 9, from which it is clearly evident that there is only one product signal at 2.28 ppm. On this evidence, it appears likely that the signal at 2.82 ppm in Figure 3b could well be due to neopentyl phosphorochloridic acid **81**.



Scheme 50. Synthesis of neopentyl phosphorochloridic acid **81**

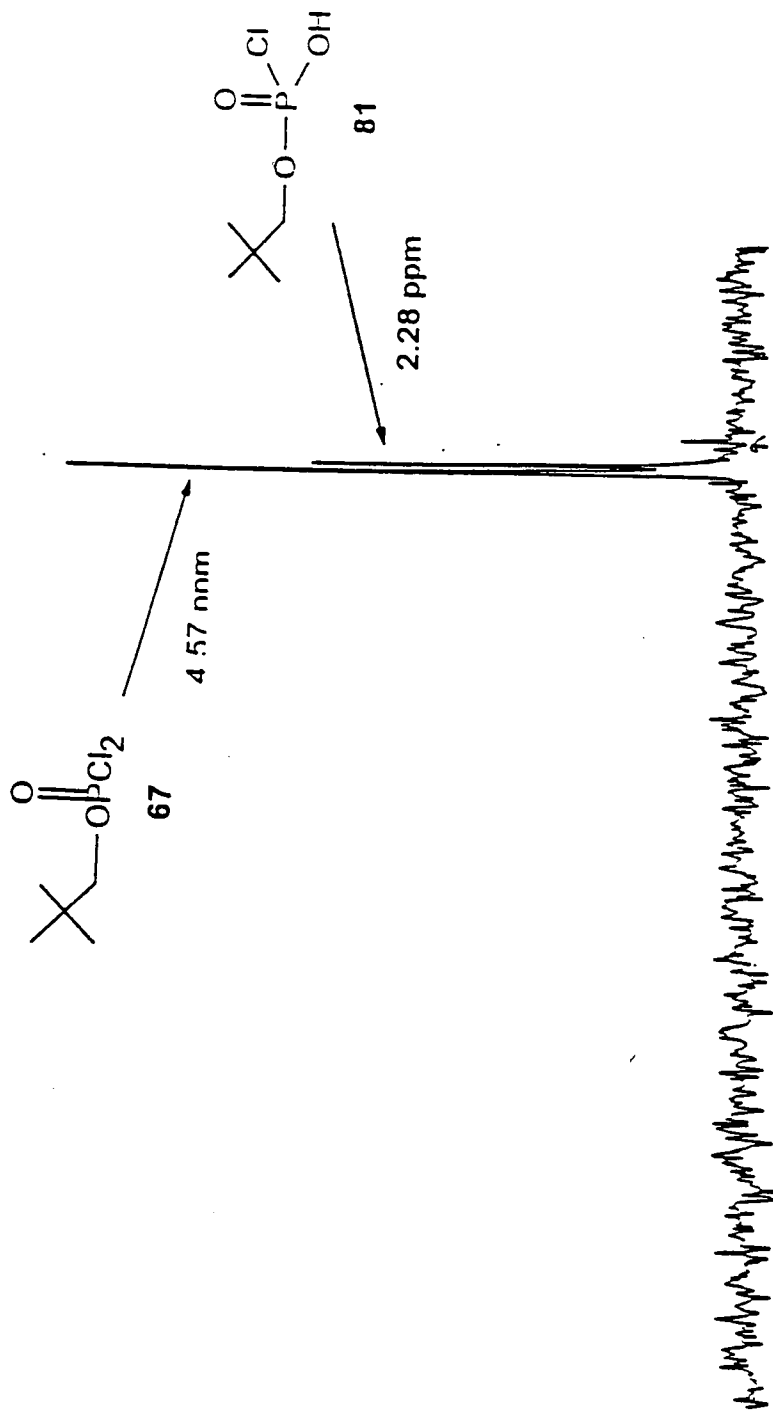


Figure 9.  $^{31}\text{P}$  NMR spectrum of the reaction mixture from the attempted synthesis of neopentyl phosphorochloridic acid **81** taken after one hour

## 2.8 Trapping of neopentyl metaphosphate 27 with styrene oxide

In view of a fuller understanding and an acceptable mechanism for the generation of neopentyl metaphosphate 27 from the condensation of neopentyl phosphorodichloridate 67 with potassium hydrogen carbonate 78, attempts were made to intercept and trap the metaphosphate which had been generated. To this end, a suitable trapping agent had to be employed, and for this purpose styrene oxide 82 was chosen. The main reason for this choice was that styrene oxide was unreactive towards the starting neopentyl phosphorodichloridate 67, but for a more detailed explanation, the reader is referred to 4.2..

When the generation of neopentyl metaphosphate 27 was carried out, under the same conditions as described previously in this chapter in the presence of one equivalent of styrene oxide, the  $^{31}\text{P}$  NMR spectrum of the reaction changed markedly. Instead of the major signals being neopentyl phosphonic acid 72 (0.26 ppm) and the self-condensation products of neopentyl metaphosphate ( $\delta$  -12 to -14 and -23 to -26 ppm regions), the spectrum consisted almost entirely of a closely matched pair of peaks at 15.94 and 15.82 ppm as shown in Figure 10. Signals in the  $\delta$  16 to 18 ppm region are characteristic to cyclic phosphates with five membered rings<sup>11,67</sup>, and on this basis the pair of peaks were assigned to the expected diastereomeric mixture of 2-neopentyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide 83. The route to 83 is shown in Scheme 51.

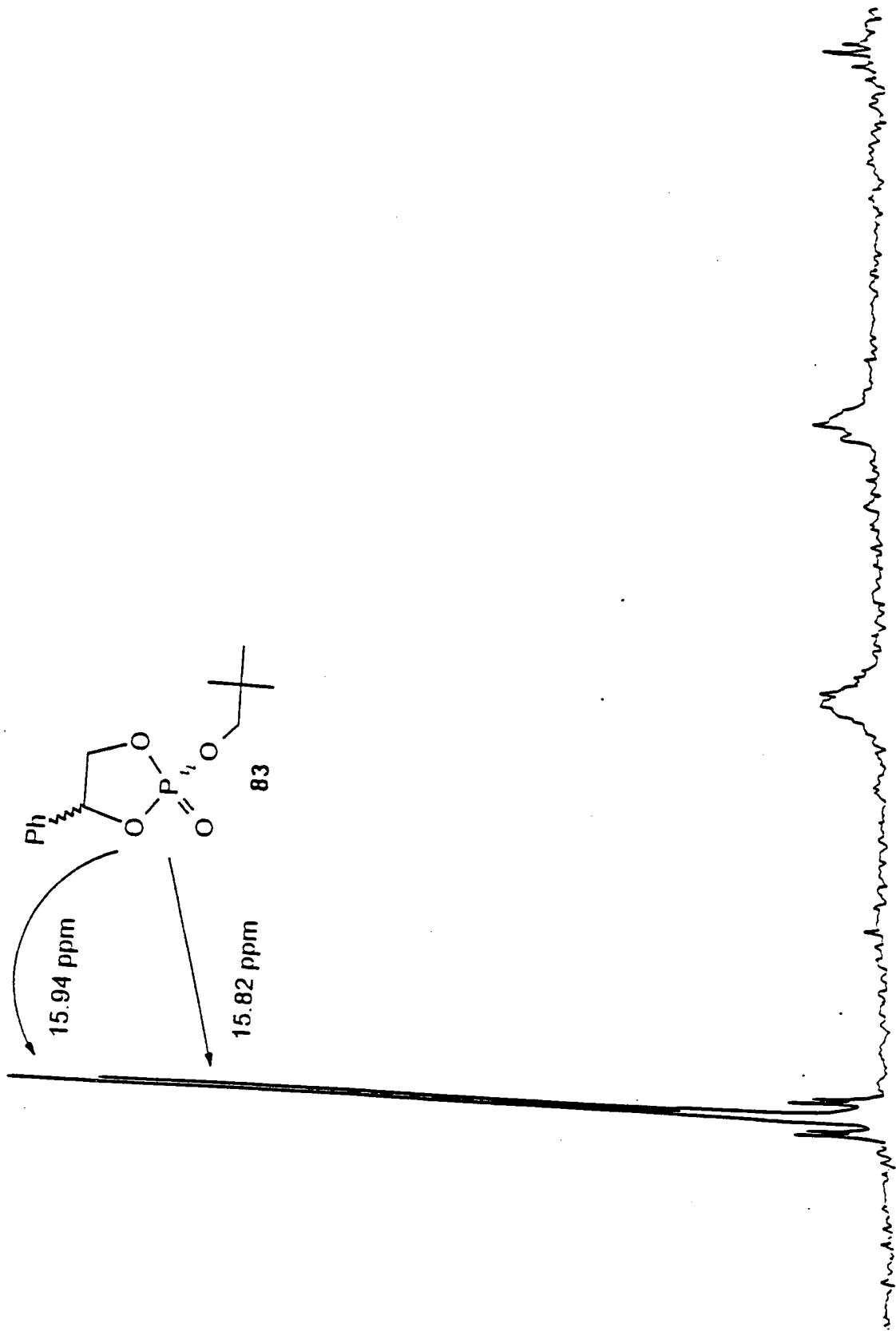
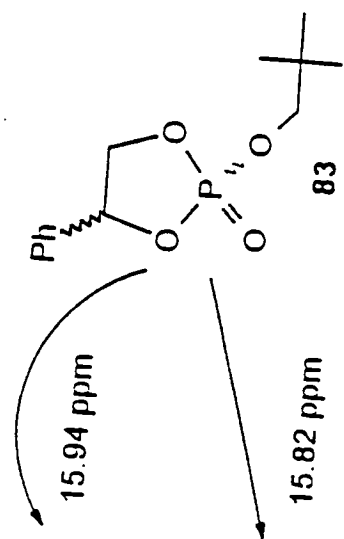
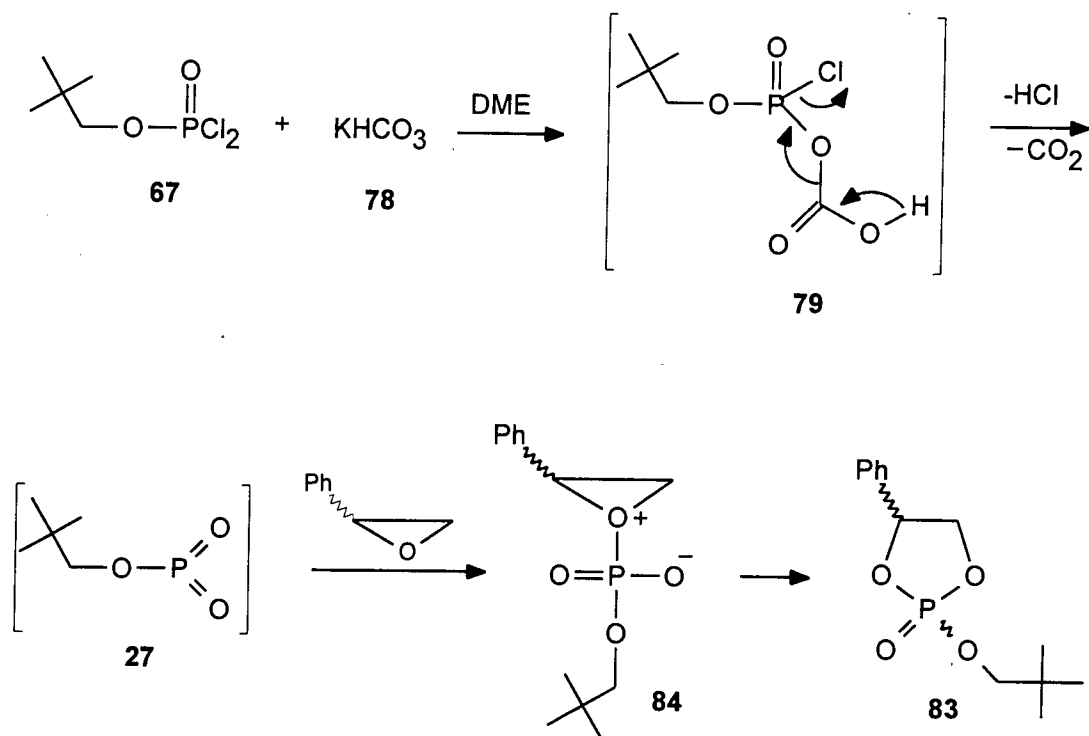


Figure 10.  $^{31}\text{P}$  NMR spectrum taken after twenty four hours from the reaction of neopentyl phosphorodichloridate 67 with potassium hydrogen carbonate 78 in the presence of styrene oxide.

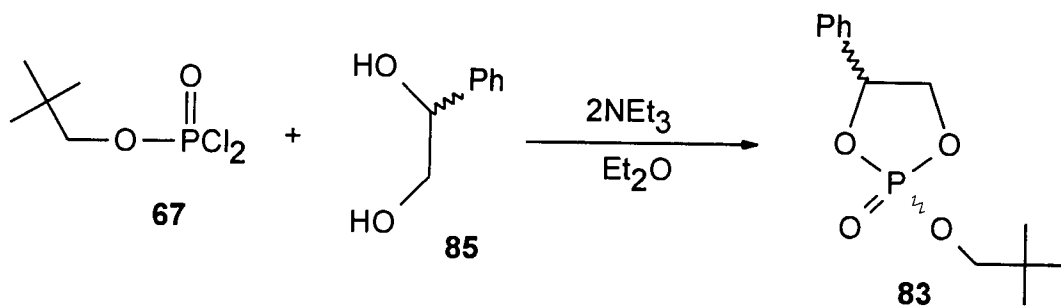


Scheme 51. Generation and trapping of neopentyl metaphosphate **27** by styrene oxide

The route to the trapped product proceeds *via* the Lewis salt<sup>11</sup> **84** which then rearranges to **83**. There are a few possibilities for mechanistic pathways leading to **83** and for a more detailed discussion of these various mechanisms, the matter is dealt with in depth in chapter 4.

In order to confirm that the closely matched pair of peaks in the spectrum shown in Figure 10 was in fact due to a diastereomeric mixture of **83**, an authentic sample was prepared and compared to the reaction mixture shown in Figure 10 by standard peak enhancement experiments.

The synthetic route to **83** is shown in Scheme 52.



Scheme 52. Synthetic route to **83**

The  $^{31}\text{P}$  NMR spectrum of the product obtained by independent synthesis is shown in Figure 11 and displays the expected closely matched pair of peaks at 16.15 and 15.99 ppm. By using the peak enhancement technique, verification was obtained, that the pair of peaks in Figure 10, generated *via* neopentyl metaphosphate, was in fact due to a diastereomeric mixture of 2-neopentyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **83**.

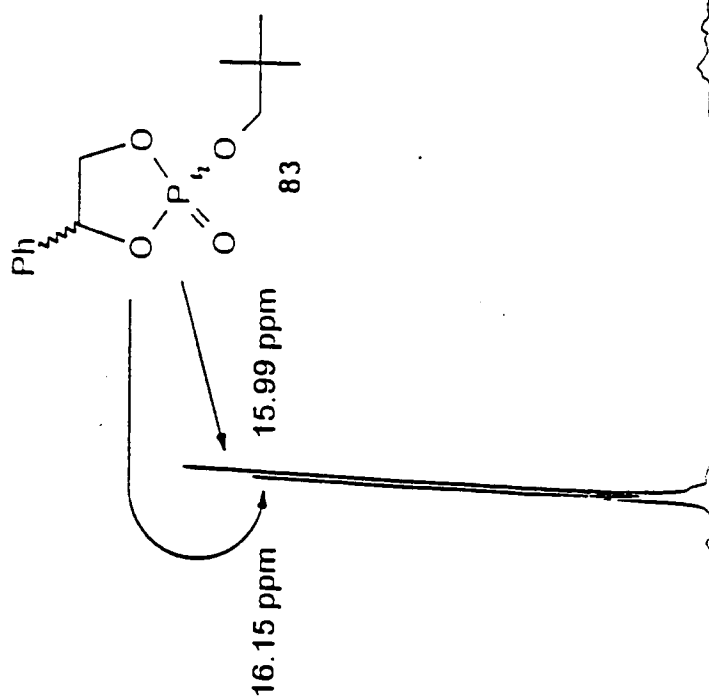


Figure 11.  $^{31}\text{P}$  NMR spectrum of the reaction mixture from the independent synthesis of an authentic sample of 2-(4-phenyl-1,3,2-dioxaphospholane-2-yl)ethane-1,1-diol 83.

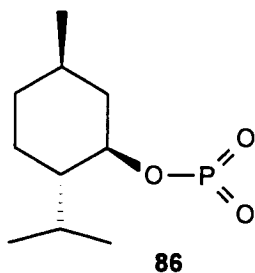
## 2.9 Conclusion

From the preceding discussion it is evident that a new and convenient route to alkyl metaphosphates has been developed by fragmentation of a mixed carbonic-phosphoric anhydride which is generated *in situ* from the reaction of potassium hydrogen carbonate with an alkyl phosphorodichloridate. Evidence to support the generation of alkyl metaphosphates and the proposed reaction pathway can be summarised as follows:

- In the absence of trapping agents, signals in the  $^{31}\text{P}$  NMR spectrum in the characteristic regions  $\delta$  -12 to -14 and -23 to -26 ppm are observed. These are due to self-condensation reactions of monomeric neopentyl metaphosphate **27** and are consistent with literature reports for such polymeric species<sup>8,11,18</sup>.
- FAB-MS confirms such species to consist of cyclic polymers of monomeric neopentyl metaphosphate.
- The observation of carbon dioxide being evolved by the classic "lime water" test is consistent with the proposed reaction pathway.
- The observation of neopentyl phosphonic acid **72** and neopentyl pyrophosphate **73** is a direct result of the involvement of water in the reaction. The water is formed from the reaction of evolved hydrochloric acid with potassium hydrogen carbonate

- In the presence of styrene oxide, neopentyl metaphosphate **27** can be generated, and then trapped as a diastereomeric mixture of 2-neopentyloxy-4-phenyl-1,3,2,-dioxaphospholane-2-oxide, which are observed as a closely matched pair of signals in the  $^{31}\text{P}$  NMR spectrum in the  $\delta$  15 to 18 ppm region<sup>11</sup>.

It is evident from these observations that neopentyl metaphosphate **27** is in fact being generated in the system under study. In order to give this new method of generating alkyl metaphosphates greater practical value, two aspects need to be studied further: a) the generation of a wider variety of alkyl metaphosphates, and b) the trapping of the metaphosphates with a greater variety of trapping agents. The first point has already been studied to a small extent with the generation of methyl **20** and (-)-menthyl **86** metaphosphate by this method. The second point has still to be investigated, and should be the focus of any future research. The major problem that can be foreseen is the possible reactions between trapping reagent, *e.g.* alcohols and amines with the acidic alkyl phosphorodichloridates, thus preventing the generation of the desired alkyl metaphosphate.



## **Chapter Three**

### **Generation of Alkyl Metaphosphates by Reaction of Alkyl Phosphorodichloridates with Disodium Pyrocarbonate**

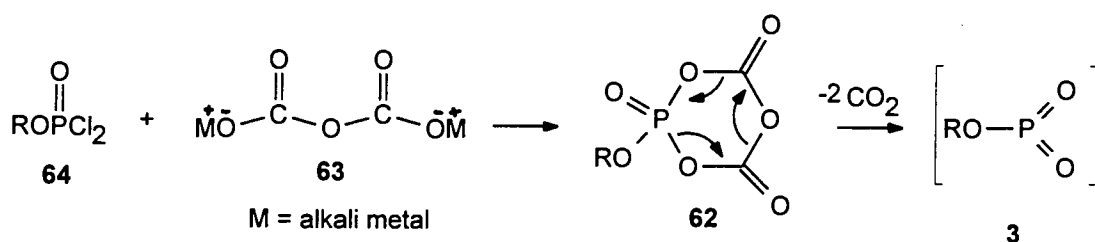
# Chapter Three

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### 3.1 Introduction

As in the previous chapter, the aim of the work described in this chapter was to attempt to synthesis novel pyrocarbonate salts **63**, and subsequently carry out condensations with alkyl phosphorodichloridates **64** to produce novel cyclic pyrocarbonate phosphates such as **62**. Again, it is envisaged that compounds such as **62** would undergo chelotropic breakdown with the release of two moles of carbon dioxide and the production of alkyl metaphosphates as shown in Scheme 40.

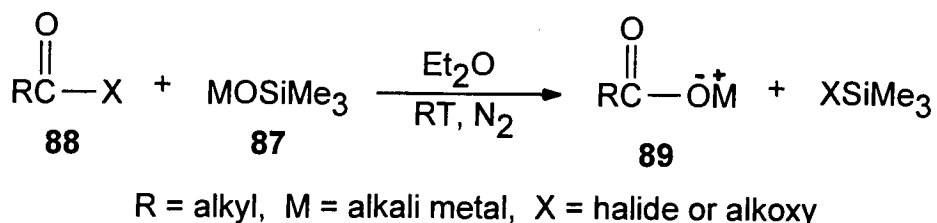


Scheme 40. Proposed generation of alkyl metaphosphates **3** *via* novel cyclic pyrocarbonate phosphate esters **62**.

### 3.2 Synthesis of disodium pyrocarbonate

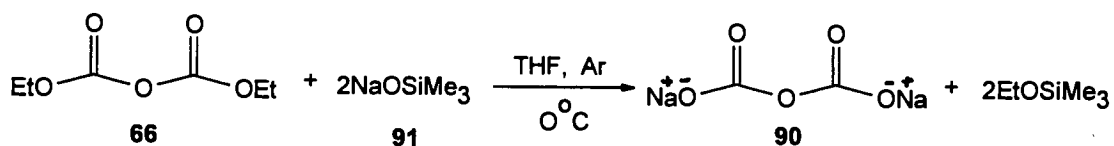
Renewed attempts to synthesis pyrocarbonate salts such as **63** were given encouragement by the finding of a literature report by Laganis and Chenard<sup>68</sup>, who reported that alkali metal trimethylsilanolates **87** convert

carboxylic acid derivatives **88** into their corresponding anhydrous acid salts **89** under the mild non-aqueous conditions depicted in Scheme 53.



Scheme 53. Preparation of anhydrous carboxylic acid salts **89**.

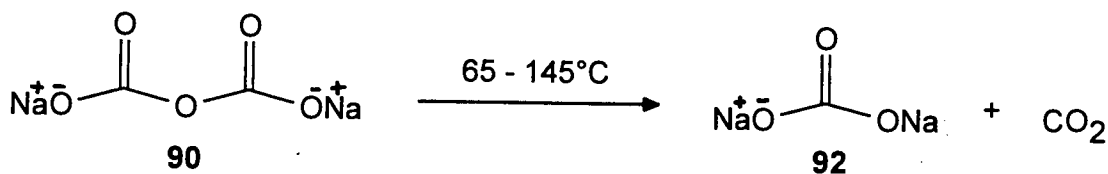
The report did not mention the possibility of preparing anhydrous pyrocarbonate salts by this method, but when attempts were made to prepare disodium pyrocarbonate **90** from diethyl pyrocarbonate **66** using this method, the procedure proved to be entirely successful (Scheme 54).



Scheme 54. Preparation of disodium pyrocarbonate **90**.

The procedure consisted simply of adding diethyl pyrocarbonate **66** to two equivalents of sodium trimethylsilanolate **91** in THF at 0°C, and

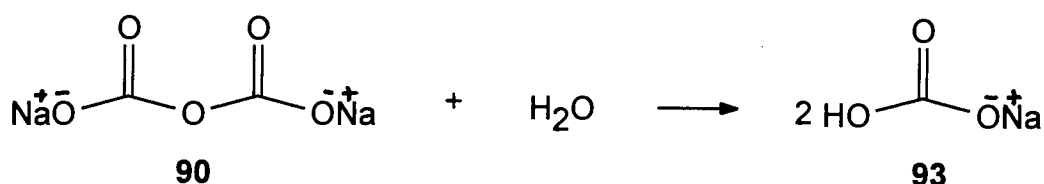
then allowing the reaction to stir overnight at room temperature. The product was obtained by filtration as a colourless solid in almost quantitative yield. A thorough analysis confirmed the identity of the solid to be disodium pyrocarbonate **90** ( $\nu_{\text{C=O}} = 1610 \text{ cm}^{-1}$ ; FAB-MS  $[\text{M}+1]^+ = 150.96199$ ,  $\text{C}_2\text{HNa}_2\text{O}_5$   $[\text{M}+\text{H}]^+$  requires 150.96200; solid state  $^{13}\text{C}$  NMR  $\delta = 162.16 \text{ ppm}$   $[\text{C}=\text{O}]$ ). Thermal gravimetric analysis (TGA) of a sample of the disodium pyrocarbonate salt also found that over a temperature range of 65 to 145°C the salt underwent decomposition *via* loss of one mole of carbon dioxide to produce sodium carbonate **92** (Scheme 55). Analysis of the TGA residue by FTIR proved the residue to be sodium carbonate by comparison with an authentic sample.



Scheme 55. Effect of temperature upon disodium pyrocarbonate **90**.

In order to confirm that water caused pyrocarbonate salts such as **90** to undergo hydrolysis to form alkali hydrogen carbonates, as occurred in chapter two (section 2.5) when diethyl pyrocarbonate was base-hydrolysed to produce potassium hydrogen carbonate, a sample of

disodium pyrocarbonate **90** was cautiously hydrolysed (Scheme 56) and the product analysed by FTIR. By comparison with an authentic sample, the product was proven to be sodium hydrogen carbonate **93** as expected.



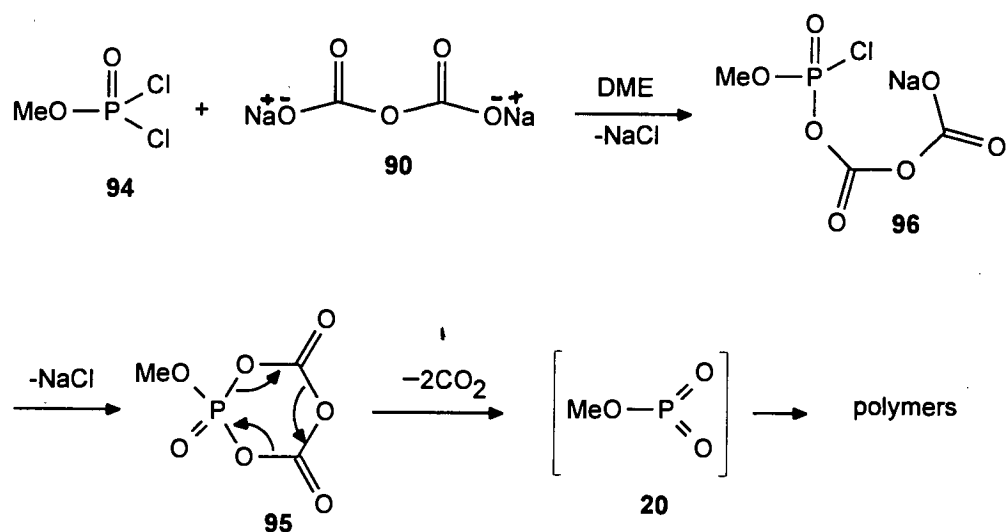
Scheme 56. Hydrolysis of disodium pyrocarbonate **90**.

### 3.3 Condensation of disodium pyrocarbonate **90** with alkyl phosphorodichloridates

#### 3.3.1 Methyl metaphosphate

Following on from the successful synthesis of disodium pyrocarbonate, the next step was to condense the salt with alkyl phosphorodichloridates. The first alkyl phosphorodichloridate to be chosen was methyl phosphorodichloridate **94**, and the procedure involved the condensation of disodium pyrocarbonate **90** with **94** at room temperature in anhydrous DME. After the addition was complete, the mixture was heated under reflux to produce the novel cyclic

pyrocarbonate phosphate (2-methoxy-1,3,5,2-trioxaphosphorinane-4,6-dione-2-oxide) **95**. Under the conditions employed, subsequent fragmentation of **95** occurred to produce methyl metaphosphate **20** as shown in Scheme 57.



Scheme 57. Generation of methyl metaphosphate **20** via the novel cyclic pyrocarbonate phosphate **95**.

As before (chapter 2), in order to follow the course of the reaction and understand the events that were occurring, the reaction was monitored by  $^{31}\text{P}$  NMR spectroscopy. The  $^{31}\text{P}$  NMR spectra illustrating the course of the reaction can be seen in Figure 12. The spectrum shown in Figure 12b provides strong evidence to support the formation of methyl metaphosphate. This is due to the presence of signals in the characteristic regions associated with polymeric products formed from the

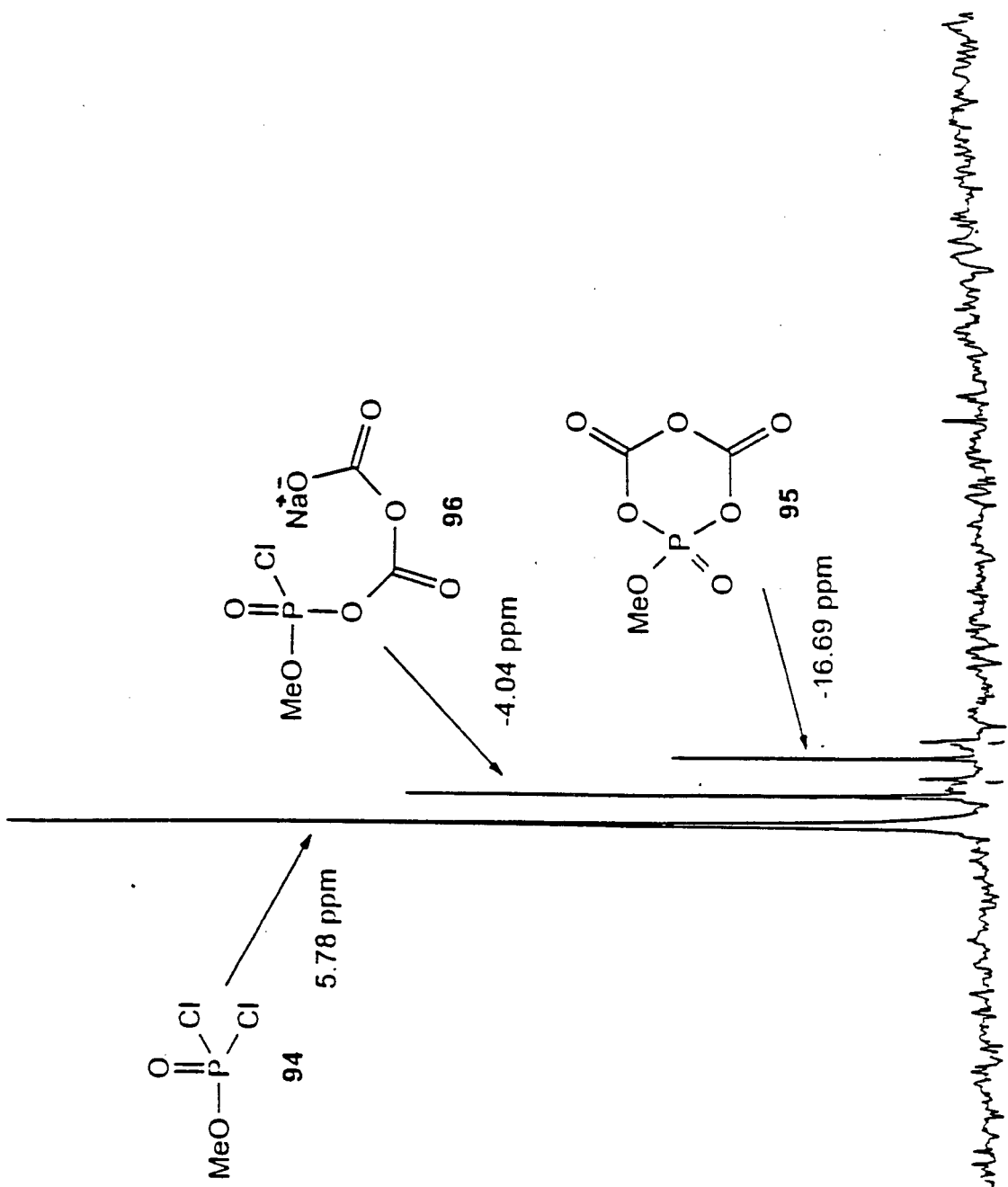


Figure 12a.  $^{31}\text{P}$  NMR spectrum from the reaction of methyl phosphorodichloridate 94 with disodium pyrocarbonate 96 after twenty minutes heating under reflux.

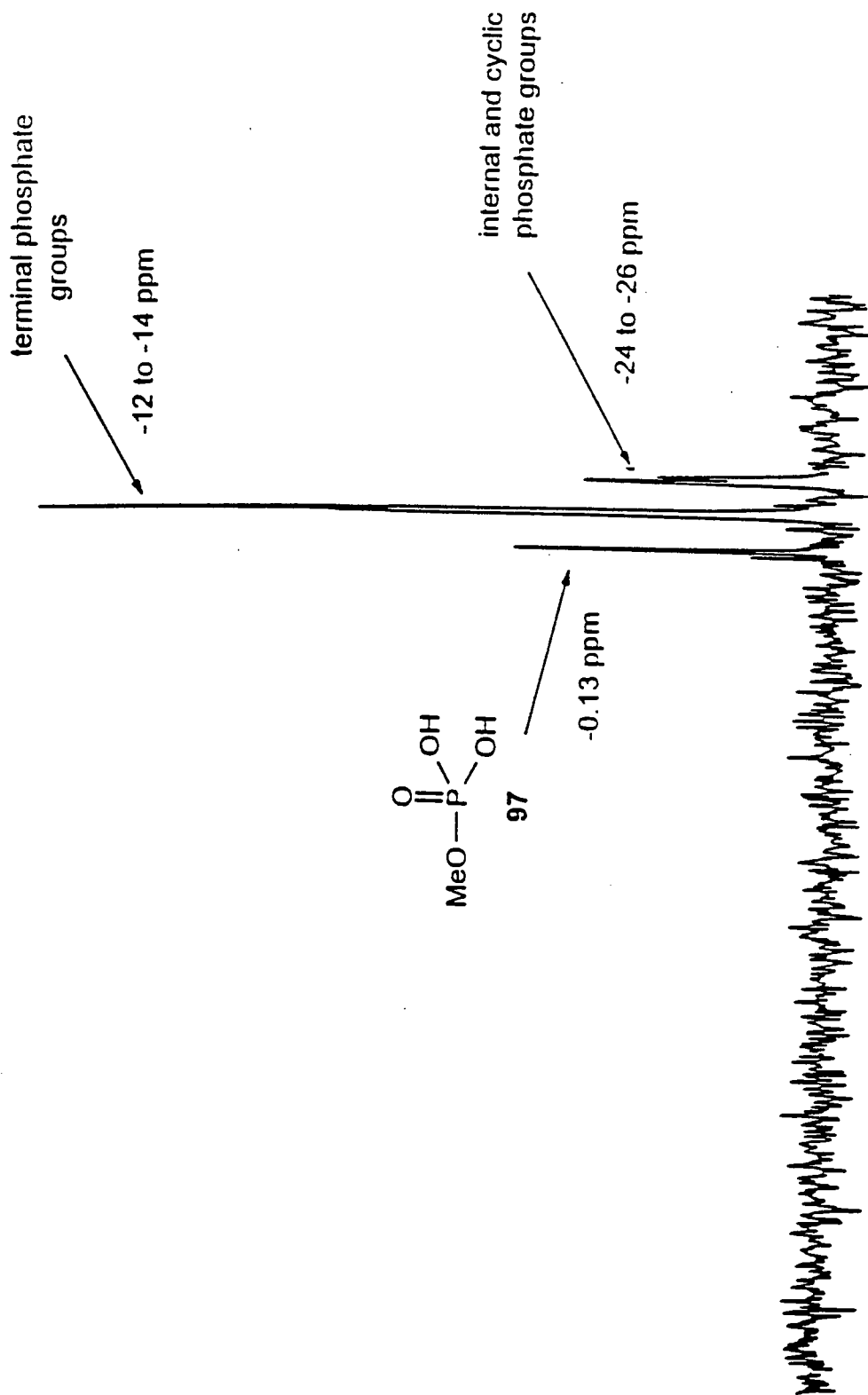
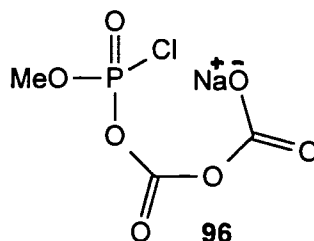
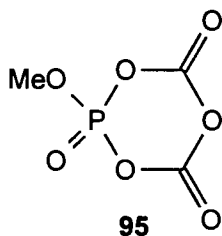


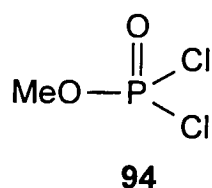
Figure 12b. <sup>31</sup>P NMR spectrum from the reaction of methyl phosphorodichloridate 94 with disodium pyrocarbonate 90 after one hour heating under reflux.

self-condensation reactions of monomeric methyl metaphosphate<sup>8,18</sup> **20**. These signals appeared in the region  $\delta$  -12 to -14 ppm, due to terminal phosphate groups, and in the region  $\delta$  -24 to -26 ppm due to internal and cyclic phosphate groups. Also present in the spectrum was a signal at -0.13 ppm which was assigned to methyl phosphonic acid **97**. Further evidence to support the proposed mechanism for the generation of methyl metaphosphate **20** (Scheme 57) was the detection of carbon dioxide being expelled from the reaction mixture. This was again detected by the classic "turning of lime-water chalky" by the gases being evolved from the reaction by the constant stream of argon.

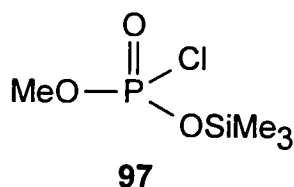
From the spectrum shown in Figure 12a, it is evident that methyl metaphosphate **20** had begun to be generated at least twenty minutes after the start of the reaction as evidenced by the appearance of characteristic signals due to polymers<sup>8,18</sup> in the regions  $\delta$  -12 to -14 ppm and -24 to -26 ppm. Some unreacted methyl phosphorodichloridate **94** was also present (5.78 ppm) in the mixture, together with two signals at -4.04 and -16.69 ppm, which are still unassigned, although it is believed that these are due to the novel cyclic pyrocarbonate phosphate (-16.69 ppm) **95**, and its partly condensed precursor (-4.04 ppm) **96**. Since these



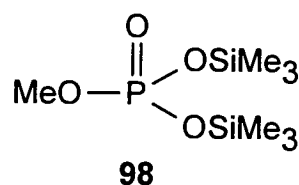
compounds were never isolated it was not possible to positively identify them, nor could a route be envisaged for their independent synthesis in order to carry out peak enhancement experiments. Tables of  $^{31}\text{P}$  NMR shift data were not helpful either in giving an indication of the possible  $^{31}\text{P}$  NMR shifts to be expected for **95** and **96** owing to their novel nature. The only piece of encouragement given to the correctness of the assignments of **95** and **96** to the signals at  $\delta$   $-4.04$  and  $-16.69$  ppm was when O-trimethylsilyl-O'-methyl phosphorochloridate **97** and bis-trimethylsilylmethyl phosphate **98** were synthesised during work described in chapter five. This emerged from the fact that when one, and



$$\delta\text{P} = 5.78 \text{ ppm}$$



$$\delta\text{P} = -4.444 \text{ ppm}$$

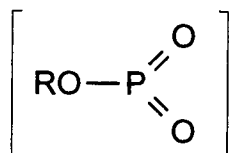


$$\delta\text{P} = -16.68 \text{ ppm}$$

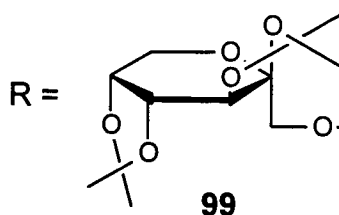
then both P-Cl bonds of **94**, were replaced by the  $-\text{OSiMe}_3$ , groups the trend in the  $^{31}\text{P}$  NMR shifts was almost identical to that of the trend in shifts of the signals to which **95** and **96** had been assigned. In each case, when the first P-Cl bond had been substituted, the shift moved from 5.78 ppm to around  $-4$  ppm, and then when the second had been substituted, the shift had moved again, in both cases to around  $-16$  ppm.

### 3.3.2 Further alkyl metaphosphates

With an appropriate mechanism and reaction pathway in hand for the generation of methyl metaphosphate **20** (Scheme 56), and having identified or assigned all of the products and intermediates observed in the  $^{31}\text{P}$  NMR spectra of the reaction, the method was extended to produce further alkyl metaphosphates. The metaphosphates that have been generated include methyl **20**, ethyl **45**, neopentyl **27**, and (-)-menthyl **86**, the generation of which is discussed in detail in chapter 4.

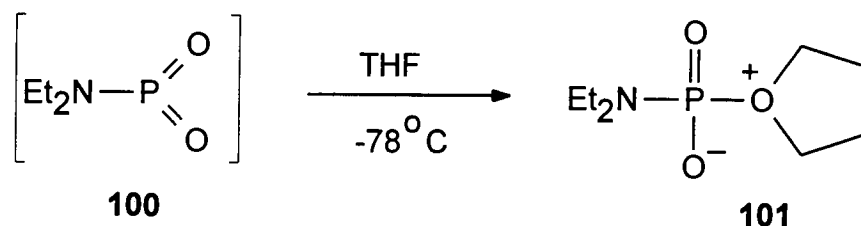


R	= methyl	<b>20</b>
	= neopentyl	<b>27</b>
	= ethyl	<b>45</b>
	= (-)-menthyl	<b>86</b>



The protected D-fructanose derived metaphosphate **99** was generated using the pyrocarbonate procedure in an attempt to directly observe for the first time ever, a free alkyl metaphosphate species. The inspiration for this approach came from the literature report by Quin<sup>69</sup>, who reported that when N,N-diethylamino metaphosphoramidate **100** was generated photochemically at  $-78^\circ\text{C}$  in THF, a sole signal appeared in

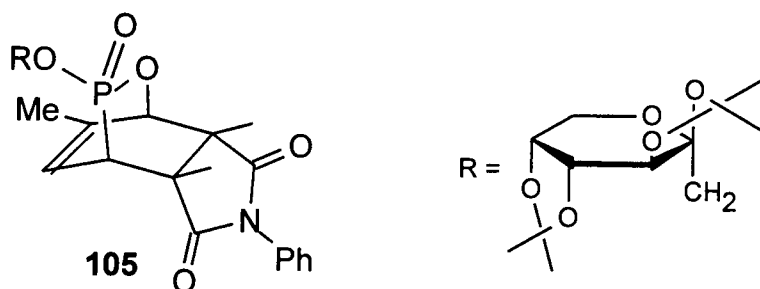
the  $^{31}\text{P}$  NMR spectrum of the reaction mixture and was assigned to the strongly solvated form of **100**, which is represented by **101** (Scheme 58).



Scheme 58

Obviously, the latter is not a free metaphosphoramidate, but a complex with THF, similar to other such structures that have been proposed with dioxane and acetonitrile<sup>18</sup>. Unfortunately, under the conditions employed, metaphosphate **99** could not be detected by  $^{31}\text{P}$  NMR spectroscopy, although the trapping with styrene oxide occurred as usual. Clearly it would be better to generate the metaphosphate **99** at  $-78^\circ\text{C}$  in a non-complexing solvent, then it may undergo internal complexation *via* the available oxygen atoms on the D-fructanose system. There is the possibility of both five and six membered rings that could be formed *via* complexation, although one cannot also rule out the possibility of insertion into a *C-H* bond. If either or both of these complexes are

formed, their observation by  $^{31}\text{P}$  NMR spectroscopy at  $-78^\circ\text{C}$ , would be the first ever direct evidence for the existence of a free metaphosphate. The next step, however, has not yet been carried out but it was planned to build in the incipient metaphosphate species **99** into Quin's bicyclooctene system to form **102** since this type of precursor has been shown to fragment photochemically<sup>5</sup> at a temperature of  $-78^\circ\text{C}$ . Experiments to try and generate the internal complexes of metaphosphate **99** would then be undertaken.

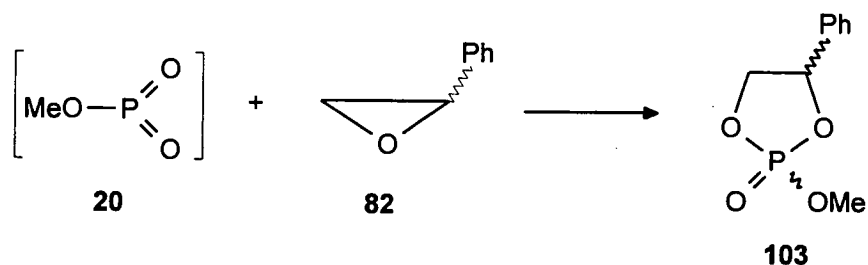


### 3.4 Trapping of alkyl metaphosphates by styrene oxide

With a better understanding of what was occurring when alkyl metaphosphates were generated from the condensation of disodium pyrocarbonate with alkyl phosphorodichloridates (Scheme 57), it was

decided to undertake trapping experiments with styrene oxide **82** as with the work described in chapter two.

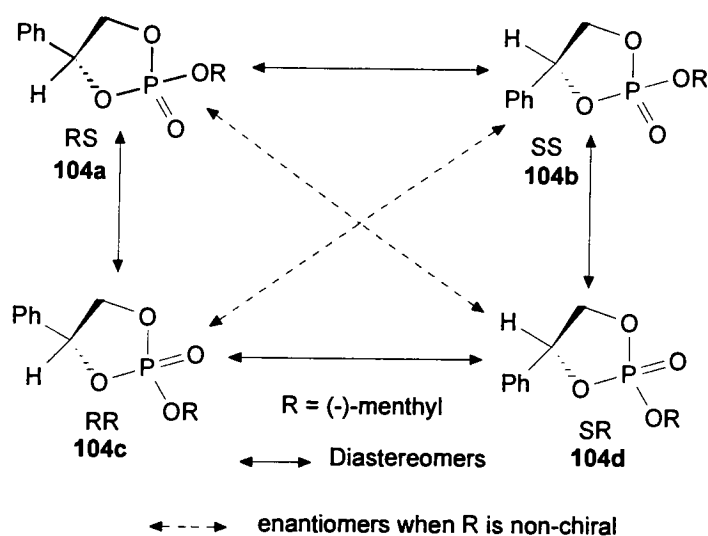
Accordingly, the generation of methyl metaphosphate **20** was carried out, under the same reaction conditions used previously, in the presence of one equiv. of styrene oxide. Almost immediately the  $^{31}\text{P}$  NMR spectrum of the reaction mixture changed markedly, and within minutes the spectrum consisted almost entirely of a closely matched pair of peaks in the region  $\delta$  15 to 18 ppm. On the basis of earlier work undertaken (see chapter 2), these signals were attributed to a diastereomeric mixture of 2-methoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **103**, resulting from the trapping of methyl metaphosphate **20** with styrene oxide as depicted in Scheme 59. When ethyl **45** and neopentyl metaphosphate **27** were also generated in the presence of styrene oxide similar results were obtained, thus demonstrating the efficiency of styrene oxide as a trapping agent.



Scheme 59

It is of interest to note that when (-)-menthyl metaphosphate **86** was generated in the presence of styrene oxide, the  $^{31}\text{P}$  NMR spectrum

obtained consisted of not two, but four closely spaced signals of almost equal intensity. As shown in Figure 13, these appeared in the region  $\delta$  15 to 18 ppm, indicating that a mixture of 1,3,2-dioxaphospholane-2-oxides had still been formed. The explanation for the presence of four signals on this occasion is that all four possible diastereomers are being observed in the  $^{31}\text{P}$  NMR spectrum due to the enantiomerically pure nature of the (-)-menthyl component of the product **104**. In previous examples, the generated metaphosphate had non-chiral alkyl groups, e.g. methyl or neopentyl, and although four diastereomers are still formed, two pairs are present as enantiomers which are indistinguishable by  $^{31}\text{P}$  NMR spectroscopy, thus resulting in only two signals being observed. The four possible products are shown in Scheme 60.



Scheme 60. Possible products from the reaction of alkyl metaphosphates with styrene oxide

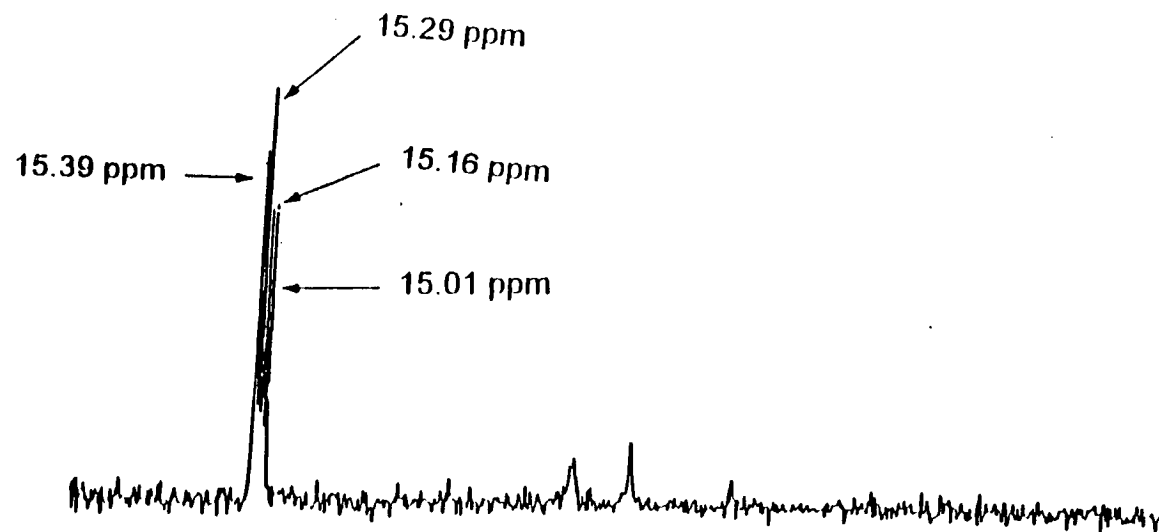
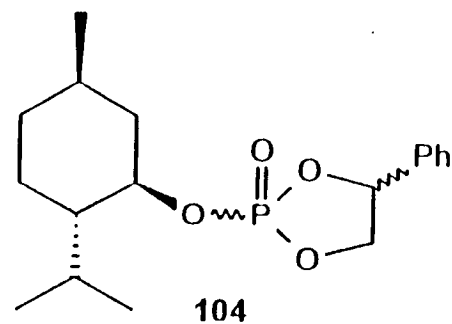


Figure 13.  $^{31}\text{P}$  NMR spectrum after 30 minutes from the reaction of (-)-menthyl phosphorodichloridate **123** with disodium pyrocarbonate **90** in the presence of styrene oxide.

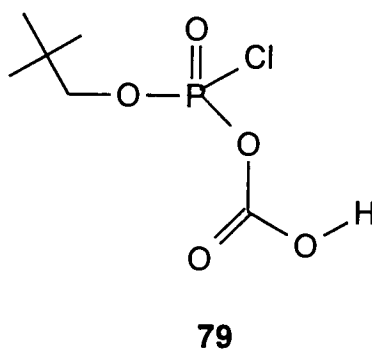
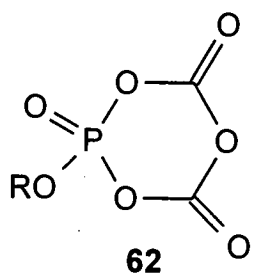
### 3.5 Conclusion

It is evident from the discussion in this chapter that a further new, and convenient, route to alkyl metaphosphates has been developed to add to the method discussed in the previous chapter. Evidence to support the generation of alkyl metaphosphates by the proposed reaction pathway outlined in Scheme 57, is summed up in the following brief points:

- In the absence of trapping agents, signals in the  $^{31}\text{P}$  NMR spectrum are observed in the characteristic regions  $\delta$  -12 to -14 ppm and -23 to -26 ppm. These are due to self-condensation reactions of the monomeric alkyl metaphosphates and are consistent with the literature reports for such compounds<sup>8,11,18</sup>.
- When alkyl metaphosphates are generated in the presence of styrene oxide, trapping occurs to yield diastereomeric mixtures of 2-alkoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxides<sup>11</sup>. These are observed in the  $^{31}\text{P}$  NMR spectrum in the region  $\delta$  15 to 18 ppm as either a closely spaced pair of signals, or four closely spaced signals, depending upon the absence or presence of chirality in the pendant alkyl group.
- The observation of carbon dioxide being evolved by the classic "lime water" test is consistent with the proposed reaction pathway.

It is obvious from these results and their consistency with literature reports for such compounds that alkyl metaphosphates are in fact being

generated *via* the cyclic pyrocarbonate phosphate ester **62**. As with the route involving the mixed carbonic-phosphoric anhydride **79**, the same two aspects need to be studied further to give the method practical value. These are a) the generation of a greater variety of metaphosphates, and more importantly, b) the trapping of the metaphosphates with a greater variety of trapping agents.



## **Chapter Four**

### **Trapping of Alkyl Metaphosphates by Styrene Oxide and the Proposed Reaction Mechanisms**

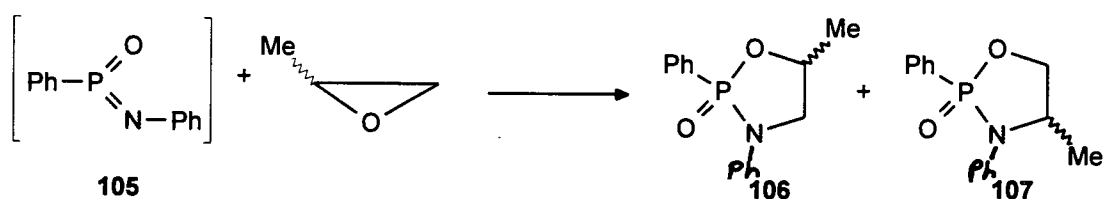
# Chapter Four

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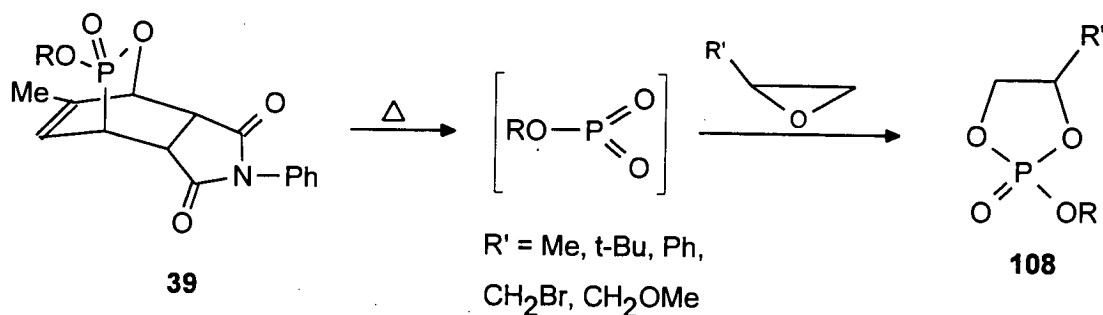
## 4.1 The use of epoxides as trapping agents

It has been well established that when alkyl metaphosphates **3** are present in solution they act as extremely powerful electrophiles and are efficient phosphorylating agents<sup>18-20</sup>. They have been used to phosphorylate hydroxy-<sup>4-7</sup> and amino-<sup>8-10</sup> compounds and can even cause electrophilic substitution on activated aromatic ring systems such as anilines<sup>8,14</sup> and *N*-methylpyrrole<sup>15</sup>. It was for these reasons that epoxides were first considered by Quin<sup>11,52</sup> as trapping agents for alkyl metaphosphates. There are many cases known where electrophiles lead to the ring-opening of epoxides with subsequent formation of cyclic products<sup>70</sup>. Amongst these is an example of another low-coordination and highly reactive phosphorus species, metaphosphonimidate **105**, which Bertrand<sup>71</sup> *et. al.* demonstrated would react with propylene oxide to form the 5-membered ring systems **106** and **107** (Scheme 61).



Scheme 61

Quin reasoned that due to the similarities in reactivity between metaphosphonimidates and alkyl metaphosphates, the same type of reaction could be exploited to trap alkyl metaphosphates, generated by the fragmentation of Quin's oxaphosphabicyclo-octene system **39**, with a number of epoxides to form 1,3,2-dioxaphospholane-2-oxides<sup>11,52</sup> **108** (Scheme 62).



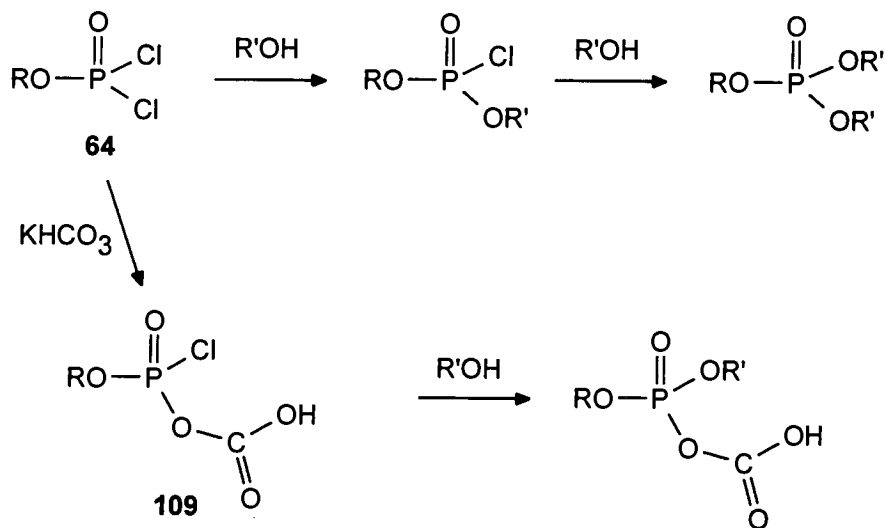
Scheme 62

Since the development of epoxides as efficient trapping agents for alkyl metaphosphates, only Quin<sup>11,52</sup> and the present study<sup>72</sup>, have made use of this reaction.

## 4.2 Choice of styrene oxide as trapping agent for the present study

In most previous studies of alkyl metaphosphates the only criterion that a trapping agent had to fulfill was to act solely as an efficient trap. In the present study, however, difficulties arise regarding the choice of trapping

agent required due to the necessary use of alkyl phosphorodichloridates **64** as starting material. If the more conventional trapping agents were to be used, such as alcohols and amines, then they could react preferentially with the alkyl phosphorodichloridate to block the formation of the precursors needed to generate the alkyl metaphosphate (Scheme 63). In the case of the reaction of **64** with potassium hydrogen carbonate, if the mixed anhydride **109** were to be formed, once again generation of the alkyl metaphosphate could be inhibited due to the competition of anhydride fragmentation with the reaction of alcohol or amine and anhydride (Scheme 63).



Scheme 63

The choice of trapping agent was therefore restricted to include only reagents which were unreactive towards alkyl phosphorodichloridate. For

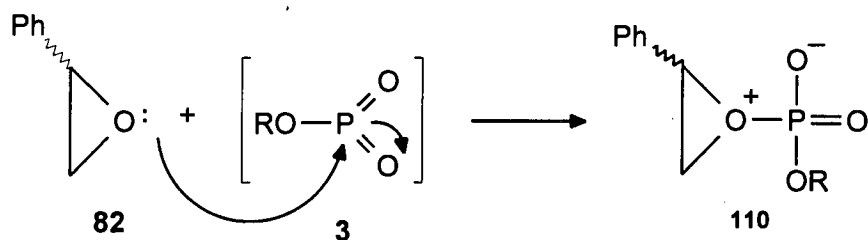
this reason, the trapping agent chosen was styrene oxide **82** which is an inexpensive and commonly available organic compound.

Another major advantage to using styrene oxide is the ease with which the trapped product could be detected by examination of the reaction mixture by  $^{31}\text{P}$  NMR spectroscopy. It is known<sup>8,18</sup> that when no trapping agent is present, or indeed if trapping is incomplete, then metaphosphates undergo self-reaction to give characteristic  $^{31}\text{P}$  NMR signals in the region  $\delta$  - 10 and -20 ppm, with signals at around 0 ppm due to unidentified phosphates also being observed. However, when styrene oxide is present as a trap, signals appear in the region 16-18ppm, which are unique to cyclic phosphates with five membered rings<sup>67</sup> and can be easily assigned to 1,3,2-dioxaphospholane-2-oxides. The assignment is made even simpler by the fact that when alkyl metaphosphates are trapped by styrene oxide, diastereomeric mixtures are formed which appear as a characteristic pair of signals in the  $^{31}\text{P}$  NMR spectrum<sup>11</sup>. The diastereomeric pairs possible are shown in Scheme 60 (*vide supra*).

### **4.3 Mechanistic considerations of the alkyl metaphosphate-epoxide reaction**

The reaction of alkyl metaphosphates with styrene oxide to form 1,3,2-dioxaphospholane-2-oxides proceeds *via* a mechanistic pathway that is complex and not yet completely understood. There are a number of mechanisms which have been proposed<sup>11</sup> and all of them will be discussed here. The common step involved in all the mechanisms is the initial formation

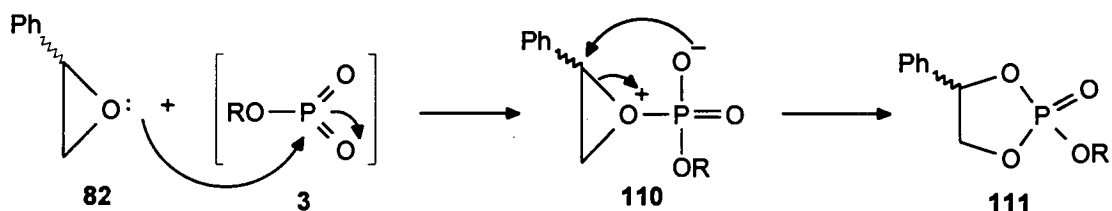
of a Lewis salt 110 from the attack on styrene oxide by the alkyl metaphosphate (Scheme 64). The formation of the Lewis salt is generally accepted since alkyl metaphosphates are extremely powerful electrophiles and are believed to co-ordinate with etheral oxygen<sup>18</sup>.



Scheme 64

#### 4.3.1 One step internal nucleophilic substitution

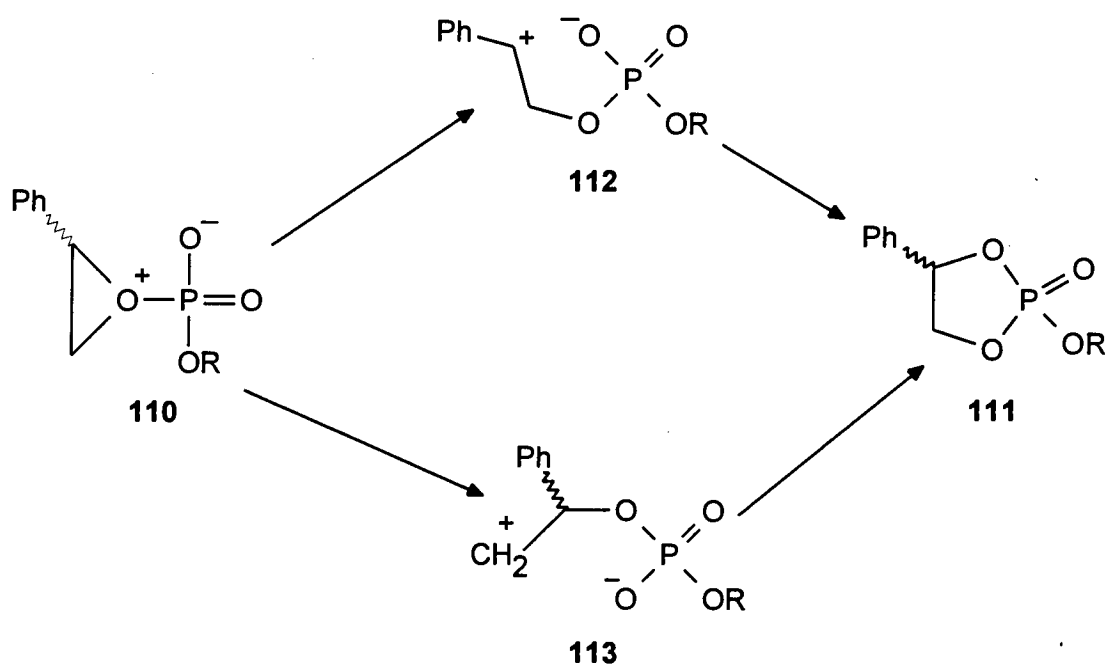
The pathway proposed in Scheme 65 involves an internal nucleophilic substitution and is shown to take place by the anion at the more sterically hindered carbon centre. However, attack can also be envisaged taking place at the methylene carbon centre of the epoxide ring which would probably be favoured on steric grounds. This pathway (*i.e.* 110 to 111) has been thought



Scheme 65

unlikely by Quin<sup>11</sup> on consideration of Baldwin's rules on ring closure<sup>73</sup>. Nonetheless, the mechanism does appear in the literature<sup>74</sup> to explain the formation of a 1,3,2-dithiaphospholane oxide from the reaction of an epoxide with ArPS<sub>2</sub>, which is also a low-coordination and highly reactive phosphorus species.

#### 4.3.2 Mechanisms involving carbocation intermediates

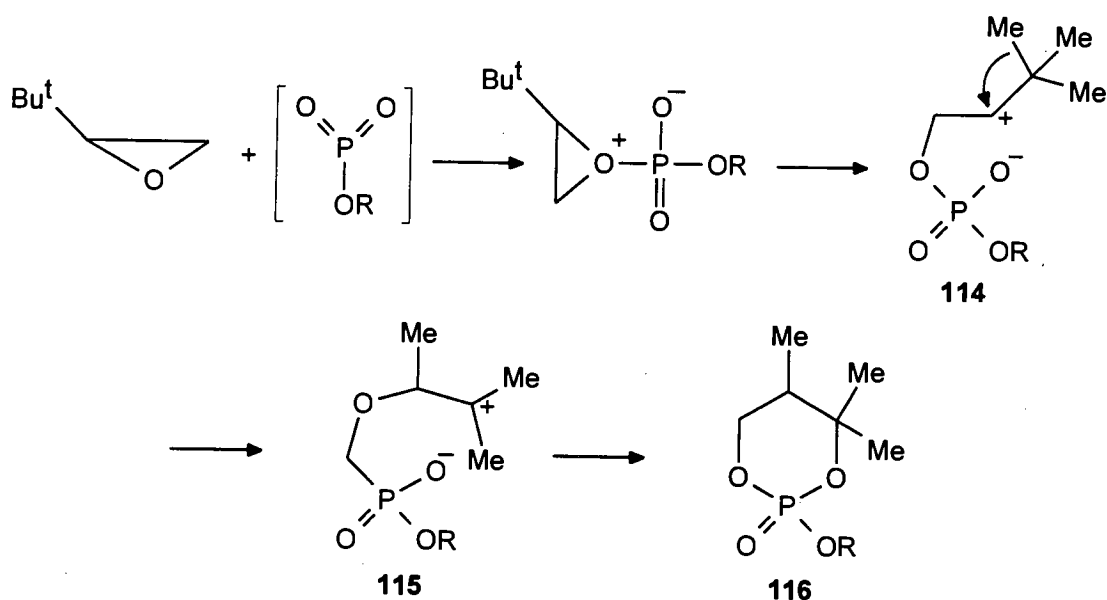


Scheme 66

The mechanism depicted in Scheme 66 shows the formation of an intermediate carbocation *via* ring-opening of the Lewis salt. Evidence to support this mechanism comes from the analogy to acid-catalysed ring-opening

of epoxides, which proceed *via* a protonated epoxide, followed by cleavage to form a carbocation<sup>70</sup>. There are two possible carbocations that can be formed in this mechanism *viz* 112 or 113. However, the one expected to be favoured is the secondary carbocation 112, which has added stabilisation from the adjacent aromatic ring.

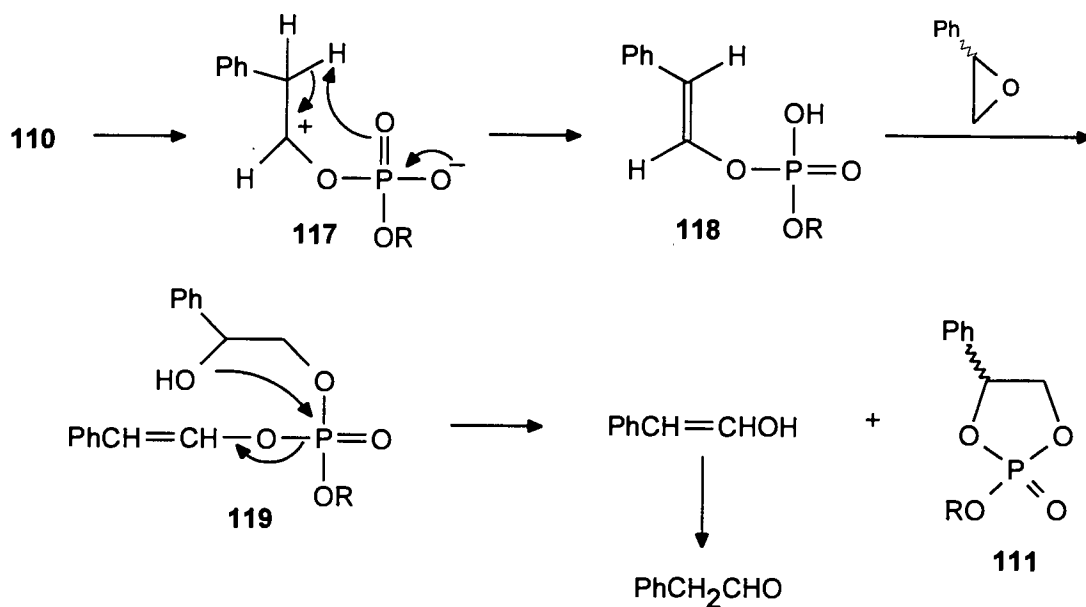
Evidence against this mechanism has been proposed by Quin<sup>11</sup>, who argued that replacement of the phenyl ring by a *tert*-butyl substituent would lead to methyl group migration<sup>75</sup> to form a new carbocation, *i.e.* 114 to 115 (Scheme 67), and subsequently the six-membered 1,3,2-dioxaphosphorinane-2-oxide 116 which he failed to observe.



Scheme 67

Finally, Scheme 68 shows a more elaborate mechanism that has been proposed by Quin<sup>11</sup>. In this particular case, the Lewis salt 110 undergoes a

rearrangement that is well known for oxonium salts formed from epoxides, and involves a [1,2] hydrogen shift<sup>11,70</sup> to form 117. Usually such species as 117 would then decompose with the release of carbonyl compounds, but Quin proposed a [1,5] hydrogen shift to give the enol phosphate 118. Attack of another molecule of styrene oxide on the hydroxy function of 118 leads to the hydroxyalkyl ester 119, which is then envisaged to undergo intramolecular displacement of the enolic group to afford the 1,3,2-dioxaphospholane oxide 111.



Scheme 68

The only evidence put forward by Quin to support this mechanism was the detection of propionaldehyde in the reaction products from 2-methyloxirane and ethyl metaphosphate **45**. Aldehydes are released as a co-

product in the mechanism shown in Scheme 68, and Quin observed the expected propionaldehyde by GC-MS, although the amount detected is quite small being only 0.53% of theory. From the information at hand, it appears that a simple experiment to test the mechanism shown in Scheme 68 had been overlooked by Quin. In the procedure employed to trap alkyl metaphosphates, Quin used three equiv. of epoxide to one equiv. of the generated alkyl metaphosphate. In the proposed mechanism only two equiv. of epoxide are required, and consequently, Quin has used an excess of epoxide. If the trapping reaction was repeated using only one equiv. of epoxide, then if the mechanism in Scheme 68 was valid, half the expected yield of trapped product would be expected compared to Quin's previous trapping experiments.

It is interesting to note that in the present study, when (-)-menthyl metaphosphate **86** was trapped with one equiv. of styrene oxide, almost 60% of the trapped product was isolated after work-up and purification by column chromatography. The theoretical yield expected if the mechanism in Scheme 68 is valid would be only 50%, and based on this result, it is evident that the reaction proceeds by a mechanism other than the one proposed by Quin in Scheme 68.

#### 4.3.3 (-)-Menthyl metaphosphate **86** as a mechanistic probe

In previous cases<sup>11,72</sup>, where alkyl metaphosphates have been trapped by *racemic* styrene oxide, a doublet is observed in the <sup>31</sup>P NMR spectrum of the reaction mixture, in keeping with a mixture of diastereomeric products (Scheme 60). Even though there are four possible diastereomers, only two

signals are observed due to the overlap of enantiomers. However, by generating an alkyl metaphosphate with a chiral alkyl substituent, an opportunity is created to observe all four diastereomers. Such a possibility arises by generating (-)-menthyl metaphosphate **86**, and observing its subsequent trapping with racemic styrene oxide by  $^{31}\text{P}$  NMR spectroscopy.

Figure 14 shows the  $^{31}\text{P}$  NMR spectrum of the products formed from the trapping of (-)-menthyl metaphosphate with racemic styrene oxide, and also the configuration of the four products observed. It can be seen that the spectrum consists of four closely spaced signals of almost equal intensity, indicating a 1:1:1:1 mixture of the four diastereomeric 1,3,2-dioxaphospholane-2-oxides **104**. In essence, this result lends strong evidence to support the initial formation of Lewis salts such as **110** (see Scheme 66) in the reaction of alkyl metaphosphates with epoxides.

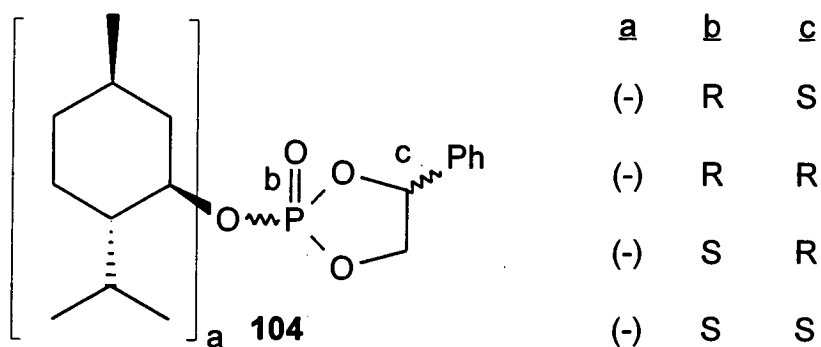


Figure 14a. Chirality of the four possible diastereomeric 2-(-)-menthyl-4-phenyl-1,3,2-dioxaphospholane-2-oxides **104**.

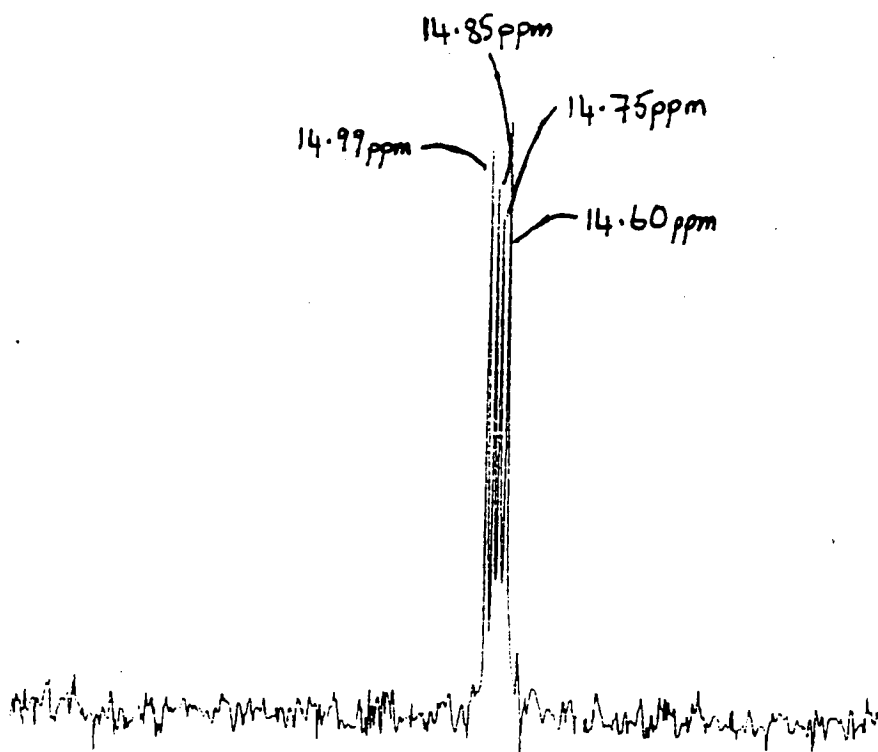
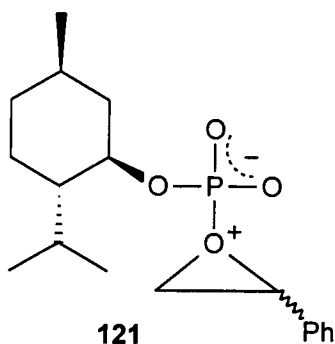


Figure 14b.  $^{31}\text{P}$  NMR spectrum of the reaction mixture obtained from the reaction of disodium pyrocarbonate **90** with (-)-menthylphosphorodichloridate **120** in the presence of styrene oxide.

Since the carbon centre (*c* in Figure 14a) in the starting styrene oxide is already racemic, it is clearly necessary for racemisation to have occurred at the phosphorus centre (*b* in Figure 14a) in order to explain the formation of all four diastereomers. This could arise due to distribution of the anionic charge between the two oxygen atoms of the Lewis salt **121**, *i.e.* either oxyanion can be used in the cyclisation step, leading to a diastereomeric mixture of the four different 1,3,2-dioxophospholane-2-oxides.

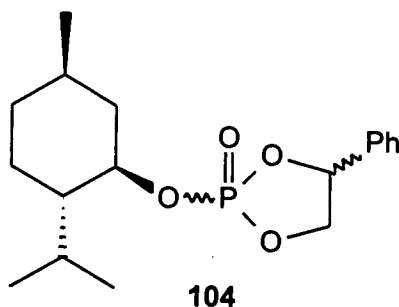


Thus, by generating (-)-menthyl metaphosphate **86** and observing its subsequent trapping with *chiral* styrene oxide, it should be possible to gain further information on the proposed reaction mechanisms and hence to discount some of the various possibilities as follows: According to the mechanisms outlined in Scheme 65, if a single step, internal nucleophilic substitution takes place at the chiral carbon centre of the styrene oxide ring, then inversion of configuration occurs and, one would expect to observe two diastereomers as two closely spaced signals of almost 1:1 intensity in the  $^{31}\text{P}$  NMR spectrum. If a single step internal nucleophilic substitution takes place at the methylene carbon centre of the styrene oxide ring, then retention of configuration occurs and, one would again expect to observe two diastereomers as two closely spaced signals of almost 1:1 intensity in the  $^{31}\text{P}$  NMR spectrum. Whereas, according to the mechanisms outlined in Scheme 66, if the mechanism proceeds *via* a stabilised carbocation on the chiral carbon centre of the styrene oxide ring, then racemisation of the chiral centre occurs and one would expect to observe all four diastereomers as four closely spaced signals of almost 1:1:1:1 intensity in the  $^{31}\text{P}$  NMR spectrum. If the mechanism proceeds

*via* a carbocation at the methylene carbon centre of the styrene oxide ring, then retention of configuration occurs and one would expect to observe two diastereomers as two closely spaced signals in the  $^{31}\text{P}$  NMR spectrum. Whilst, according to Quin's mechanism<sup>11</sup> outlined in Scheme 68, if the mechanism proceeds *via* the carbocation 117 and the subsequent enol phosphate 118, then retention of configuration occurs at the carbon centre and one would expect to observe two closely spaced signals in the  $^{31}\text{P}$  NMR spectrum.

#### 4.3.3.1 Trapping of (-)-menthyl metaphosphate 86 by both (R) and (S)-styrene oxide

In order to shed some light onto the mechanism of the reaction of alkyl metaphosphates with styrene oxide, the proposed trapping reactions of (-)-menthyl metaphosphate 86 with both (R) and (S)-styrene oxides were carried out. As explained previously, if one of the proposed reaction mechanisms held true then due to the chiral menthyl component attached to the resulting 1,3,2-dioxaphospholane -2-oxide 104 its  $^{31}\text{P}$  NMR spectrum should display either all *four* diastereomers (4 signals) due to *racemisation* of the chiral centre on the styrene oxide, or *two* diastereomers (2 signals) due to *inversion* or *retention* of configuration at the same chiral centre.



When this set of reactions was carried out, the results were unexpected, and unfortunately proved to be inconclusive by either supporting fully, or ruling out, any of the proposed reaction mechanisms. Thus, in the case of the reaction with (*S*)-styrene oxide the  $^{31}\text{P}$  NMR spectrum of the reaction mixture was found to consist of all four diastereomers, although two of the diastereomers were present only as minor signals (Figure 15). A similar result was obtained with (*R*)-styrene oxide, but as expected, the  $^{31}\text{P}$  spectrum was almost a mirror image of the spectrum obtained with (*S*)-styrene oxide, *i.e.* the aforementioned minor signals were now the major signals (Figure 16).

One explanation for these observations is that there is no single mechanism involved, but instead competition between differing pathways. For example, the observations can be accounted for if a small proportion of the reaction proceeded *via* the formation a carbocation formed at the chiral centre of the epoxide (see Scheme 66), and in turn, led to racemisation and the observation of four signals in the  $^{31}\text{P}$  NMR spectrum. In other words, most of the reaction proceeds by only one of the other proposed mechanisms that results in the observation of only two major diastereomeric signals. The combination of these two mechanisms in the appropriate ratio would result in a product mixture consistent with that observed in the  $^{31}\text{P}$  NMR spectrum.

The most plausible explanation for the observed results is that a single pathway is involved, but that competition occurs between the two carbon centres of the epoxide ring for attack by the oxygen anion of the Lewis salt **110**. If attack of the anion at one of the carbon centres is predominant then a reaction mixture consistent with that observed in the  $^{31}\text{P}$  NMR spectrum would result.

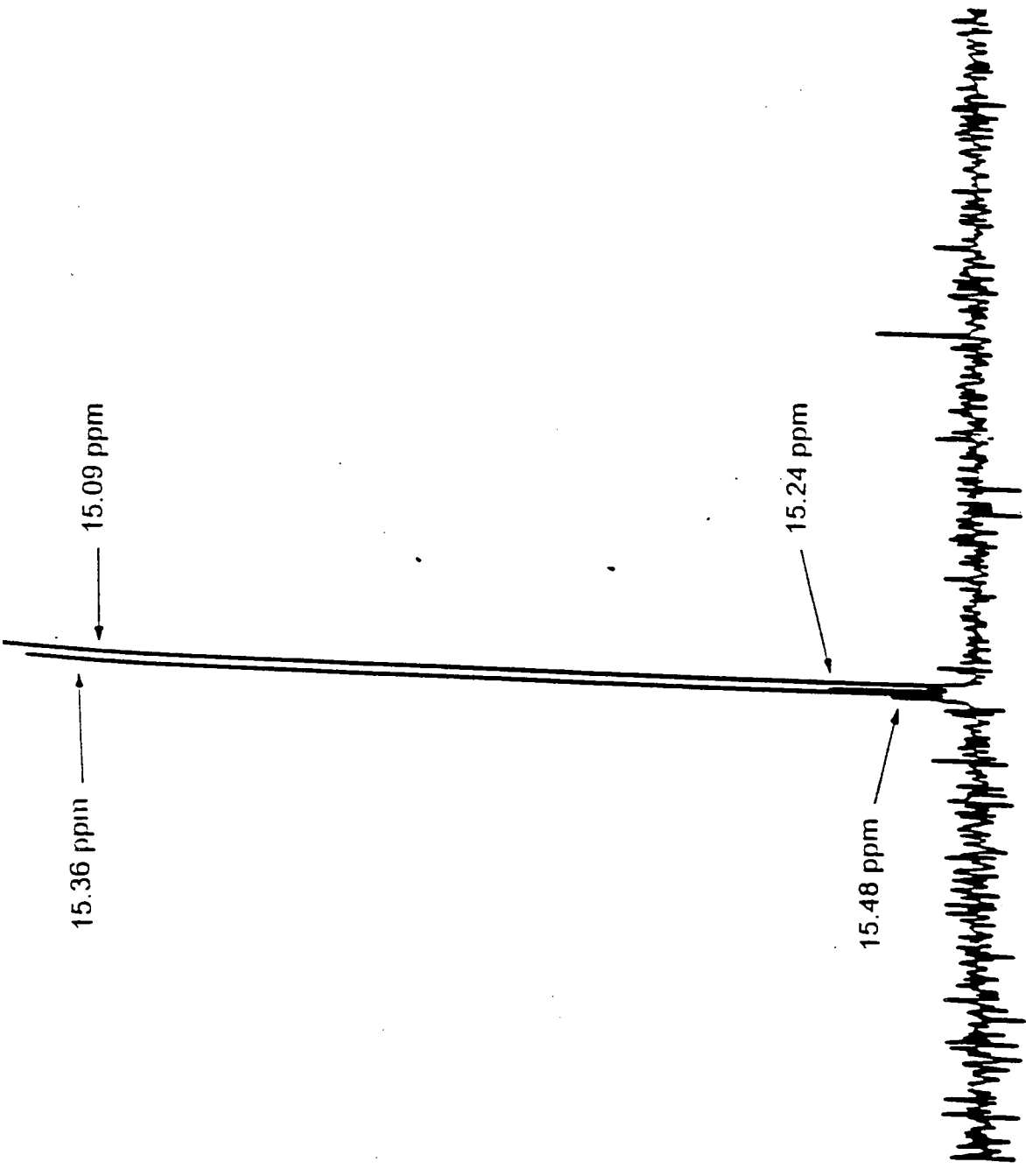


Figure 15. 30P NMR spectrum of the reaction mixture obtained from the reaction of disodium pyrocarbonate 90 with (-)-menthyl phosphorodichloridate 123 in the presence of (S)-styrene oxide

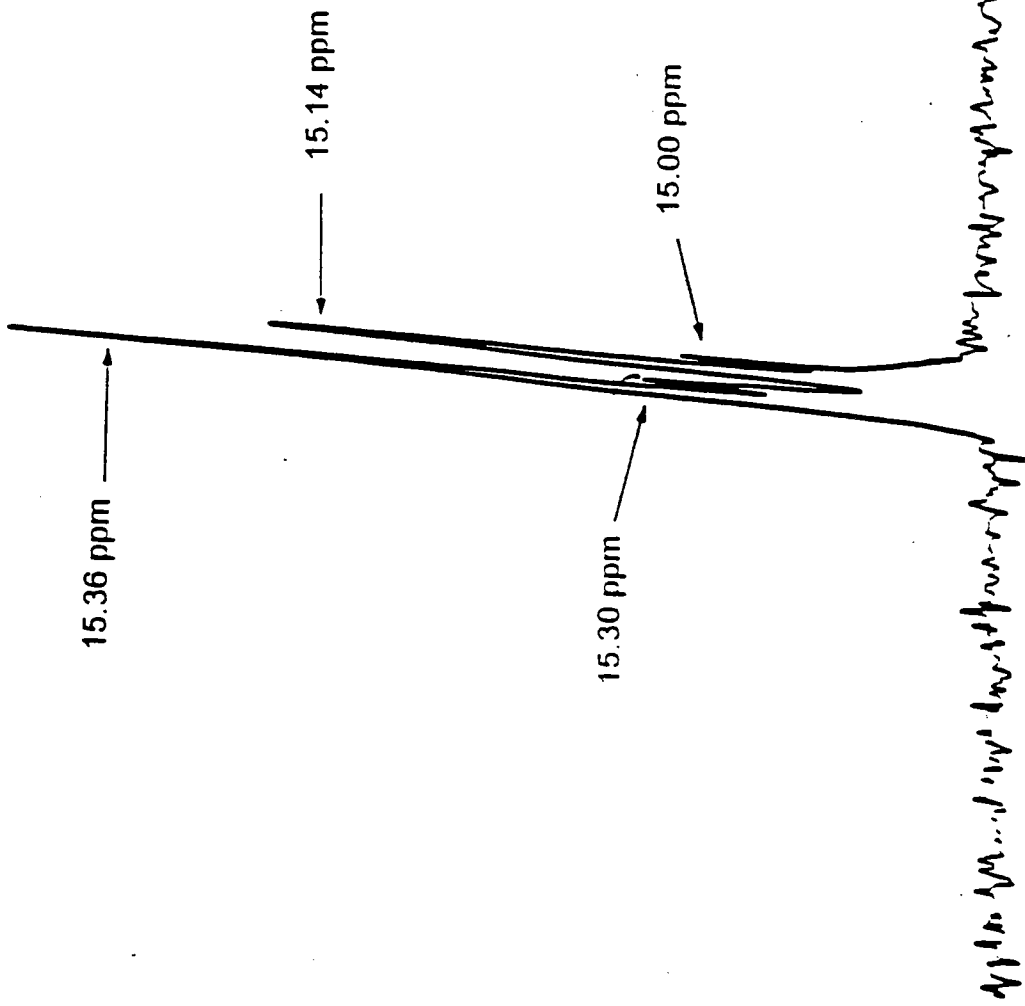
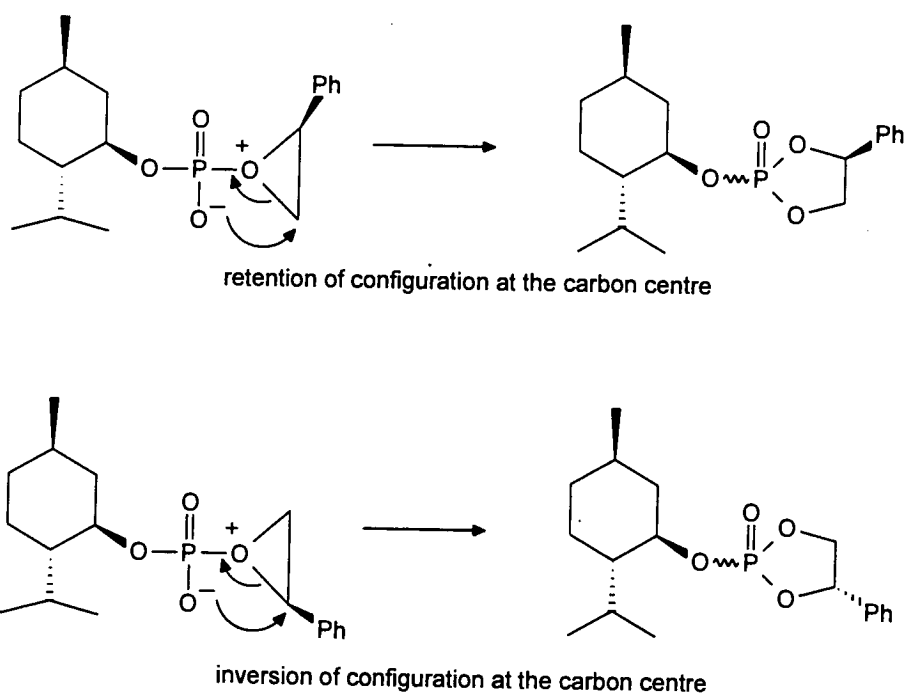


Figure 16.  $^{31}\text{P}$  NMR spectrum of the reaction mixture obtained from the reaction of disodium pyrocarbonate 90 with (-)-menthyl phosphorodichloridate 123 in the presence of (R) styrene oxide.

Two mechanisms are possible as proposed earlier:

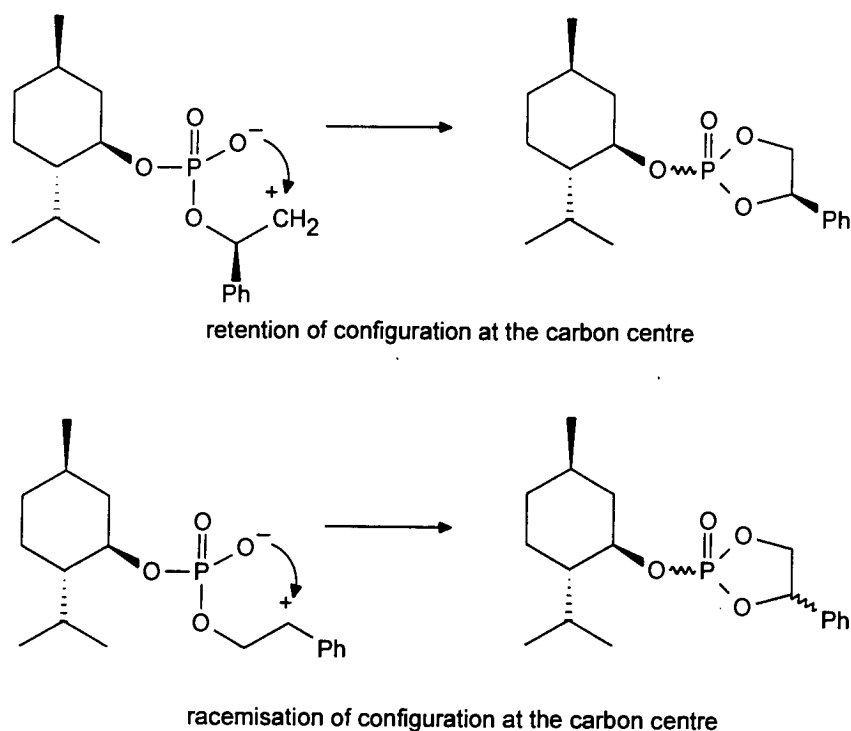
- A one step internal nucleophilic substitution reaction in which competition exists for attack by the oxyanion at both carbon centres, *i.e.* attack at the methylene carbon leads to retention of configuration at the chiral centre, whereas attack at the chiral carbon centre results in inversion of configuration as shown in Scheme 69.



Scheme 69. One step internal nucleophilic substitution.

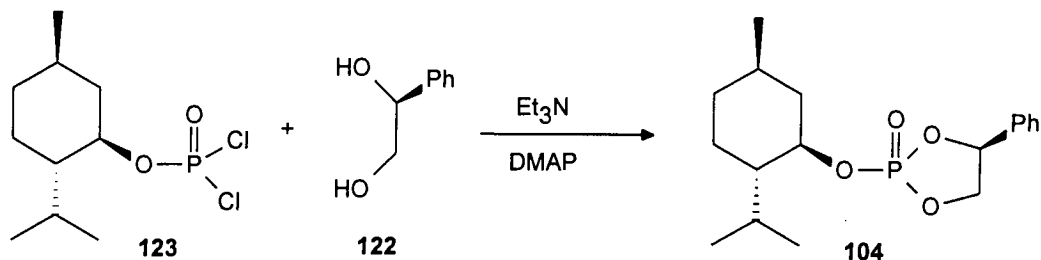
- Formation of a carbocation at both carbon centres of the epoxide ring, such that the carbocation formed at the chiral centre results in racemisation, but that at the methylenic centre allows retention of configuration (see Scheme 70). If the latter mechanism were to hold, but this seems very unlikely,

then attack at the methylenic carbocation would have to predominate to fit in with the experimental observations.



Scheme 70. Formation of a carbocation intermediate.

It seems clear that to gain a better understanding of what mechanism is operative, it would be advantageous to identify whether the reaction is occurring with predominate retention or inversion of configuration at the chiral centre of the epoxide. This prompted us to attempt an independent synthesis of 1,3,2-dioxaphospholane-2-oxides **104** with specific chirality at the crucial carbon centre. This was carried out by independently reacting both (*R*) and (*S*)-1-phenyl-1,2-ethanediol **122** with (-)-menthyl phosphorodichloridate **123** in the presence of triethylamine and DMAP (Scheme 71). The reaction



Scheme 71

was expected to proceed with the chirality at carbon intact, but with racemisation occurring at phosphorus *i.e.* giving a pair of diastereomers with specific chirality at the important carbon centre. Unfortunately, the <sup>31</sup>P NMR spectrum of the reaction mixture showed the presence of three closely spaced signals, and not two, indicating that three products had been formed (see Figure 17). At this stage it is unclear how three diastereomeric products could arise from the mechanisms suggested. Obviously, four products are possible if the chiral diol had racemised, but analysis showed that the optical rotation was in agreement with literature values. The starting (-)-menthyl phosphorodichloridate was also re-analysed and found to be consistent with the original sample.

From the initial results presented so far it can be seen that the trapping of an alkyl metaphosphate containing a chiral alkyl group by styrene oxide can be used to provide some information, albeit little, on the mechanism of trapping. These have been only preliminary experiments and the studies need to be investigated further. It would be particularly useful if the 1,3,2-dioxaphospholane-2-oxide **104** with fixed chirality at C-5 were to be synthesised since this would enable one to identify whether the mechanism went predominately *via* retention or inversion at its centre.

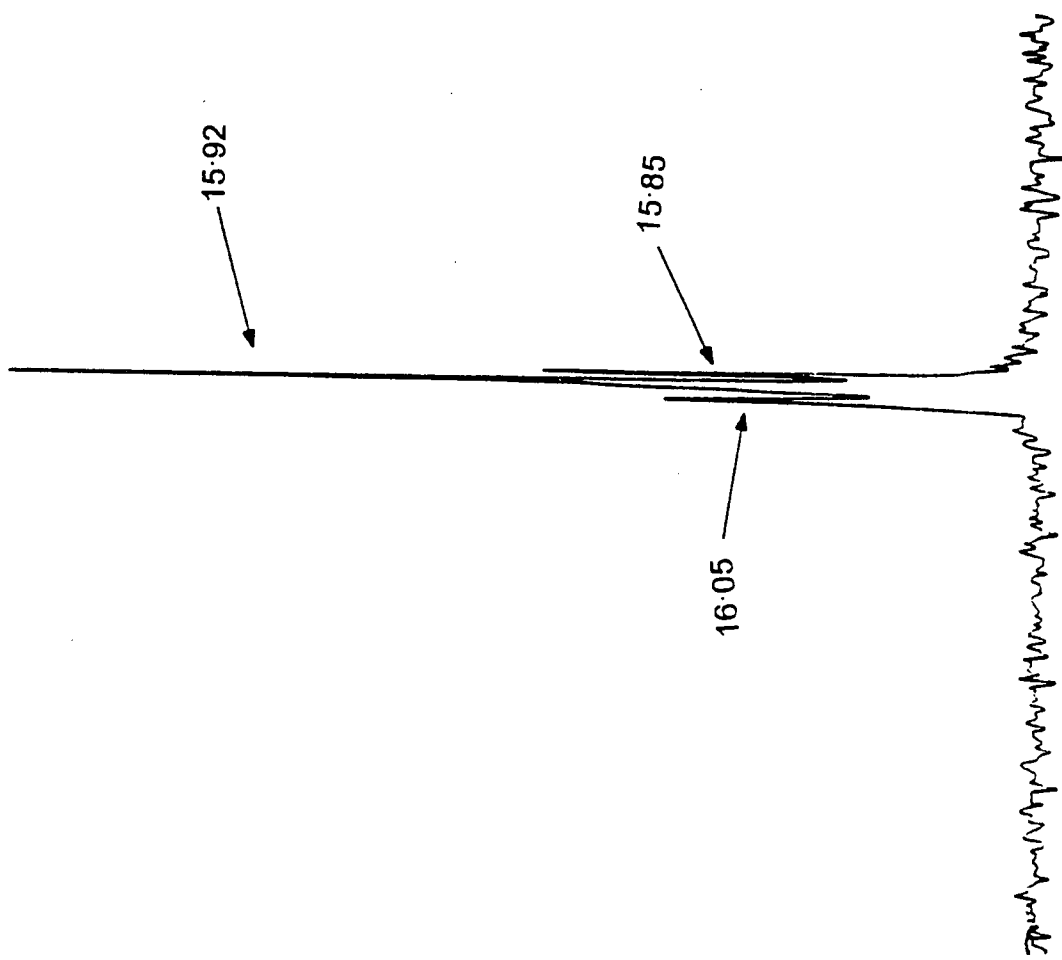


Figure 17a.  $^{31}\text{P}$  NMR spectrum of the reaction mixture obtained from the reaction of (-)-menthyl phosphorodichloridate 123 with (*R*)-1-phenyl-1,2-ethanediol 122.

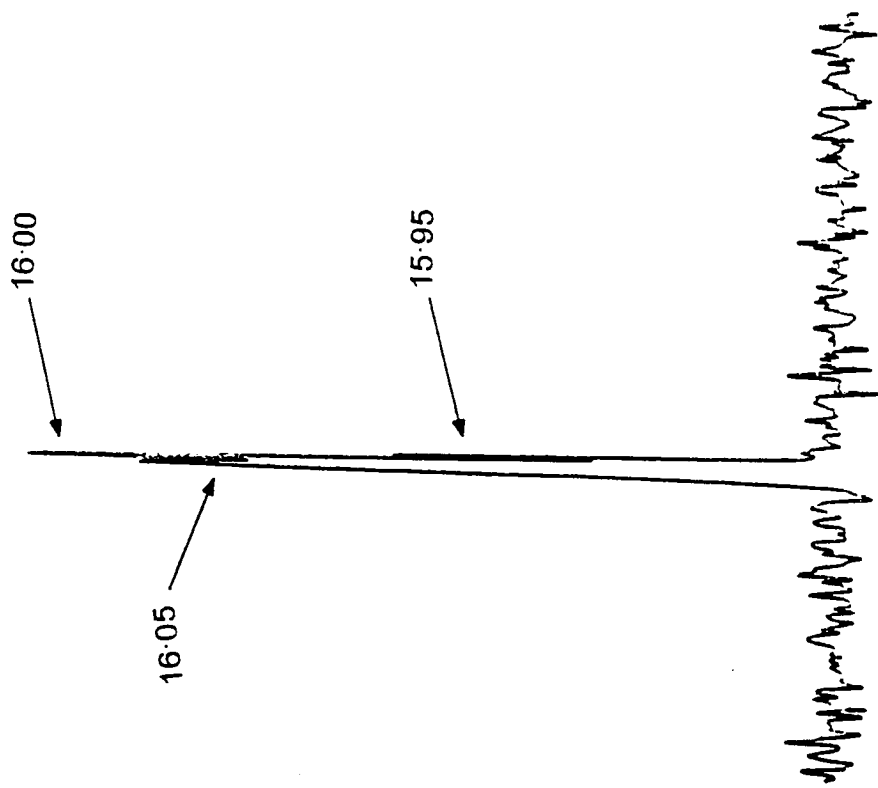


Figure 17b.  $^{31}\text{P}$  NMR spectrum of the reaction mixture obtained from the reaction of (-)-menthyl phosphorodichloridate 123 with (S)-1-phenyl-1,2-ethanediol 122.

## **Chapter Five**

### **Further Possible Routes Towards the Generation of Alkyl Metaphosphates in Solution**

# Chapter Five

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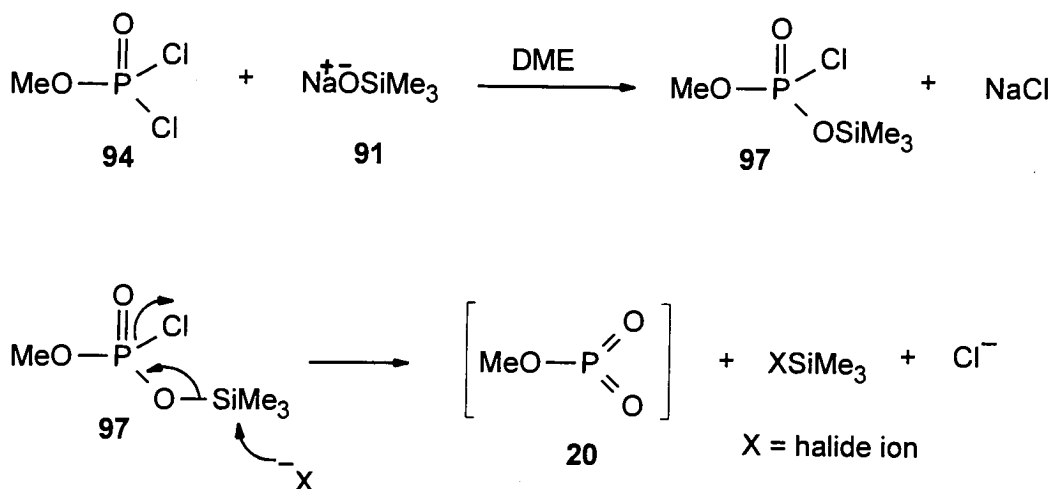
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## 5.1 Introduction

This chapter sets out to discuss other possible novel routes towards alkyl metaphosphates in solution, which have not been fully investigated, but have had preliminary experiments carried out in order to assess their possible potential. The three methods to be discussed involve a) reaction of methyl phosphorodichloridate with sodium trimethylsilanolate, b) fragmentation of *O*-trimethylsilyl-*O'*-methyl phosphorochloridate, and c) reaction of neopentyl phosphorodichloridate with sodium trimethylsilyl carbonate.

## 5.2 Reaction of methyl phosphorodichloridate 94 with sodium trimethylsilanolate 91

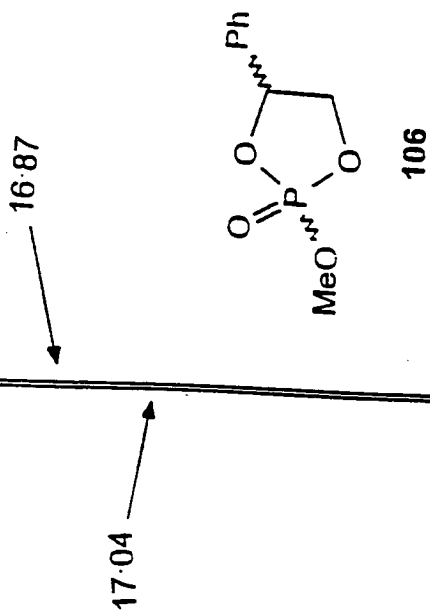
The following method for the generation of alkyl metaphosphates revolves around the known ability of halide ions to cleave *O*-*Si* bonds of silyl ethers and related compounds<sup>76,77</sup>. It was assumed that if methyl phosphorodichloridate 94 was condensed with sodium trimethylsilanolate 91, the reaction would yield *O*-trimethylsilyl-*O'*-methyl phosphorochloridate 97 which upon treatment by halide ion, such as caesium fluoride, would undergo fragmentation as depicted in Scheme 72 to generate methyl metaphosphate 20. By carrying out the fragmentation in the presence of styrene oxide as in previous experiments, the intermediacy of 20 can be verified from the formation of a diastereomeric mixture of trapped products,



Scheme 72. Proposed generation of methyl metaphosphate **20**.

2-methoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxides **106**. However, when the reaction was carried out, the outcome was unexpected. Instead of showing *O*-trimethylsilyl-*O*-methyl phosphorochloridate **97**, the  $^{31}\text{P}$  NMR spectrum of the mixture after 15 min. consisted almost entirely of a closely matched pair of signals at 17.04 and 16.87 ppm typical of the trapped product<sup>11</sup> **106**. This result confirmed that methyl metaphosphate had already been generated, and trapped by styrene oxide, despite the fact that fluoride ions had not yet been added to the reaction mixture.

The  $^{31}\text{P}$  NMR spectrum of the reaction mixture is shown in Figure 18, and besides signals due to **106**, also contains signals in the characteristic regions associated with polymeric products formed from the self-condensation reactions of methyl metaphosphate<sup>8,11,18</sup> ( $\delta$  -12 to -13 and -26 to -28 ppm).



internal and cyclic  
phosphate groups  
-26 to -28 ppm

terminal phosphate  
groups  
-12 to -13 ppm

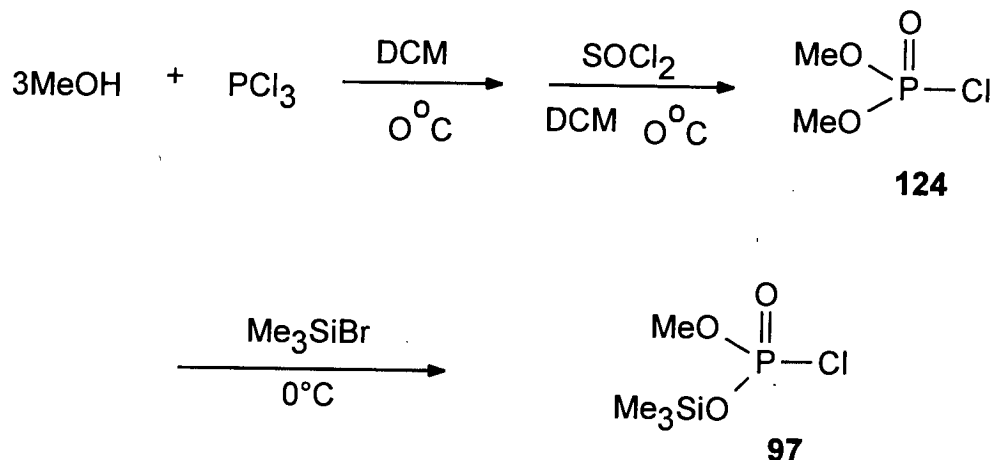
Figure 18.  $^{31}\text{P}$  NMR spectrum of the reaction mixture obtained from the reaction of methyl phosphorodichloridate **91** with sodium trimethylsilanolate **91** in the presence of styrene oxide after 15 minutes.

From a detailed examination of the reaction and the proposed reaction pathway, it soon became apparent that the chloride ion produced in the initial condensation of **94** and **91** was responsible for the cleavage of the trimethylsilyl group, and therefore the fragmentation of **97** to produce methyl metaphosphate. The reaction was also repeated, but this time without the addition of styrene oxide. As expected the appearance of signals in the  $^{31}\text{P}$  NMR spectrum in the characteristic regions  $\delta$  -12 to -13 and -24 to -26 ppm verified that methyl metaphosphate had been generated, but this time without trapping. A further signal was observed at -3.63 ppm, and this was attributed to *O*-trimethylsilyl-*O'*-methyl phosphorochloridate **97**, the precursor to metaphosphate itself (see Scheme 72). In order to verify the origin of the metaphosphate **20**, it was decided to isolate **97** and observe its fragmentation directly.

### **5.3 Fragmentation of *O*-trimethylsilyl-*O'*-methyl phosphorochloridate **97****

As indicated in the previous section (5.2), the next logical step was to try to synthesise and isolate *O*-trimethylsilyl-*O'*-methyl phosphorochloridate **97** and determine whether or not the addition of halide ions would, in fact, result in fragmentation and the production of methyl metaphosphate **20**. The synthesis of **97** was achieved by the route shown in Scheme 73, and it was isolated as a colourless oil (b.pt. =

22°C/0.001 mmHg ), the purity of which was confirmed by a single peak at - 4.44 ppm in the  $^{31}\text{P}$  NMR spectrum.



Scheme 73. Synthesis of *O*-trimethylsilyl-*O'*-methyl phosphorochloridate **97**

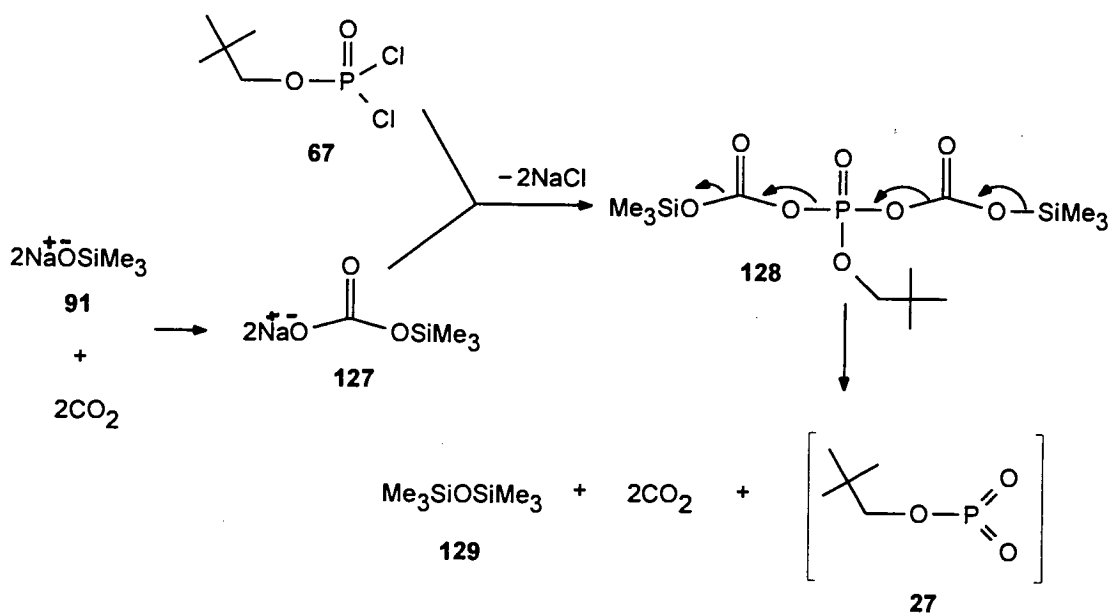
In order to evaluate the utility of phosphorochloridate **97** as a precursor for the generation of methyl metaphosphate by the addition of halide ion, **97** was added to a solution of styrene oxide in anhydrous DME. Once again, however, when the  $^{31}\text{P}$  NMR spectrum of the resulting mixture was taken *prior to the addition of halide ion*, it was found that the spectrum consisted of a closely matched pair of signals at 16.60 and 16.40 ppm due to the presence of a diastereomeric mixture of 2-methoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide<sup>11</sup> **106**, thus establishing that methyl metaphosphate had already been generated. Since it was already



methyl metaphosphate **20**. It is clear that a fuller understanding of what is occurring in this reaction is required, and this hopefully will be the focus of any future investigations.

#### 5.4 Reaction of neopentyl phosphorodichloridate **67** with sodium trimethylsilyl carbonate **127**

The final method to be described in this chapter involved the reaction of neopentyl phosphorodichloridate **67** with trimethylsilyl carbonate **127** to form the derivative **128** as shown in Scheme 75. In view

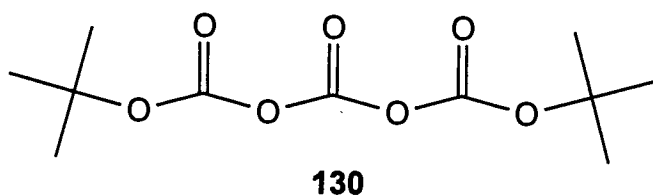


Scheme 75

of the likely unstable nature of **128**, it was believed that fragmentation would ensue to generate neopentyl metaphosphate **27** by loss of two

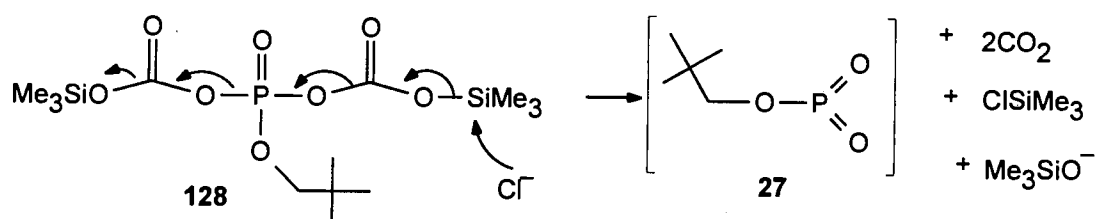
moles of carbon dioxide and one mole of the trimethylsilyl ether **129** as depicted. Thus, when the reaction was carried out at room temperature, in the presence of styrene oxide, evidence was obtained that neopentyl metaphosphate **27** had in fact been generated due to the appearance of a characteristic closely matched pair of signals at 15.88 and 15.68 ppm in the  $^{31}\text{P}$  NMR spectrum due to trapped neopentyl metaphosphate<sup>11</sup>. When the reaction was carried out in the absence of styrene oxide, further evidence to support the generation of neopentyl metaphosphate was obtained by the observation in the  $^{31}\text{P}$  NMR spectrum of signals in the regions  $\delta$  -12 to -13 and -24 to -25 ppm that can be attributed to polymeric products formed by self-condensation reactions of neopentyl metaphosphate<sup>8,18</sup>.

The fragmentation of **128** at room temperature is of interest, when compared with the carbon analogue, di-*t*-butyl tricarbonatate **130**, which is



a commercial foaming agent and is quoted in the literature<sup>78,79</sup> as undergoing thermal fragmentation with loss of isobutene and  $\text{CO}_2$  only

when heated above its melting point of 65°C. This difference in behaviour can be accounted for by the fact that in the case of **128**, trimethylsilyl ether is formed and in this instance, the generation of neopentyl metaphosphate **27** has the driving force of formation of the Si-O-Si bond. Moreover, the mechanism involves chloride ion, which is produced from initial condensation of neopentyl phosphorodichloridate **67** with trimethylsilyl carbonate **130**. As shown in Scheme 76, this could



Scheme 76. Halide induced fragmentation of **128**

lead to cleavage of one of the trimethyl silyl groups, and cause the sequential fragmentation of **128** to occur. Whatever pathway the reaction proceeds by, it is clear that the method requires further investigation as a promising and mild procedure for generation of alkyl metaphosphates in solution.

# **Chapter Six**

## **EXPERIMENTAL**

# Chapter Six

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## 6.1 Instrumentation and General Techniques

### 6.1.1 NMR Spectroscopy

#### $^1\text{H}$ NMR

Routine continuous wave  $^1\text{H}$  NMR spectra were obtained using a JEOL PMX-60 spectrometer. Higher field fourier transform spectra were obtained on a Bruker WP-80 or a Bruker WP-200 spectrometer operated by Mr J. Miller, Miss H. Grant and Mr W. Kerr, or on a Bruker WH-360 spectrometer operated by either Dr D. Reed or Dr I. Sadler.

Chemical shifts ( $\delta$ ) are reported in parts per million using tetramethylsilane ( $\delta$  0.0) as a reference.

#### $^{13}\text{C}$ NMR

$^{13}\text{C}$  NMR spectra were recorded at 50.3 MHz on a Bruker WP-200 spectrometer operated by Mr J. Miller, Miss H. Grant and Mr W. Kerr, or at 90.6 MHz on a Bruker WH-360 spectrometer operated by Dr D. Reed or Dr I. Sadler.

Chemical shifts ( $\delta$ ) are reported in parts per million using tetramethylsilane ( $\delta$  0.0) as a reference.

#### $^{31}\text{P}$ NMR

$^{31}\text{P}$  NMR spectra were recorded at 36.23 MHz on a JEOL FX-90Q spectrometer. When reactions were being monitored by  $^{31}\text{P}$  NMR spectroscopy, the  $^{31}\text{P}$  NMR spectrum of the reaction mixture was recorded

by placing a sample direct from the reaction mixture into an NMR tube along with a  $d_6$ -acetone capillary lock

Chemical shifts ( $\delta$ ) are reported in parts per million with reference to 85% phosphoric acid ( $H_3PO_4$ ); shifts to high frequency (low field) are positive in sign.

### **6.1.2 Mass Spectrometry**

FAB and Accurate mass measurements were obtained on a Kratos MS-50 TC spectrometer, operated by Mr A. Taylor.

### **6.1.3 Infra-Red Spectroscopy**

Infra-red spectra were recorded either on a Perkin-Elmer 781 spectrometer or on a Biorad FTS-7 spectrometer. Liquid samples were recorded as thin films and solid samples as nujol mulls, both on sodium chloride plates. Calibration for the former instrument was achieved by reference to the characteristic polystyrene peak at  $1603\text{ cm}^{-1}$ .

### **6.1.4 Elemental Analysis**

Elemental analysis for carbon, hydrogen and nitrogen were carried out on a Perkin-Elmer 2400 CHN elemental analyser, operated by Miss E. Stevenson. Halide analysis was carried out by technical staff at B.P. Research Centre, Sunbury.

### **6.1.5 Melting Points and Boiling Points**

Melting points were measured on a digital Gallenkamp capillary tube apparatus and are uncorrected.

Boiling points were measured using a Buchi Kugelrohr distillation apparatus.

### **6.1.6 Flash Column Chromatography**

Flash column chromatography was carried out routinely using Fluka silica gel 60 (mesh size 0.040-0.063 mm) as solid support and a pressure of 10 p.s.i. of compressed air to aid solvent elution.

### **6.1.7 Thin Layer Chromatography**

For analytical purposes, aluminium backed plates, coated with a 0.2 mm layer of silica gel 60, and containing fluorescent indicator were used. Component spots were visualised by ultra-violet light, iodine vapour or by dipping into a 5% sulphuric acid-in-ethanol solution, followed by gentle flaming.

### **6.1.8 Drying and Purification of Solvents**

Toluene, DME, chloroform, triethylamine and pyridine were dried by standing over finely divided calcium hydride overnight. Acetonitrile and dichloromethane were dried by distilling from calcium hydride and stored over calcium hydride. THF and diethyl ether were dried by

distilling from sodium and benzophenone, under a nitrogen atmosphere; these solvents were collected when the deep purple colour, due to sodium benzophenone ketyl, had formed.

### **6.1.9 Drying of Glassware and Inert gases**

Before conducting moisture sensitive reactions, reaction flasks were scrupulously dried by heating with a strong Bunsen flame whilst flushing with a strong pulse of dry argon, and allowing to cool under this strong pulse of gas.

Argon gas used for reactions was dried by passing through a series of dreschel vessels containing concentrated sulphuric acid, calcium chloride and self-indicating silica gel.

### **6.1.10 Drying and Evaporation of Organic Extracts**

Organic extracts obtained from reaction were dried by standing over anhydrous magnesium sulphate for approximately 30 minutes. They were then evaporated under reduced pressure using a rotary evaporator. To remove the last traces of solvent, evaporation was conducted on a high vacuum rotary evaporator connected to an oil pump

## 6.2 Preparation of Starting Materials

### 6.2.1 Attempted preparation of dipotassium pyrocarbonate (65)

To a solution of potassium hydroxide (0.81g,  $1.44 \times 10^{-2}$  mol) in distilled water (5ml) at 0°C was added diethyl pyrocarbonate (1.00g, 6.16mmol) and the reaction mixture was then stirred at 0°C until all the diethyl pyrocarbonate had dissolved. The reaction mixture was kept at 0°C and freeze dried to yield the product as a colourless solid. The product was later found to be potassium hydrogen carbonate by comparison with an authentic sample.

### 6.2.2 Preparation of disodium pyrocarbonate (90)

To a solution of sodium trimethylsilanolate (91) (1.45g,  $1.29 \times 10^{-2}$  mol, 2eq) in dry THF (30ml), at 0°C, under argon, was added a solution of diethyl pyrocarbonate (66) (1.05g,  $6.48 \times 10^{-2}$  mol) in THF (15ml) at a rate of 1ml/min *via* a perfusor. Once the addition was complete the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then filtered, the precipitate washed with ether (2x50ml) and dried under vacuum to yield disodium pyrocarbonate (90) as a colourless solid (0.91g, 94%). The product was used in future stages without purification;  $^{13}\text{C}$  CPMAS NMR (50.3 MHz)  $\delta$  162.16 (C=O) ppm; IR (KBR disc)  $\nu_{\text{max}}$  1610 (C=O)  $\text{cm}^{-1}$ ; Accurate Mass (FAB), Found: 150.96199;  $\text{C}_2\text{HNa}_2\text{O}_5$  (M+H)<sup>+</sup> requires: 150.96200.

### 6.2.3 Preparation of Neopentyl Phosphorodichloridate (67)

A solution of neopentyl alcohol (2.00g,  $2.27 \times 10^{-2}$  mol) in dry toluene (20ml,  $\text{CaH}_2$ ) at  $0^\circ\text{C}$  was treated with butyllithium (1.6M in hexane, 15ml,  $2.40 \times 10^{-2}$  mol) and the reaction mixture brought to room temperature and stirred for 30 minutes. The resultant mixture was transferred dropwise *via* a cannula into a solution of phosphoryl chloride (6.97g,  $4.54 \times 10^{-2}$  mol, 2eq) in toluene (20ml) and stirred at room temperature for three hours after which time it was observed by  $^{31}\text{P}$  NMR that the reaction had gone to completion. The solvents were then removed under vacuum and the residue purified by kugelrohr distillation to yield neopentyl phosphorodichloridate (67) as a colourless oil (3.63g, 78%); **Bp** =  $95^\circ\text{C}/15\text{mmHg}$ ;  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ )  $\delta$  4.06 (2H, d,  $J = 7.10\text{Hz}$ ,  $\text{CH}_2$ ), 1.04 (9H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ )  $\delta$  85.23 (d,  $J = 10.62\text{ Hz}$ ,  $\text{CH}_2$ ), 32.64 (d,  $J = 6.74\text{ Hz}$ , quat C), 26.32 ( $3 \times \text{CH}_3$ ) ppm;  $^{31}\text{P}$  NMR (36.23 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 ppm; IR (thin film)  $\nu_{\text{max}}$  1280 ( $\text{P}=\text{O}$ )  $\text{cm}^{-1}$ .

### 6.2.4 Preparation of (-)-Menthyl Phosphorodichloridate (123)

To a solution of phosphoryl chloride (4.50g, 0.029 mol) in dry ether (60ml) at  $0^\circ\text{C}$  was added a solution of (-)-menthol (4.59g, 0.029mol) and pyridine (2.32g, 0.029 mol) in dry ether (50ml) at a rate of 1ml/min *via* a perfusor. Once the addition was complete the reaction mixture was allowed to stir overnight after which time it was observed by  $^{31}\text{P}$  NMR

that the reaction had gone to completion. The reaction mixture was then filtered, the precipitate washed with ether (2 x 50ml) and the filtrate evaporated to yield (-)-menthyl phosphorodichloridate **123** as a viscous colourless oil (7.2g, 90% crude). Attempts to purify the oil by kugelrohr distillation resulted in decomposition with the cleavage of the phosphorus centre from the menthol structure and so the product was used in future stages without further purification;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  4.69-4.51 (1H, cm, CH), 2.34-2.26 (1H, cm, CH), 2.09-2.01 (1H, cm, CH), 1.74-1.50 (1H, cm, CH), 1.48-0.98 (6H, cm,  $\text{CH}_2$ ), 0.93 (3H, d,  $J = 6.76$  Hz,  $\text{CH}_3$ ), 0.90 (3H, d,  $J = 6.82$  Hz,  $\text{CH}_3$ ), 0.80 (3H, d,  $J = 6.90$  Hz,  $\text{CH}_3$ ) ppm;  $^{13}\text{C NMR}$  (50.3 MHz,  $\text{CDCl}_3$ )  $\delta$  86.34 (d,  $J = 10.81$  Hz, CH), 47.93 (d,  $J = 8.12$  Hz, CH), 41.86 ( $\text{CH}_2$ ), 33.35 ( $\text{CH}_2$ ), 31.45 (CH), 25.23 (CH), 22.73 ( $\text{CH}_2$ ), 21.51 ( $\text{CH}_3$ ), 20.48 ( $\text{CH}_3$ ), 15.48 ( $\text{CH}_3$ ) ppm;  $^{31}\text{P NMR}$  (36.23 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23 ppm; IR (thin film)  $\nu_{\text{max}}$  1295 (P=O)  $\text{cm}^{-1}$ ; MS (FAB)  $m/z$  271 (M-1) $^+$ .

### 6.2.5 Preparation of 2,3:4,5-O-isopropylidene-D-Fructanose (**131**)

From the procedure of D. McDougall<sup>80</sup>.

To a stirred solution of acetone (700ml) and conc. sulphuric acid (35.0ml), at 0°C, was added D-fructose (36.0g, 0.20 mol) over a period of 10 minutes. After allowing to warm to room temperature and stirring for 90 minutes, the reaction mixture was cooled to 0°C again and an ice-cold solution of sodium hydroxide (110g, 2.75 mol) in water (500ml) was

gradually added. After evaporation of acetone the product was extracted into DCM (3x100ml) and the combined organic extracts then washed with water (100ml), dried with anhydrous magnesium sulphate and evaporated to yield a yellow crystalline solid which after recrystallisation from a diethyl ether/n-pentane mixture (1:1) provided 2,3:4,5-O-isopropylidene-D-fructanose **131** as a colourless solid (42.6g, 82%); **Mp** = 92°C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 4.57 (1H, dd, J = 2.6, 7.9 Hz, CH), 4.30 (1H, d, J = 2.6 Hz, CH), 4.19 (1H, ddd, J = 1.1, 1.9, 7.9 Hz, CH), 3.87 (1H, dd, J = 1.1, 13.0 Hz, CH), 3.71 (1H, dd, J = 1.1, 13.0 Hz, CH), 3.63 (2H, s, CH<sub>2</sub>), 2.60 (1H, bs, OH), 1.50 (3H, s, CH<sub>3</sub>), 1.43 (3H, s, CH<sub>3</sub>), 1.35 (3H, s, CH<sub>3</sub>), 1.30 (3H, s, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (50.3 Mz, CDCl<sub>3</sub>) δ 108.86 (quat. C), 108.33 (quat. C), 102.87 (quat.C), 70.72 (CH), 70.58 (CH), 69.83 (CH), 65.21 (CH), 61.03 (CH<sub>2</sub>), 26.26 (CH<sub>3</sub>), 25.56 (CH<sub>3</sub>), 25.14 (CH<sub>3</sub>), 23.76 (CH<sub>3</sub>) ppm; IR (thin film) ν<sub>max</sub> 3290 (OH) cm<sup>-1</sup>.

### **6.2.6 Preparation of 2,3:4,5-O-isopropylidene-D-Fructanose-1β-phosphorodichloridate (132)**

To a solution of phosphoryl chloride (1.76g, 0.0115 mol) in dry ether (150ml) at 0°C was added a solution of the protected fructose **131** (3.00g, 0.0115 mol), triethylamine (1.16g, 0.0115 mol) and DMAP (5%) in dry ether (50ml) at a rate of 2ml/min *via* a perfusor. Once the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 30 minutes after which time it was observed

by  $^{31}\text{P}$  NMR that the reaction had gone to completion. The reaction mixture was then filtered and the filtrate evaporated to yield 2,3:4,5-O-isopropylidene-D-fructose-1 $\beta$ -phosphorodichloridate **132** as a yellow viscous oil (3.47g, 80% crude). The product was used in future stages without further purification;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  4.59 (1H, dd,  $J = 7.87, 2.67$  Hz, CH), 4.31 (1H, d,  $J = 2.67$  Hz, CH), 4.23 (1H, m, CH), 4.21 (2H, m,  $\text{CH}_2$ ), 3.81 (2H, m,  $\text{CH}_2$ ), 1.51 (3H, s,  $\text{CH}_3$ ), 1.43 (3H, s,  $\text{CH}_3$ ), 1.37 (3H, s,  $\text{CH}_3$ ), 1.30 (3H, s,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ )  $\delta$  109.34 (quat. C), 108.98 (quat. C), 100.25 (d,  $J = 13.53$  Hz, quat. C), 70.37 (CH), 69.78 ( $\text{CH}_2$ ), 69.62 (2xCH), 61.31 ( $\text{CH}_2$ ), 26.33 ( $\text{CH}_3$ ), 25.66 ( $\text{CH}_3$ ), 25.00 ( $\text{CH}_3$ ), 23.77 ( $\text{CH}_3$ ) ppm;  $^{31}\text{P}$  NMR (36.23 MHz,  $\text{CDCl}_3$ )  $\delta$  6.86 ppm; IR (nujol mull)  $\nu_{\text{max}}$  1285 (P=O)  $\text{cm}^{-1}$ ; Accurate mass (FAB), Found: 377.03237;  $\text{C}_{12}\text{H}_{20}^{35}\text{C}_{12}\text{O}_7\text{P}$  (M+H) $^+$  requires: 377.03236.

### 6.2.7 Preparation of Dimethyl Phosphorochloridate (124)

Procedure adapted from that of G. Sosnovsky and E. H. Zaret<sup>81</sup>

To a solution of methanol (26.90g, 0.84mol, 3eq) in dry DCM (75ml), at 0°C, was added dropwise a solution of phosphorus trichloride (38.65g, 0.281mol) in dry DCM (75ml). The reaction mixture was stirred at 5-10°C for one hour after the addition and then treated dropwise at 0°C with a solution of thionyl chloride (113.45g, 0.95mol) in dry DCM (150ml). The reaction mixture was then warmed to room temperature, stirred overnight, concentrated and distilled by kugelrohr distillation to yield

dimethyl phosphorochloridate **124** as a colourless oil (31.33g, 77%); **Bp** = 85°C/25 mmHg, (Lit.<sup>81</sup> = 85°C/25 mmHg); <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) δ 3.95 (6H, d, J = 10.2 Hz, 2xCH<sub>3</sub>) ppm; <sup>31</sup>P NMR (36.23 MHz, CDCl<sub>3</sub>) δ 7.54 ppm.

### 6.2.8 Preparation of *O*-Trimethylsilyl-*O'*-Methyl Phosphorochloridate (**97**)

Adapted from the procedure of J. Chojnowski<sup>82</sup> *et al.*

Dimethyl phosphorochloridate (**124**) (24.95g, 0.172mol), 2eq) was treated dropwise with bromotrimethylsilane (13.20g, 8.60x10<sup>-2</sup>mol) at 0°C under argon. Once the addition was complete the reaction mixture was allowed to warm to room temperature and stirred overnight. <sup>31</sup>P NMR spectroscopy showed the mixture to consist of starting material and product in approximately a 2:1 ratio. With conventional distillation having failed to separate the mixture, *O*-trimethylsilyl-*O'*-methyl phosphorochloridate (**97**) was finally purified and isolated as a colourless oil by spaltrohr distillation. By combination of the fractions containing pure product a yield of 4.90g, 14.01% was obtained; **Bp** = 22°C/0.001 mmHg; <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) δ 3.92 (3H, d, J = 13.80 Hz, CH<sub>3</sub>), 0.40 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>) ppm; <sup>31</sup>P NMR (36.23 MHz, CDCl<sub>3</sub>) δ -4.44 ppm.

## 6.3 Preparation of Authentic Reaction Products and Intermediates

### 6.3.1 Preparation of Di-*t*-Butyl Phosphorobromidate (75)

Prepared from the procedure of T. Gajda and A. Zwierzak<sup>63</sup>

A Solution of di-*t*-butylphosphite (9.70g, 0.05mol) in dry DCM (15ml) was added dropwise with efficient stirring to a two phase system consisting of DCM (30ml), tetrabromomethane (8.30g, 0.025mol), 20% aqueous sodium hydroxide (20ml), and benzyltriethylammonium chloride (0.5g, ~5 mol%) at room temperature. The mixture was then stirred at room temperature for a further 3 hours. The pale-yellow solution was diluted with DCM (50ml), the organic layer was separated, washed with water (2x50ml), and dried over anhydrous magnesium sulphate. Evaporation of solvents and removal of volatile impurities yielded di-*t*-butyl phosphorobromide **75** as a colourless oil (12.73g, 92%); <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) δ 1.46 (s, 18H, 6xCH<sub>3</sub>) ppm; <sup>31</sup>P NMR (36.23 MHz, CDCl<sub>3</sub>) δ -21.53 ppm, (Lit.<sup>63</sup> -22.85 ppm in CCl<sub>4</sub>)

### 6.3.2 Preparation of Neopentyl Dihydrogen Phosphate (72)

Adapted from the procedure of T. Gajda and A. Zwierzak<sup>64</sup>

A Solution of neopentyl alcohol (4.13g, 4.7x10<sup>-2</sup>mol) in dry toluene (80ml) at 0°C was treated dropwise with butyllithium (1.6M, 29.37ml, 3.01g, 4.7x10<sup>-2</sup>mol), allowed to warm to room temperature and stirred for

30 minutes. di-*t*-butylphosphorobromidate **75** (12.73g,  $4.66 \times 10^{-2}$ mol) was then added dropwise and the reaction mixture allowed to stir at room temperature overnight. The resultant mixture was diluted with toluene (50ml), washed with water (3x25ml), dried with anhydrous magnesium sulphate and evaporated in vacuo to a volume of 50ml. TFA (6.11g, 0.054mol) was then added, the solution set aside for 24 hours at room temperature and then evaporated. Crude neopentyl dihydrogen phosphate **72**, obtained as a thick oil, was dissolved in ethanol (25ml) and aniline (4.99g, 0.054mol) added to the solution. The anilinium salt **76** precipitated immediately, was isolated and recrystallised from ethanol (7.10g, 58%); **Mp** = 168 °C, (Lit.<sup>64</sup> = 169.5-172 °C); <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) δ 7.70-7.40 (5H, m, Ar), 3.70 (2H, d, J = 5.0 Hz, CH<sub>2</sub>), 0.90 (9H, s, 3xCH<sub>3</sub>) ppm.

The anilinium salt **76** (2.0g, 7.65 mmol) was then dissolved in DME (50ml) and treated with TFA (0.87g, 7.65mmol) to obtain neopentyldihydrogenphosphate **72** as the free acid; <sup>31</sup>P NMR (36.23 MHz, DME, d<sub>6</sub>-acetone capillary lock) δ -1.21 ppm; **Accurate mass** (FAB), Found: 169.062964; C<sub>5</sub>H<sub>14</sub>O<sub>4</sub>P (M+H)<sup>+</sup> requires: 169.06296.

### 6.3.3 Preparation of Neopentyl Pyrophosphate (**73**)

A solution of neopentyl phosphorodichloridate **67** (0.50g, 2.43 mmol) in dry DME (5ml) was treated with a solution of water (0.065g, 3.65 mmol, 1.5eq) in dry DME (3ml). The reaction mixture was stirred at

room temperature and monitored by  $^{31}\text{P}$  NMR spectroscopy. After a period of 7 days the reaction had appeared to go to completion and analysis by  $^{31}\text{P}$  NMR was observed to consist of two signals in the regions  $\delta$  0 and -14 ppm which were assigned to neopentyl phosphate **72** and neopentyl pyrophosphate **73** respectively. Solvents were removed under vacuo and the residue analysed by mass spectrometry.

Neopentyl dihydrogen phosphate **72**;  $^{31}\text{P}$  NMR (36.23 MHz, DME,  $\text{d}_6$ -acetone capillary lock)  $\delta$  -0.134 ppm; **Accurate mass** (FAB), Found: 169.062964;  $\text{C}_5\text{H}_{14}\text{O}_4\text{P}$  (M+H) $^+$  requires: 169.06296.

Neopentyl pyrophosphate **73**;  $^{31}\text{P}$  NMR (36.23 MHz, DME,  $\text{d}_6$ -acetone capillary lock)  $\delta$  -14.134 ppm; **Accurate mass** (FAB), Found: 319.10753;  $\text{C}_{10}\text{H}_{25}\text{O}_7\text{P}_2$  (M+H) $^+$  requires: 319.10754.

#### 6.3.4 Preparation of Neopentyl Phosphorochloridic Acid (**81**)

A solution of neopentyl phosphorodichloridate **67** (0.50g, 2.43 mmol) in dry DME (4ml) at 0°C under an argon atmosphere was treated with a solution of water (0.24g, 2.43 mmol) in DME (1ml). The reaction mixture was allowed to warm to room temperature, stirred and monitored by  $^{31}\text{P}$  NMR spectroscopy. After a period of 90 minutes the reaction consisted of a single signal at 2.42 ppm which was assigned to neopentyl phosphorochloridic acid **81**. Also present was a minor signal at 4.44 ppm (unreacted starting material) and minor signals in the  $\delta$  -11 to -14 ppm

range (probably due to polymerisation reactions of the starting material and products).

### 6.3.5 Preparation of Trimeric Neopentyl Metaphosphate (77)

Adapted from the procedure of D. W. Chasar<sup>66</sup> *et al*

A solution of neopentyl phosphorodichloridate **67** (1.00g, 4.87 mmol) in dry DME (10ml), at 0°C under argon, was treated with a solution of triethylamine (0.98g, 9.75 mmol, 2eq) and water (0.087g, 4.87 mmol) in DME (2ml) over a period of 2-3 minutes. Once addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 15 minutes. After this time the reaction was observed, by <sup>31</sup>P NMR spectroscopy, to have gone to completion by the appearance of a single peak at -28 ppm which was assigned to trimeric neopentyl metaphosphate **77**; <sup>31</sup>P NMR (36.23 MHz, DME, d<sub>6</sub>-acetone capillary lock) δ -28.404 ppm, (Lit.<sup>8,18</sup> shifts of -23 to -26 ppm for cyclic phosphoryl groups).

### 6.3.6 Separation and isolation of cis and trans 2-(-)-menthyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide (104) from the trapping reaction of menthyl metaphosphate (86) by styrene oxide.

A solution of (-)-menthyl phosphorodichloridate **123** (1.24g, 4.5x10<sup>-3</sup> mmol) in dry DME (3ml), was added dropwise to a stirred suspension of disodium pyrocarbonate **90** (0.68g, 4.5x10<sup>-3</sup> mmol) in dry

DME (5ml), at room temperature, under argon. After addition, the reaction mixture was heated under reflux for 1.5 hours. The reaction mixture was then filtered, the precipitate washed with DME (2x10ml) and the filtrate evaporated. The resulting residue was subjected to flash column chromatography (30g, SiO<sub>2</sub>) using gradient elution with n-hexane:ethyl acetate 100:0 to 0:100 which afforded 2-(-)-menthyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **104** as two fractions, both colourless solids [(R<sub>f1</sub> = 0.40, 0.38g) and (R<sub>f2</sub> = 0.23, 0.57g) overall yield = 0.95g, 62%]. From the <sup>31</sup>P NMR spectrum of the two fractions it was observed that each fraction contained two closely spaced signals in the region around 16 ppm suggesting that one fraction contains the two cis isomers with the other containing the two trans isomers; Physical data for the cis isomers <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ 7.43-7.33 (5H, cm, Ar CHs), 5.60-5.54 (1H, cm, CH), 4.64-4.53 (1H, cm, CH), 4.42-4.33 (1H, cm, CH), 4.15-4.05 (1H, cm, CH), 2.28-2.06 (2H, cm, 2xCH), 1.68-1.63 (1H, cm, CH), 1.51-0.97 (6H, cm, 3xCH<sub>2</sub>), 0.92 (3H, d, J = 6.73 Hz, CH<sub>3</sub>), 0.90 (3H, d, J = 6.80 Hz, CH<sub>3</sub>), 0.83 (3H, d, J = 6.93 Hz, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>) δ 135.66 (Ar CH), 129.26 (Ar CH), 128.81 (Ar 2xCH), 125.95 (Ar 2xCH), 80.90 (d, J = 6.70 Hz, CH), 79.05 (CH), 71.79 (d, J = 18.19 Hz, CH<sub>2</sub>), 48.09 (d, J = 7.47 Hz, CH), 42.45 (CH<sub>2</sub>), 33.82 (CH<sub>2</sub>), 31.33 (CH), 25.80 (CH), 22.87 (CH<sub>2</sub>), 21.72 (CH<sub>3</sub>), 20.63 (CH<sub>3</sub>), 15.72 (CH<sub>3</sub>) ppm; <sup>31</sup>P NMR (36.23 MHz, CDCl<sub>3</sub>) δ 16.11, 16.05 (fraction 1, R<sub>f1</sub> = 0.40), 16.17, 16.02 (fraction 2, R<sub>f2</sub> = 0.23) ppm; IR (nujol mull) ν<sub>max</sub> 1260 (P=O) cm<sup>-1</sup>;

Accurate mass (FAB), Found: 339.17208;  $C_{18}H_{28}O_4P$  (M+H)<sup>+</sup> requires: 339.17252.

**6.3.7 Preparation of an authentic sample of 2-(-)-menthyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide (104) from reaction of 1-phenyl-1,2-ethanediol (122) with (-)-menthyl phosphorodichloridate (123).**

To a solution of (-)-menthyl phosphorodichloridate **123** (1.36g,  $4.98 \times 10^{-3}$  mmol) in dry ether (150ml), at 0°C, under argon, was added a solution of 1-phenyl-1,2-ethanediol (0.69g,  $4.99 \times 10^{-3}$  mmol), triethylamine (1.01g,  $9.96 \times 10^{-3}$  mmol, 2eq) and DMAP (5%) in ether (40ml) at a rate of 1ml/min *via* a perfusor. Once the addition was complete the reaction mixture was heated under reflux for one hour after which time it was observed by <sup>31</sup>P NMR that the reaction had gone to completion. The reaction mixture was then filtered, the precipitate washed with ether (2x20ml) and the filtrate evaporated to yield crude 2-(-)-menthyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **104** as a colourless solid. Analysis by <sup>31</sup>P NMR and <sup>13</sup>C NMR showed the product to be identical to that obtained by the trapping of (-)-menthyl metaphosphate **86** with styrene oxide and shows the characteristic four peaks in the region of 16 ppm in the <sup>31</sup>P NMR spectrum due to the pairs of cis and trans isomers. Physical data was in agreement with that of **104** synthesised in 6.3.6..

## 6.4 Generation of Alkyl Metaphosphates (3) by the Reaction of Alkyl Phosphorodichloridates (64) with Potassium Hydrogen Carbonate (78).

### 6.4.1 General procedure in the absence of trapping agents

To a stirred suspension of potassium hydrogen carbonate **78** (1.00g, 9.98 mmol) in dry DME (10ml), at room temperature, under argon, was added a solution of the appropriate alkyl phosphorodichloridate **64** (9.98 mmol) in dry DME (3ml). Once the addition was complete the reaction was stirred at room temperature and monitored by  $^{31}\text{P}$  NMR spectroscopy.

#### 6.4.1.1 Neopentyl metaphosphate (27)

After 2 hours stirring at room temperature the  $^{31}\text{P}$  NMR spectrum of the reaction mixture consisted of major signals at 0.26 ppm and in the regions  $\delta$  -13 and -24 ppm. The signal at 0.26 ppm was assigned to neopentyl dihydrogen phosphate **72** with the other signals being attributed to linear and cyclic phosphates arising from the self-condensation reactions of neopentyl metaphosphate<sup>8,18</sup>. A minor signal at 2.82 ppm attributed to neopentyl phosphorochloridic acid **81** was also present. After 24 hours at room temperature the spectrum consisted solely of two signals at 0.53 and -12.65 ppm and were assigned to

neopentyl dihydrogen phosphate and neopentyl pyrophosphate respectively, by comparison with authentic samples of each.

#### **6.4.1.2 Methyl metaphosphate (20)**

After 30 minutes stirring at room temperature the  $^{31}\text{P}$  NMR spectrum of the reaction mixture consisted of starting methyl phosphorodichloridate **94** (5.78 ppm), a signal at 3.63 ppm attributed to methyl phosphorochloridic acid **133** and linear and cyclic phosphate signals in the regions  $\delta$  -12 and -24 ppm arising from self-condensation reactions of the initially formed methyl metaphosphate<sup>8,18</sup>. After 24 hours at room temperature the spectrum consisted solely of two signals at 0.67 and -13.06 ppm and were assigned to methyl dihydrogen phosphate **97** and methyl pyrophosphate **134** respectively, by comparison with authentic samples of each.

#### **6.4.2 General procedure in the presence of styrene oxide**

To a stirred suspension of potassium hydrogen carbonate **78** (1.00g, 9.98 mmol) in dry DME (10ml), at room temperature, under argon, was added styrene oxide (9.98 mmol) and then a solution of the appropriate alkyl phosphorodichloridate **64** (9.98 mmol) in dry DME (3ml). Once the additions were complete the reaction mixture was stirred at room temperature and monitored by  $^{31}\text{P}$  NMR spectroscopy.

In each case after 24 hours the  $^{31}\text{P}$  NMR spectrum of the reaction mixture consisted almost entirely of either two or four signals, dependant upon the nature of the alkyl group. These signals appeared in the  $\delta$  15 to 18 range and were attributed to diastereomeric mixtures of 2-alkoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxides **111** formed by the reaction of alkyl metaphosphates with styrene oxide<sup>11</sup>. Minor signals were also present in the region  $\delta$  0 to -28 ppm due to side reactions and self-condensation reactions of a small amount of untrapped alkyl metaphosphate.

#### **6.4.2.1 Methyl metaphosphate (20)**

Methyl metaphosphate was trapped by styrene oxide to form 2-methoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **103** and was observed in the  $^{31}\text{P}$  NMR spectrum as two signals of nearly 1:1 composition ( $\delta$  17.05 and 16.86 ppm).

#### **6.4.2.2 Neopentyl metaphosphate (27)**

Neopentyl metaphosphate was trapped by styrene oxide to form 2-neopentyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **83** and was observed in the  $^{31}\text{P}$  NMR spectrum as two signals of nearly 1:1 composition ( $\delta$  16.15 and 15.98 ppm).

#### 6.4.2.3 (-)-Menthyl metaphosphate (86)

The reaction proceeded much slower with the alkyl group being (-)-menthyl than with lower alkyl groups. After 24 hours the  $^{31}\text{P}$  NMR spectrum showed the reaction to have barely started and so the reaction mixture was heated under reflux for one hour. After this time the main product was 2-(-)-menthyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **104** observed as four signals of nearly 1:1:1:1 composition (15.43, 15.32, 15.19 and 15.04 ppm) formed by the reaction of (-)-menthyl metaphosphate with styrene oxide.

### 6.5 Generation of Alkyl Metaphosphates (3) by Reaction of Alkyl Phosphorodichloridates (64) with Disodium Pyrocarbonate (90)

#### 6.5.1 General procedure in the absence of trapping agents

To a stirred suspension of disodium pyrocarbonate **90** (1.00g, 6.66 mmol) in dry DME (15ml), at room temperature, under argon, was added a solution of the appropriate alkyl phosphorodichloridate **64** (6.66 mmol) in dry DME (5ml). Once the addition was complete the reaction was heated under reflux and monitored by  $^{31}\text{P}$  NMR spectroscopy.

### 6.5.1.1 Methyl metaphosphate (20)

After 10 minutes the spectrum consisted of two major products at -4.03 and -16.69 ppm which were attributed to the mixed phosphoric-pyrocarbonic anhydride, sodium salt **96** and 2-methoxy-1,3,5,2-trioxaphosphorinane-4,6-dione-2-oxide **95** respectively. Some starting material was also present at 5.92 ppm. Minor products were also present in the regions  $\delta$  -12 and -24 ppm which are characteristic  $^{31}\text{P}$  NMR signals for linear and cyclic phosphates and presumably arose from the initially generated methyl metaphosphate **20**. After one hour the  $^{31}\text{P}$  NMR spectrum consisted almost entirely of self-condensation products of methyl metaphosphate<sup>8,18</sup> which were methyl dihydrogen phosphate **97** (-0.13 ppm), terminal phosphoryl units in chains (-12.0 to -14.0 ppm) and internal phosphoryl units in chains or cycles (-23.9 to -26.0 ppm)

### 6.5.1.2 Ethyl metaphosphate (45)

After 20 minutes the spectrum consisted of two major products at -5.52 and -18.01 ppm which were attributed to the mixed phosphoric-pyrocarbonic anhydride, sodium salt **135** and 2-ethoxy-1,3,5,2-trioxaphosphorinane-4,6-dione-2-oxide **136** respectively. There were also minor products in the regions  $\delta$  12 and -24 ppm which are characteristic  $^{31}\text{P}$  NMR signals for linear and cyclic phosphates and presumably arose from the initially generated ethyl metaphosphate **45**. Further heating led to the gradual disappearance of two signals at -5.52 and -18.01 ppm.

After one hour the  $^{31}\text{P}$  NMR spectrum consisted almost entirely of self-condensation products of ethyl metaphosphate<sup>8,18</sup> which were ethyl dihydrogen phosphate **137** (-0.40 ppm), terminal phosphoryl units in chains (-12.0 to -14.0 ppm) and internal phosphoryl units in chains and cycles (-23.0 to -26.0 ppm).

### 6.5.1.3 Neopentyl metaphosphate (27)

After 5 hours  $^{31}\text{P}$  NMR spectroscopy showed the reaction mixture to consist mainly of a signal at -18.17 ppm which was attributed to 2-neopentyloxy-1,3,5,2-trioxaphosphorinane-4,6-dione-2-oxide **138**. Other minor signals were also present at -4.9 ppm ascribed to the mixed phosphoric-pyrocarbonic anhydride, sodium salt **139**, and in the regions  $\delta$  -14 and -24 ppm which were ascribed to the self-condensation reaction of the initially formed neopentyl metaphosphate **27**. Further heating led to the gradual disappearance of the signal at -18.17 ppm. After 48 hours, the  $^{31}\text{P}$  NMR spectrum consisted almost entirely of signals due to self-condensation reactions of neopentyl metaphosphate<sup>8,18</sup> leading to neopentyl dihydrogen phosphate **72** (-0.134 ppm), terminal phosphoryl units in chains (-12.0 to -14.0 ppm) and internal phosphoryl units in chains and cycles (-23.0 to -26.0 ppm).

#### 6.5.1.4 (-)-Menthyl metaphosphate (86)

After 20 minutes the spectrum consisted entirely of self-condensation products of (-)-menthyl metaphosphate<sup>8,18</sup> **86** which were (-)-menthyl dihydrogen phosphate **140** (-1.08 ppm), terminal phosphoryl units in chains (-12.0 to -14.0 ppm) and internal phosphoryl units in chains and cycles (-26.0 to -29.0 ppm).

#### 6.5.2 General procedure in the presence of styrene oxide

To a stirred suspension of disodium pyrocarbonate **90** (1.00g, 6.66 mmol) in dry DME (15ml) at room temperature, under argon, was added styrene oxide (6.66 mmol) and then a solution of the appropriate alkyl phosphorodichloridate **64** (6.66 mmol) in dry DME (5ml). Once the additions were complete the reaction mixture was heated under reflux and monitored by <sup>31</sup>P NMR spectroscopy.

In each case after 30 minutes the <sup>31</sup>P NMR spectrum of the reaction mixture consisted almost entirely of either two or four signals, dependant upon the nature of the alkyl group. These signals appeared in the  $\delta$  15 to 18 range and were attributed to diastereomeric mixtures of 2-alkoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxides **111** formed by the reaction of alkyl metaphosphates with styrene oxide<sup>11</sup>. Minor signals were also present in the region  $\delta$  0 to -28 ppm due to side reactions and self-condensation reactions of a small amount of untrapped alkyl metaphosphate.

#### **6.5.2.1 Methyl metaphosphate (20)**

Methyl metaphosphate was trapped by styrene oxide to form 2-methoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **103** and was observed in the  $^{31}\text{P}$  NMR spectrum as two signals of nearly 1:1 composition ( $\delta$  16.70 and 16.60 ppm).

#### **6.5.2.2 Ethyl metaphosphate (45)**

Ethyl metaphosphate was trapped by styrene oxide to form 2-ethoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **141** and was observed in the  $^{31}\text{P}$  NMR spectrum as two signals of nearly 1:1 composition ( $\delta$  15.75 and 15.58 ppm).

#### **6.5.2.3 Neopentyl metaphosphate (27)**

Neopentyl metaphosphate was trapped by styrene oxide to form 2-neopentyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **83** and was observed in the  $^{31}\text{P}$  NMR spectrum as two signals of nearly 1:1 composition ( $\delta$  15.94 and 15.82 ppm).

#### **6.5.2.4 (-)-Menthyl Metaphosphate (86)**

(-)-Menthyl metaphosphate was trapped by styrene oxide to form 2-(-)-menthyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **104** and was

observed in the  $^{31}\text{P}$  NMR spectrum as four signals of nearly 1:1:1:1 composition ( $\delta$  15.39, 15.29, 15.16 and 15.01 ppm).

#### **6.5.2.5 (D)-Fructanose Metaphosphate 99**

(D)-Fructanose metaphosphate was trapped by styrene oxide to form 2-[(D)-fructanos-1 $\beta$ -yloxy]-4-phenyl-1,3,2-dioxaphospholane-2-oxide **142** and was observed in the  $^{31}\text{P}$  NMR spectrum as four signals of nearly 1:1:1:1 composition ( $\delta$  15.07, 14.98, 14.86 and 14.75 ppm).

### **6.6 Generation of Methyl Metaphosphate (20) by Reaction of Methyl Phosphorodichloridate (94) with Sodium Trimethylsilanolate (91)**

#### **6.6.1 In the absence of trapping agent**

To a solution of sodium trimethylsilanolate **91** (0.26g, 2.30 mmol) in dry DME (3ml), under argon at 0°C, was added a solution of methyl phosphorodichloridate **94** (0.34g, 2.30 mmol) in dry DME (1ml). Once the addition was complete the reaction mixture was allowed to warm to room temperature, continuously stirred and monitored by  $^{31}\text{P}$  NMR spectroscopy.

After one and a half hours  $^{31}\text{P}$  NMR spectroscopy showed the reaction mixture to consist partly of unreacted methyl

phosphorodichloridate **94** (5.78 ppm), an unidentified signal at 3.13 ppm and a signal at -3.63 ppm attributed to *O*-trimethylsilyl-*O'*-methyl phosphorochloridate **97**. The most important signals were those in the regions  $\delta$  -13 and -24 which are characteristic  $^{31}\text{P}$  NMR signals for linear and cyclic polyphosphates formed by the self-condensation of monomeric alkyl metaphosphates<sup>8,18</sup>.

### 6.6.2 In the presence of styrene oxide

To a solution of sodium trimethylsilanolate **91** (0.18g, 1.60 mmol) in dry styrene oxide (2ml), under argon, was added a solution of methyl phosphorodichloridate **94** (0.23g, 1.60 mmol) in dry styrene oxide (1ml). Once the addition was complete the reaction mixture was stirred at room temperature and monitored by  $^{31}\text{P}$  NMR spectroscopy.

After 45 minutes the  $^{31}\text{P}$  NMR spectrum of the reaction mixture consisted almost entirely of a closely matched pair of peaks at 16.87 and 17.04 ppm. These peaks were attributed to a diastereomeric mixture of 2-methoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **103** formed by the trapping of methyl metaphosphate **20** with styrene oxide<sup>11</sup>. A small amount of methyl metaphosphate failed to be trapped and was observed in the  $^{31}\text{P}$  NMR spectrum as unidentified phosphates (-0.3 to -0.7 ppm), terminal phosphoryl units in chains (-12 to -13 ppm) due to self-condensation of methyl metaphosphate and internal phosphoryl units in

chains or cycles (-26.9 to -28.3 ppm) also due to self-condensation of methyl metaphosphate.

## **6.7 Generation of Methyl Metaphosphate (20) by the Fragmentation of *O*-Trimethylsilyl-*O'*-Methyl Phosphorodichloridate (97).**

### **6.7.1 In the presence of styrene oxide.**

To a solution of *O*-trimethylsilyl-*O'*-methyl phosphorodichloridate **97** (0.10g,  $4.93 \times 10^{-4}$  m) in dry DME (1.0 ml), under argon at room temperature, was added a solution of styrene oxide (0.06g,  $4.93 \times 10^{-4}$  m) in dry DME (1.0 ml). Once the addition was complete the reaction mixture was stirred at room temperature and monitored by  $^{31}\text{P}$  NMR spectroscopy.

After 30 minutes  $^{31}\text{P}$  NMR spectroscopy of the reaction mixture showed a closely matched pair of signals at 16.60 and 16.40 ppm which were attributed to a diastereomeric mixture of 2-methoxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide<sup>11</sup> **103**. A small amount of starting material was also present at -5.92 ppm.

## 6.8 Generation of Neopentyl Metaphosphate (27) by the Reaction of Neopentyl Phosphorodichloridate (67) with Sodium Trimethylsilyl Carbonate (127)

### 6.8.1 In the absence of trapping agents

Through a solution of sodium trimethylsilanolate **91** (1.13g, 9.75 mmol) in DME (25ml), at 0°C under an argon atmosphere, was passed a stream of carbon dioxide for a period of 45 minutes. The addition of carbon dioxide resulted in the formation of sodium trimethylsilyl carbonate **127** as a thick, creamy slurry in the reaction flask. The reaction mixture was then treated dropwise with a solution of neopentyl phosphorodichloridate **67** (1.00g, 4.87 mmol) in DME (10ml). Once the addition was complete the reaction mixture was allowed to warm to room temperature, stirred and monitored by <sup>31</sup>P NMR spectroscopy.

After 30 minutes at room temperature <sup>31</sup>P NMR spectroscopy, showed the reaction mixture to consist of the starting neopentyl phosphorodichloridate **67** (431 ppm), a signal at -7.10 ppm attributed to **143** and a third signal at -16.80 ppm attributed to **128**. After a period of 5 hours at room temperature the <sup>31</sup>P NMR spectrum consisted of signals in the regions  $\delta$  -12 to -13 and  $\delta$  -24 to -25 ppm which are characteristic <sup>31</sup>P NMR signals for linear and cyclic polyphosphates formed by the self-condensation reactions of monomeric neopentyl metaphosphate<sup>8,18</sup>. Minor

signals around 0 ppm were also present which were probably due to side reactions.

### 6.8.2 In the presence of styrene oxide

Through a solution of sodium trimethylsilanolate **91** (1.13g, 9.75 mmol) in DME (25ml), at 0°C under an argon atmosphere, was passed a stream of carbon dioxide for a period of 45 minutes. The addition of carbon dioxide resulted in the formation of sodium trimethylsilyl carbonate **127**. The reaction mixture was then treated dropwise with a solution of styrene oxide (0.585g, 4.87 mmol) and neopentyl phosphorodichloridate **67** (1.00g, 4.87 mmol) in DME (10ml). Once the addition was complete the reaction mixture was allowed to warm to room temperature, stirred and monitored by <sup>31</sup>P NMR spectroscopy.

After a period of 1.5 hours the <sup>31</sup>P NMR spectrum consisted almost exclusively of a closely matched pair of peaks at 15.88 and 15.68 ppm, which were attributed to a diastereomeric mixture of 2-neopentyloxy-4-phenyl-1,3,2-dioxaphospholane-2-oxide **83** formed by the reaction of neopentyl metaphosphate with styrene oxide.

**Part II. Synthesis of Novel**  
**Phosphorus-Containing Scale**  
**Inhibitors for Use in Oil-field**  
**Operations**

# **Chapter Seven**

## **Introduction**

# Chapter Seven

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## 7.1 Background<sup>83-85</sup>

Scaling or precipitation fouling can be defined as the unwanted deposition of a solid layer of salts on a surface. Scale formation is almost inevitable in all processes where water is involved. Scale is formed when the saturation of the ions required for its formation is exceeded. Supersaturation can be caused by a number of factors, examples of which are as follows:

- (i) concentration of solutions as can happen in processes such as evaporation or freezing.
- (ii) mixing of waters from different origins as in oil production.
- (iii) changes in temperature as happens in heat exchangers and cooling towers.
- (iv) pressure decreases as in  $\text{CaCO}_3$  deposition due to loss of  $\text{CO}_2$ .
- (iv) pH increases as occurs at the release of  $\text{CO}_2$  which leads to  $\text{CaCO}_3$  deposition.

When scale formation is involved in a process then the efficiency of the process is always influenced resulting in a rise in operating and production costs. Scaling affects the economics of a process by bringing about heat insulation in heat exchangers, reduction in pipe-carrying capacity, and the clogging of pores, *e.g.* in rock formations that occur around bore wells in the oil industry. Processes are also affected by local corrosion, insulation of electricity in electrolytical processes, and down-time and maintenance.

It has already been mentioned that scaling is inevitable where water is used, and consequently many industrial systems and processes are affected; this report will only deal with the effects of scale in oil-field operations.

## **7.2 Scale formation in oil-field production**<sup>83-85</sup>

Since the mid 1950's injection of water into an oil-field has developed as the leading method for secondary oil recovery, *i.e.* to maintain reservoir pressure and to create a driving force to flood the oil from the sub-surface strata into the production wells. At an early stage, water that is produced together with the oil will be 'formation' water *i.e.* water from within the rock formation itself. Later, when secondary oil recovery is practised, the produced water will be a mixture of 'formation' water and returned 'injection' water. As a consequence of the chemistry of the two waters and their mixing, low solubility compounds are present which under certain conditions may precipitate out and form scale build-up. When scale does form it can lead to severe deposition in oil surface equipment (*e.g.*, oil/water separators, flow lines, transfer pumps), down-hole near the injection point or near the production point, or even worse, throughout the formation itself.

### **7.2.1 Scaling potential for sea-water.**

The chemical composition of sea-water varies according to where in the world it originates. For example, Table 2 gives details of typical major chemical components for North Sea and Arabian Gulf sea-waters<sup>83</sup>. It can be seen that sea-water contains ions that in combination could give rise to compounds known to have low solubility. In the case of the North Sea, this is limited to calcium carbonate formed by the initial decomposition of bicarbonate. Other combinations of low solubility such as calcium sulphate, barium sulphate and strontium sulphate are not present in sufficient concentration to give rise to precipitation, and hence possible scaling.

### **7.2.2 Scaling potential of produced waters.**

Produced waters may consist of purely 'formation' water, or may be a combination of 'formation' water and sea-water, which has arisen by injection due to secondary oil recovery. The stage when injected sea-water is first discovered with produced 'formation' water is called "sea-water breakthrough". This can occur within months or years after seawater injection has commenced, depending on the reservoir geology and the rate of injection.

**Table 2** Typical major components for the chemical analysis of North Sea and Arabian Gulf waters\*.

	<u>North Sea</u>	<u>Arabian Gulf</u>
Sodium (Na)	11000	13700
Potassium (K)	460	-
Calcium (Ca)	476	576
Magnesium (Mg)	1440	1670
Barium (Ba)	0.1	NIL
Strontium (Sr)	7	NIL
Iron (Fe)	0.05	NIL
Chloride (Cl)	19990	24500
Sulphate	2725	3400
Carbonate (CO <sub>3</sub> )	NIL	NIL
Bicarbonate (HCO <sub>3</sub> )	145	159
Hydroxide (OH)	NIL	NIL
Total Dissolved Salts	35000	44000
pH	7.8	7.8

\*All data measured in mg/l

The composition of 'formation' waters varies considerably over limited areas and even in different wells operating from the same platform. For example, analysis of four different produced waters from areas of the North Sea<sup>83</sup> is given in Table 3. In each case, sea-water breakthrough has not yet occurred, but it can be seen from the chemical components that the possibility of calcium carbonate scaling exists. Although barium and strontium are present there is no indication of sulphate, and consequently, scaling from barium or strontium sulphate does not exist. However, on sea-water breakthrough this situation changes radically since sea-water contains on average 2725mg/l of sulphate ion. In practice only a small amount of sea-water breakthrough is required to bring about the possibility of barium or strontium sulphate precipitation. A typical example of the effect of sea-water breakthrough on formation water<sup>83</sup> is shown in Table 4. It can be seen that the presence of approximately 6% sea-water composition is sufficient to provide enough sulphate ions to satisfy the stoichiometry of the reaction to produce barium sulphate. Indeed, after the occurrence of only approximately 20% sea-water breakthrough, there is sufficient sulphate ion to satisfy the stoichiometry of both barium and strontium sulphate formation. This is an important point to note since barium and strontium sulphate scales are by far the most insoluble compounds formed in oil-field water systems and are notoriously difficult to remove once deposited as scale.

**Table 3** Formation water analysis from the North Sea production zones

	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
Sodium	17280	9330	8370	29370
Potassium	580	198	200	372
Calcium	2890	460	240	2808
Magnesium	310	56	52	504
Barium	5	42	43	252
Strontium	195	40	46	574
Iron	19	0.1	0.1	-
Chloride	31950	14820	13000	52360
Sulphate	NIL	NIL	NIL	11
Carbonate	NIL	NIL	NIL	NIL
Bicarbonate	312	980	1100	496
Hydroxy	NIL	NIL	NIL	NIL
A.T.D.S.	53541	25926	23051	86747
pH	6074	7076	8.0	-

Notes:

1. All data measured in mg/l
2. Waters 2 and 3 are from individual wells on the same production platform.
3. A.T.D.S. = approximate total dissolved salts.

**Table 4** Effect of sea-water breakthrough on a formation water-barium sulphate deposition

Analytical parameters	100% fw	95/5 fw/sw	90/10 fw/sw	85/15 fw/sw	80/20 fw/sw	75/25 fw/sw	100% sw
Barium	252	239	227	214	202	189	NIL
Strontium	574	546	517	489	461	432	7
Sulphate	11	147	282	418	544	689	2725
Stoichiometric ratio Ba:SO <sub>4</sub> (theoretical =1:0.7)	1:0.04	1:0.61	1:1.24	1:1.95	1:2.7	1:3.64	-
Excess SO <sub>4</sub> <sup>2-</sup> after reaction with Barium(i.e. available for Sr)	NIL	NIL	123	268	403	537	-
Stoichiometric ratio Sr:SO <sub>4</sub> <sup>2-</sup> (theoretical =1:1.09)	-	-	1:0.24	1:0.55	1:0.87	1:1.24	-

Notes:

1. fw = formation water and sw = sea water.
2. There is sufficient sulphate ion for complete barium precipitation at 6% sea-water breakthrough.
3. There is sufficient sulphate ion to satisfy the stoichiometry of barium and strontium at approximately 20% sea-water breakthrough.

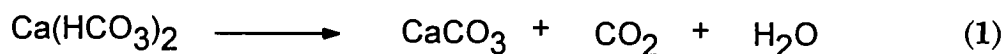
### 7.3 Physical factors affecting scale formation<sup>84</sup>

The important factors that may influence scaling in oil-field systems are temperature, pressure, pH value and total ionic strength of the solution containing the scaling ions.

The following section will deal with the four most common scales found in oil-field water systems and the physical factors affecting each.

### 7.3.1 Calcium carbonate scaling

As mentioned earlier, carbonate in the water concerned comes from the initial decomposition of bicarbonate by the reaction in equation (1).



The solubility of calcium carbonate in pure water at 25°C is 53.0mg/l<sup>83</sup>, but the presence of CO<sub>2</sub> has the effect of lowering the pH, and hence, increasing the solubility of calcium carbonate. However, when the CO<sub>2</sub> concentration is reduced, as may occur in many oil-field processes and systems, the solubility of calcium carbonate decreases and this favours scale formation.

The CO<sub>2</sub> partial pressure also has an effect on the solubility of calcium carbonate and this effect over a range of temperatures is shown in Figure 19<sup>83</sup>. It can be seen from the graph that when pressure-drop occurs, as often happens in oil-field processes, then scaling is favoured.

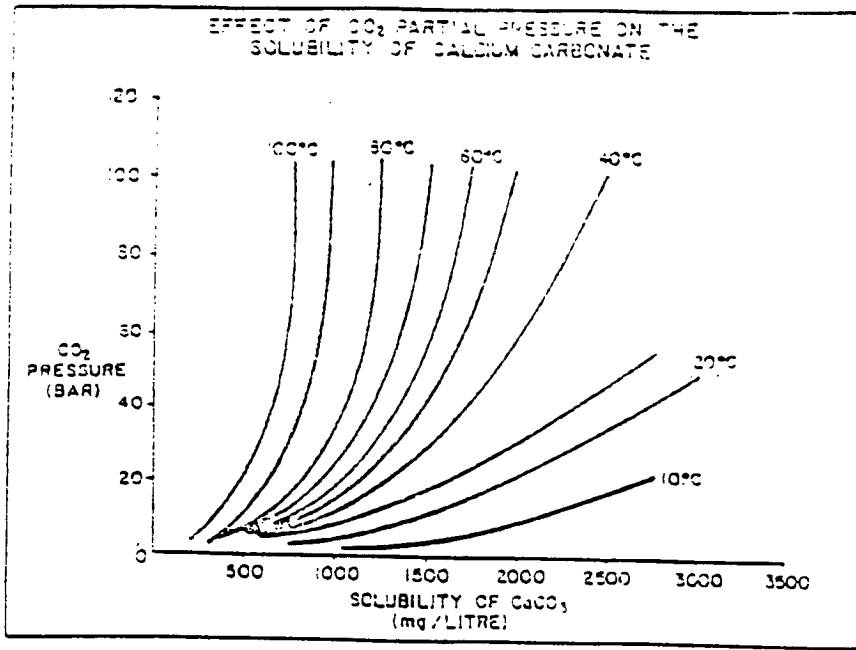


Figure 19. The effect of CO<sub>2</sub> partial pressure on the solubility of calcium carbonate

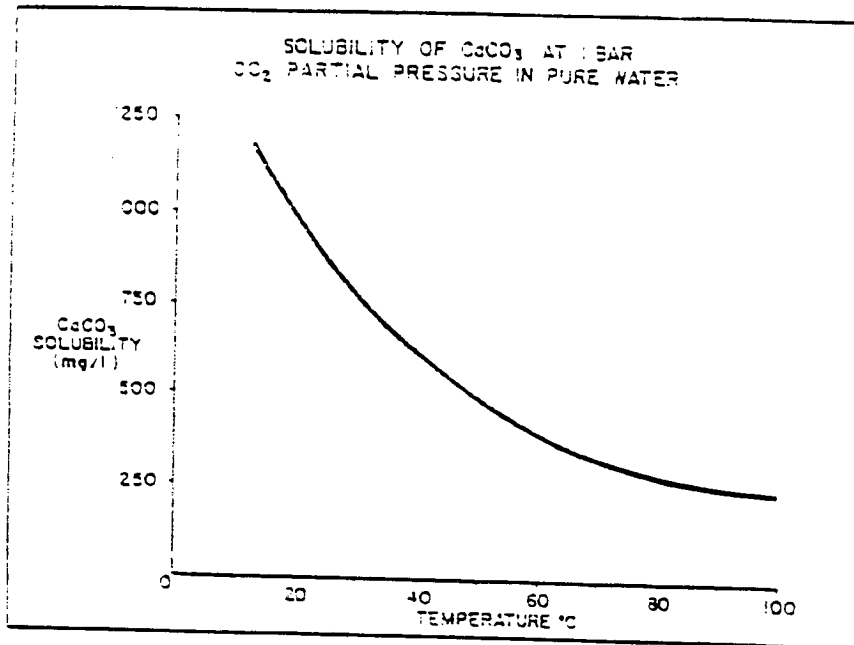
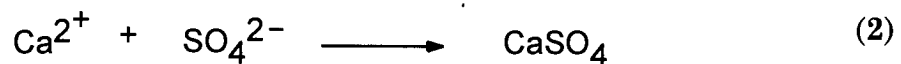


Figure 20. The effect of temperature on the solubility of calcium carbonate at 1 bar CO<sub>2</sub> partial pressure in pure water.

Figure 20 also illustrates the effect of temperature on the solubility of calcium carbonate and shows that unlike conventional solubility behaviour, the solubility decreases with increasing temperature<sup>83</sup>. The result is that calcium carbonate formation is favoured further down-hole an oil well due to higher temperatures.

### 7.3.2 Calcium sulphate scaling

Calcium sulphate is found in some oil-field waters owing to the simple reaction shown in equation (2). Its solubility of in pure water at 25°C is 2080mg/l<sup>83</sup>.

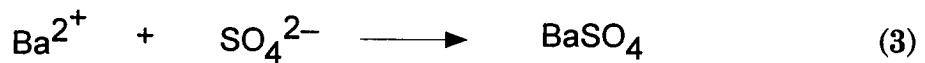


It is important to know the operational temperature when there is the possibility of calcium sulphate scaling. At temperatures up to 40°C, the degree of hydration of calcium sulphate is  $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$  and the solubility increases with increasing temperature. However, over the temperature range 40-110°C, the water of crystallisation is driven off and leads to the formation of the hemi-hydrate and anhydrous salt; consequently the solubility decreases.

On the other hand, an increase of pressure has the effect of increasing the solubility of calcium sulphate, until at very high pressures, the opposite occurs, and the solubility decreases.

### 7.3.3 Barium sulphate scaling

Barium sulphate is one of the most insoluble compounds to be found in oil-field water systems. The reaction for its formation is simple as shown in equation (3), and its solubility in pure water at 25°C is only 2.3mg/l<sup>83</sup> (cf. CaSO<sub>4</sub>)..



The solubility of barium sulphate increases with temperature in both pure water and brine solutions. For example, its solubility is 2.3mg/l at 25°C and increases to 3.9mg/l at 95°C in pure water. In 5% brine, the corresponding values are 20mg/l and 42mg/l, respectively. In essence, barium sulphate is exceedingly insoluble under all conditions and it can be seen that when barium sulphate is present in oil-field operations, there is the possibility of scaling as the temperature decreases from the bottom to the top of the well.

The ionic strength of the solution also has an effect on barium sulphate solubility, and from the data in Figure 21<sup>83</sup> it is evident that an increase in ionic strength brings about an increase in the solubility of barium sulphate.

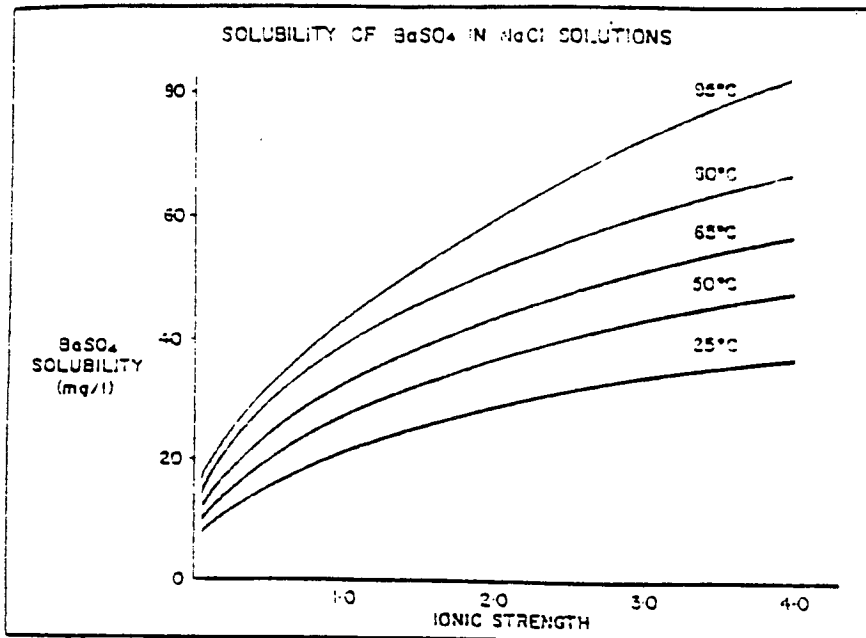


Figure 21. Solubility of barium sulphate in NaCl solutions.

### 7.3.4 Strontium sulphate scaling

Under high sulphate ion concentrations, strontium may precipitate as strontium sulphate according to the reaction shown in equation (4).



The solubility of strontium sulphate in pure water at 25°C is 150mg/l<sup>83</sup> up to an ionic strength of 1.3 (Figure 22). However, it is worth noting that strontium sulphate is never found alone, but co-precipitates with barium sulphate.

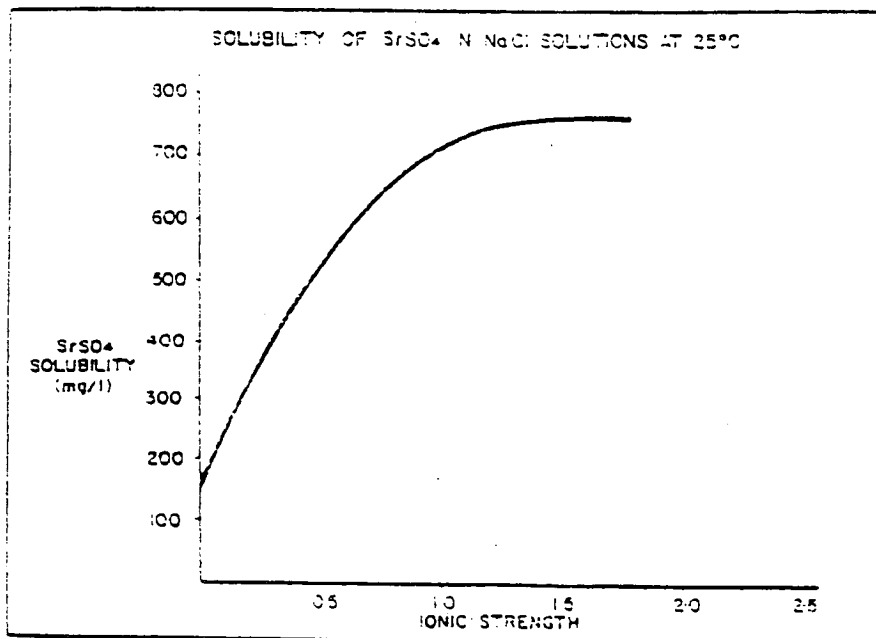


Figure 22. Solubility of strontium sulphate in NaCl solutions at 25°C.

In summary, a list of the common scaling species found in oil-field systems and the physical conditions affecting their formation is summarised in Table 5.

**Table 5.** Common scaling species in oil-field systems with influencing physical factors<sup>83,84</sup>

Scale Type	Influencing Physical Factors
Calcium Carbonate	Partial pressure Temperature Total dissolved salts
Calcium Sulphate	Temperature Total dissolved salts Pressure
Barium Sulphate	Temperature Pressure Total dissolved salts
Strontium Sulphate	Temperature Total dissolved salts

#### **7.4 Treatment of scale<sup>83-85</sup>**

When scale is allowed to deposit, it frequently has to be removed by chemical or mechanical methods. The removal of scale is not only

expensive, due to lost production time, but also involves the risk of failure. Consequently, the treatment of scale is focussed on prevention rather than removal, but since no two-water systems are identical there is no general method of scale treatment and each system often has its own specific requirements for scale prevention.

The prevention of scale can be divided into three methods of treatment, (i) mechanical, (ii) physical, and (iii) chemical; these methods are discussed in the following sections.

#### **7.4.1 Mechanical treatment of scale<sup>84</sup>**

All mechanical methods are based on some form of abrasive action exerted on the walls of the systems. One of the simplest methods to keep surfaces scale-free is the addition of sand particles to the water that is fed into the system. Another method is an automatic brush-cleaning system whereby the walls of the system are continually scrubbed. Soft foam balls have also been used and are pumped continuously throughout the system to keep it free from scale. It must be noted, however, that mechanical methods only prevent scale formation within the region of their action. If conditions beyond or before that region favour scale then it is likely that scale will be formed.

#### **7.4.2 Physical treatment of scale<sup>84</sup>**

Physical methods for the treatment of scale are aimed at the prevention of scale deposition on the walls of the system, while crystallisation in the bulk of the solution is allowed, and sometimes stimulated, provided the suspended solids can be removed easily. Physical treatment is mainly concerned with both ultra-sonic treatment and the 'seeding' technique.

##### **7.4.2.1 Ultrasonic treatment**

There are two methods of ultra-sonic treatment. In the indirect method, the transducer is placed not too far from the scaling surface and the explanation for scale inhibition is that erosion of the scale occurs due to cavitation of the scale surface. On the other hand, the direct ultra-sonic method has the transducer connected to the metal surface, and the scale is supposed to be dislodged by vibration of the metal.

##### **7.4.2.2 Seeding technique**

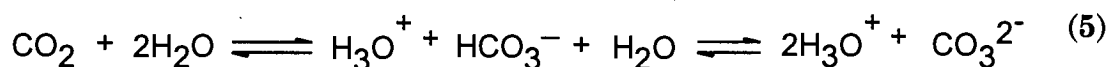
The 'seeding' technique is based on the creation of a large surface area favourable for crystallisation. The surface area of the seeds must be able to compete with the walls of the oil-field system in the consumption of the scaling components. The seeds used can be of the same material as the scale, or be other materials provided that they don't dissolve in the solution, and that preferential crystallisation occurs on these seeds.

### 7.4.3 Chemical treatment of scale<sup>83,84</sup>

Chemical treatment of scale affects the whole system, not only on the walls, where scale can be expected, but also in the bulk of the solution and in the rest of the equipment.

#### 7.4.3.1 Acid-dosing and CO<sub>2</sub> injection

Acids like sulphuric acid are used to prevent deposition of alkaline scale by reducing the pH of the solution. As the pH is lowered, the equilibrium in equation (5) is shifted to the left. Acid treatment is

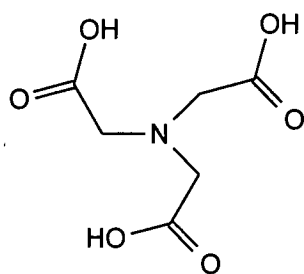


commonly used to suppress CaCO<sub>3</sub> and Mg(OH)<sub>2</sub> scaling, whilst CO<sub>2</sub> injection is also used to prevent scale formation. Such injections reduce the thermal decomposition of bicarbonate and also lower the pH of the solution, and consequently can be used to suppress CaCO<sub>3</sub> scaling.

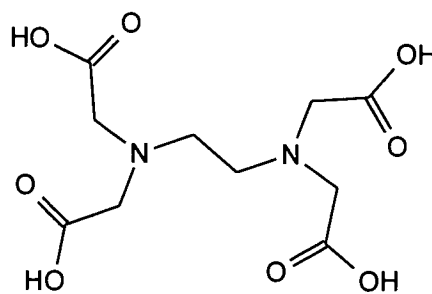
#### 7.4.3.2 The addition of complex-forming agents

Complex-forming agents are added to aqueous solutions to sequester metal-ions, thereby reducing the driving force for mineral crystallisation. The amount of complexing agent required is usually at

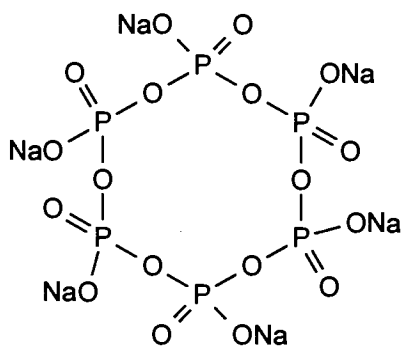
least stoichiometric. The most common agents employed are nitrilotriacetic acid ( NTA ) 147, *N,N,N',N'*-ethylenediaminetetra-acetic acid ( EDTA ) 148 and other amino polycarboxylates, sodium cyclohexametaphosphate 149, and penta-sodium triphosphate 150. Since treatment with complexing agents requires considerable amounts of often expensive chemicals, its application is limited to systems where large volumes of water are not involved.



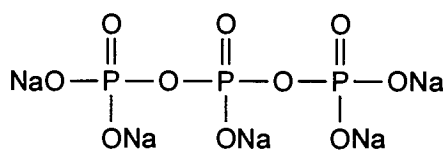
147



148



149



150

### **7.4.3.3 The addition of scale inhibitors<sup>83-85</sup>**

The prevention of scale deposition by the addition of trace amount of growth inhibitors is called scale-inhibition. It is given the term “threshold effect” and describes the effective application of inhibitors at concentrations far below the levels required to sequester the scale-forming metal ions. It is believed that scale inhibitors act by retarding the growth of the crystals in solution, and by distorting the normal regular shape of the crystals, thus reducing adhesion between individual particles or to solid surfaces<sup>86,87</sup>. It is also thought that inhibitors are adsorbed onto the crystal surface and block the active growth sites<sup>86,87</sup>. The effect of an inhibitor on different compounds such as calcium carbonate, calcium sulphate, barium sulphate and strontium sulphate varies markedly, and consequently, there is no scale-inhibitor that works well for every form of scale.

There are a large variety of inhibitors and these can be divided into four different classes; (i) inorganic phosphates, (ii) organic phosphate esters, (iii) organic polymers, and (iv) phosphonates.

#### **7.4.3.3.1 Inorganic phosphates<sup>83,84</sup>**

The inorganic phosphates were the earliest and most simple inhibitors. They contain one or more repeating O-P-O groupings, examples of which, include polyphosphates, metaphosphates, and pyrophosphates. The most common are penta-sodium triphosphate 150

and sodium cyclohexametaphosphate 149, both of which can also act as complexing agents at higher concentrations. The disadvantage of these agents is that they undergo slow hydrolysis in the presence of water to give ineffective orthophosphates, especially at higher temperatures and low pH values.

#### **7.4.3.3.2 Organic phosphate esters<sup>83,84</sup>**

The second class of phosphate inhibitors are the organic phosphate esters, which are much less stable than their inorganic counterparts, and consequently are commonly used under low temperature conditions. Examples of such compounds include phosphate esters of polyalcohols such as long-chain phosphate esters of glycerol, and hydroxyalkylamine phosphate esters like triethanolamine ester.

#### **7.4.3.3.3 Organic polymers<sup>83,84</sup>**

This class of compounds are also referred to as poly-electrolytes and include polyacrylamides and polyacrylates. They have the benefit of being usable at temperatures up to 200°C, but suffer from the disadvantage that unlike other phosphorus-containing inhibitors, difficulties are experienced in monitoring the concentration of the returning inhibitor in the produced water of oil-fields due to the lack of a readily analysed functional group

#### 7.4.3.3.4 The phosphonates<sup>83,84</sup>

The phosphonates are the most widely used scale inhibitors in oil-field water systems for the following reasons: (i) reasonable thermal stability, (ii) failure to hydrolyse in water at any pH value, and (iii) availability of a readily analysable functional group, *i.e.* such compounds are readily converted into phosphates, which can be determined by calorimetric means. For a brief review of a variety of commercially available phosphonate scale inhibitors and their synthesis, see section 7.6.

### 7.5 Evaluation of scale inhibitors

There are two main methods used by oil companies to evaluate the potential of phosphonates as scale inhibitors, *viz static precipitation method* introduced by B.P. Research, and the *dynamic test method* originally developed by Shell Petroleum.

#### 7.5.1 The static precipitation test<sup>88</sup>

This method is essentially a beaker technique, whereby solutions of incompatible scaling ions or of incompatible waters, *e.g.* sea water and formation water, are prepared separately, adjusted to the desired pH, pre-heated to the chosen test temperature and then mixed in the desired ratio in small glass bottles. The test bottles are then placed in a constant temperature oven for a fixed period, *e.g.* 16 hours, after which the

solutions are filtered through millipore filters. The residual levels of calcium, barium, and/or strontium are measured by Inductively Coupled Plasma (ICP) or atomic absorption spectroscopy. Tests are carried out on blanks, and if the intention is to identify the best scale inhibitor, on a number of potential inhibitors at a range of concentrations. A plot of inhibitor efficiency at a given dose for a given range of water ratios indicates the ranking of the inhibitor studied. By considering a range of dose levels, the best inhibitor and its optimum application level may be determined.

#### **7.5.2 Dynamic tube blocking test<sup>83</sup>**

In the *dynamic tube blocking test* the solutions of incompatible ions or brines, and an amount of scale inhibitor, are injected at a constant flow-rate through peristaltic pumps into a mixing cell. The resultant mixture is pumped through a stainless steel capillary tube, which is immersed in a thermostatic bath. Since scale deposition leads to a significant reduction in the bore of the capillary, the resulting build-up in back pressure can be measured. The absence of pressure build-up is indicative of the most effective scale inhibitor under test.

### **7.6 Phosphonates as scale inhibitors**

As mentioned earlier in section 7.4.3.3.4, phosphonates have been the most widely used scale inhibitors in oil-field water systems, the

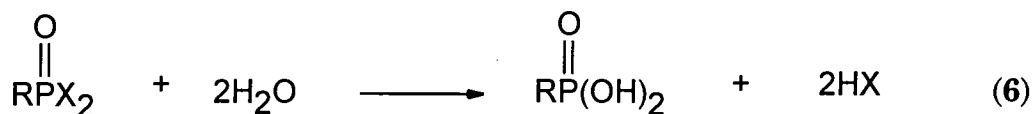
reason being that they have reasonable thermal stability, fail to hydrolyse in water at any pH, and possess a readily analysable functional group.

The following section will seek to give a brief over-view of the type of phosphonate scale-inhibitors available and the method of their synthesis, although it should be noted that most scale inhibitors have been synthesised within industrial companies, and consequently, the vast majority of relevant literature is either unpublished or in the form of patents. Moreover, these patents normally state that the chemicals of interest act as scale inhibitors, but do not give information on their performance. As a result, it is difficult to compare the performance of inhibitors relative to each other. This section will deal with the following topics: (i) general methods of phosphonic acid synthesis, (ii) general methods of phosphonic acid diester synthesis, (iii) dequest phosphonates currently in use in oil-field systems, and (iv) examples of other patented scale inhibitors.

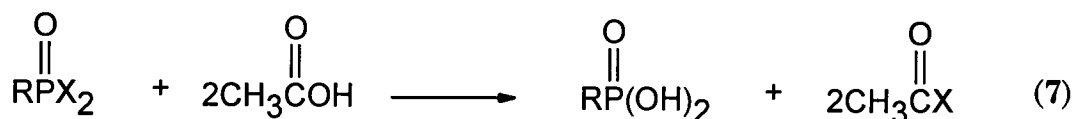
## **7.6.1 General methods of phosphonic acid synthesis<sup>89</sup>**

### **7.6.1.1 Hydrolysis of phosphonic acid halides**

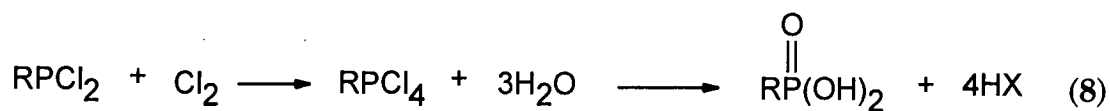
As early as 1873, Michaelis<sup>90</sup> discovered that phosphonic acid halides can be hydrolysed to the corresponding acid by the addition of water. Phosphonic acid halides of general formula  $RP(O)X_2$  are hydrolysed according to equation (6).



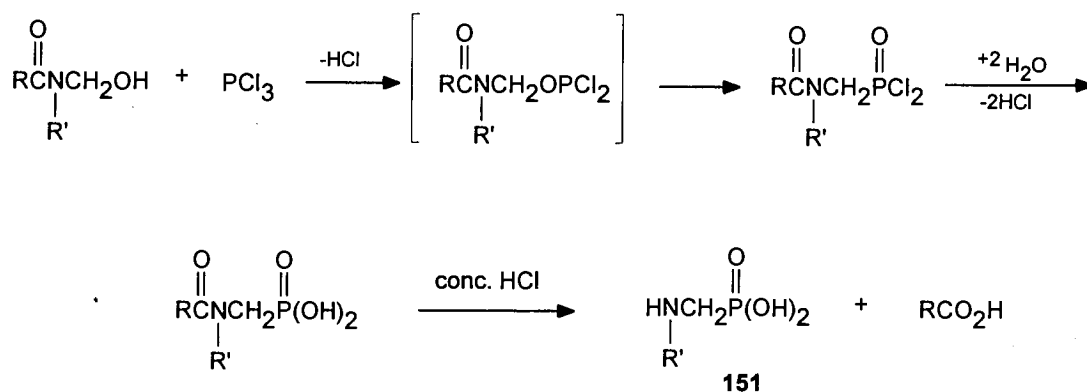
When anhydrous phosphonic acids are required, it is necessary to carry out the hydrolysis in a solvent b.pt. < 100°C with the theoretical amount of water<sup>91</sup>. Pertinently, short chain carboxylic acids are also suitable for the transformation of phosphonic acid halides into phosphonic acids. The most common carboxylic acid used is acetic acid<sup>92,96</sup> with the subsequent formation of acetyl chloride as depicted in Equation 7.



Michaelis also found that orthophosphonic acid tetrahalides, which can be obtained by addition of chlorine to dihalophosphines, are also hydrolysed to the corresponding phosphonic acids<sup>90</sup> by the general reaction shown in equation (8).



Of particular relevance to scale inhibitors is the reaction of carboxylic acid hydroxymethylamides with  $\text{PCl}_3$  to yield a phosphoryl dichloride, which can be hydrolysed to the corresponding acylaminomethylene phosphonic acid<sup>93</sup> (Scheme 74). Further treatment with hydrochloric acid leads to removal of the acyl group and the formation of the desired aminomethylenephosphonic acids **151**.



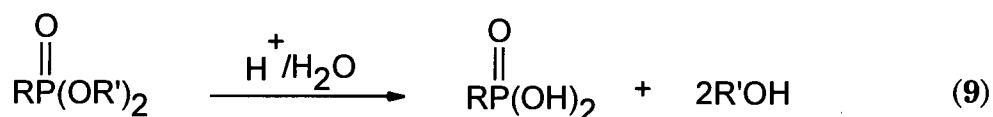
Scheme 74

Aminomethylenephosphonic acids are very common scale inhibitors and are normally synthesised by reaction of an amine with formaldehyde and phosphorous acid<sup>94</sup> (section 7.6.1.7); such a procedure

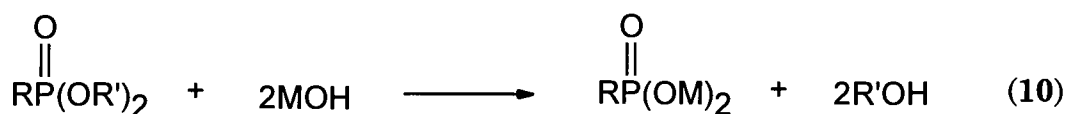
phosphonomethylates every available N-H bond, but Scheme 74 depicts a route to aminomethylenephosphonic acids with free N-H bonds if such compounds are desired.

### 7.6.1.2 Hydrolysis of phosphonic acid esters

Hydrolysis of phosphonic acid esters with mineral acids generally leads to phosphonic acids directly without cleavage of the C-P bond<sup>89</sup> as shown in equation (9).

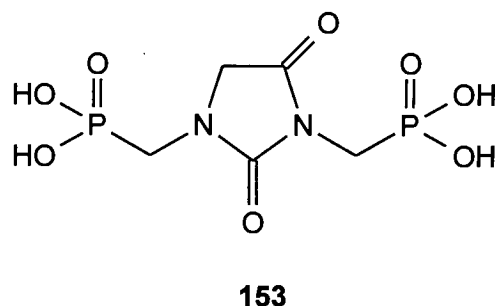
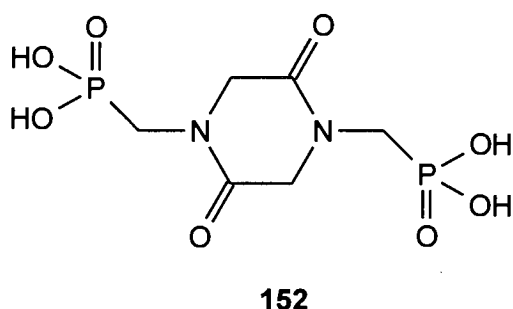


In the same way hydrolysis with base leads to the corresponding phosphonic acid salts<sup>89</sup> according to equation (10).



The principal problem with hydrolysis is that if a compound contains other functional groups that are sensitive to hydrolysis, these are also generally hydrolysed due to the harsh conditions used. In these

cases, other methods of cleaving the ester groups have to be pursued (see following sections), although Natchev<sup>95</sup> has recently found a way around the problem by employing enzymes to catalyse the hydrolysis. He was engaged in synthesising *N*-phosphonomethylated amides such as 152 and 153, but found the expected problems in hydrolysing the



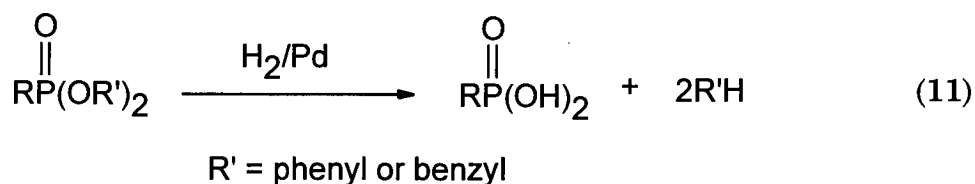
corresponding phosphorus diesters. He was aware of the fact that phosphoesterase enzymes are frequently employed in solving problems with nucleic acids, and upon investigating these enzymes further, found that phosphodiesterase I and alkaline phosphatase can be successfully used for catalysing the hydrolysis of esters of organophosphorus acids. The general method simply involves stirring the substrate and enzyme in a set ratio for six hours at 37°C in an aqueous buffer medium. Once the enzyme is removed the acid can be isolated with yields normally being quantitative. Such hydrolyses are strictly selective and hitherto have

been found not to affect any other hydrolysable group within the molecule.

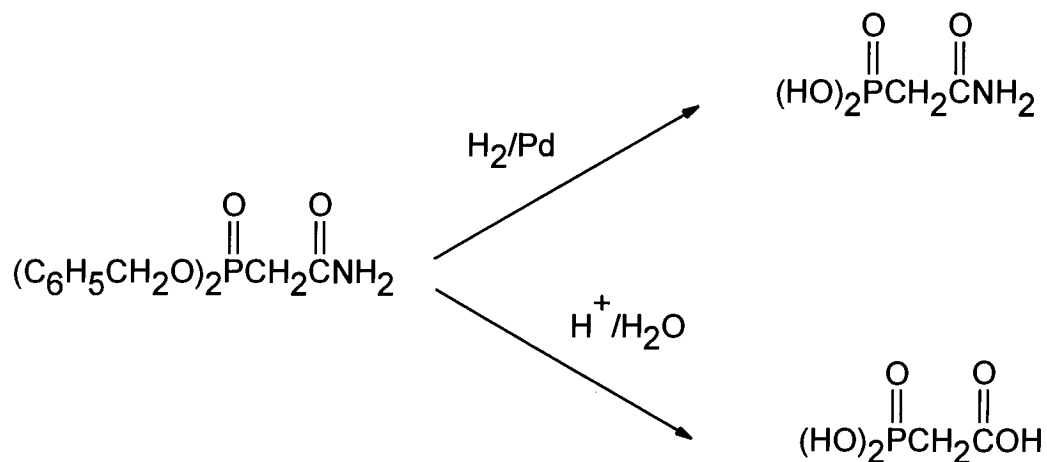
Similar to phosphonic acid esters are ester amides which may also be hydrolysed to the free acid normally by 12M HCl<sup>96</sup>.

### 7.6.1.3 Hydrogenation of benzyl and phenyl esters

Catalytic reduction of benzyl and phenyl esters with Pd/H<sub>2</sub> leads to the corresponding phosphonic acids according to equation (11).



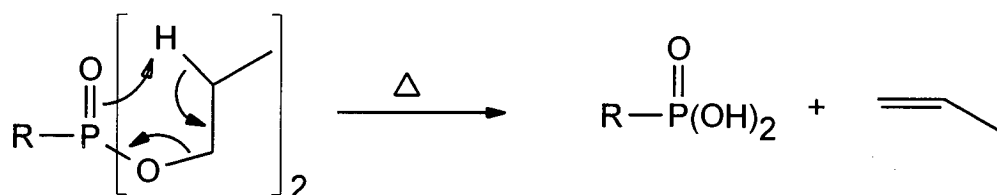
This method is preferred over hydrolysis when the compound in question contains other hydrolysable groups that need to be retained<sup>97,98</sup>. For example, carbamidomethylene phosphonic acid is obtained from its benzyl ester by hydrogenation, whereas hydrolysis leads to phosphonoacetic acid<sup>97</sup> (Scheme 75).



Scheme 75

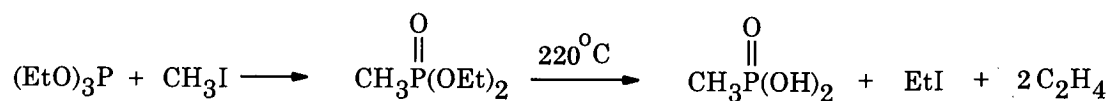
#### 7.6.1.4 Pyrolysis of esters

Phosphonic acid alkyl esters, with the exception of methyl esters, are cleaved upon heating into olefins and phosphonic acids<sup>89</sup>. The reaction requires the presence of an abstractable  $\beta$ -hydrogen as shown in Scheme 76, where the example chosen is a propyl ester.



Scheme 76

Probably one of the earliest examples of this type of reaction was reported by Michaelis<sup>99</sup> who, when carrying out his initial work on the Michaelis-Arbuzov reaction (section 7.6.2.1), reacted triethylphosphite with methyl iodide and produced methylphosphonic acid instead of the expected diethyl ester. The reaction had obviously formed the diester, but under the conditions used (12 hours, 220°C), it had eliminated ethylene to yield the free acid (Scheme 77).

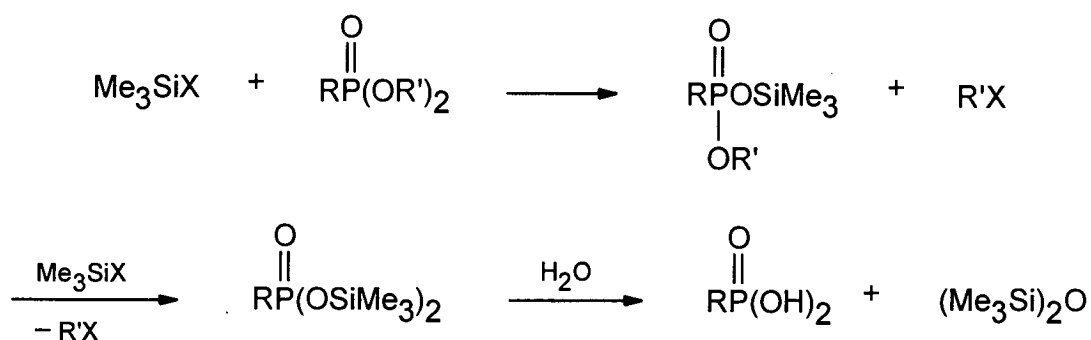


Scheme 77

The temperature required for eliminations of this type depends upon the alkyl group concerned. Ethyl esters require temperatures in the range 200-280°C, whilst *i*-propyl esters decompose at 120-180°C. On the other hand, butyl esters especially *t*-butyl esters, undergo pyrolysis at even lower temperatures, but the temperature can be reduced once the reaction has started since the reaction is catalysed by traces of acid<sup>89</sup>.

### 7.6.1.5 Dealkylation of esters by halotrimethylsilanes

Phosphonic acid dialkyl esters are transformed into the corresponding bis-trimethylsilyl esters upon treatment with halotrimethylsilanes. Subsequent hydrolysis of these products leads to phosphonic acids under mild conditions<sup>100,101</sup> (Scheme 78).

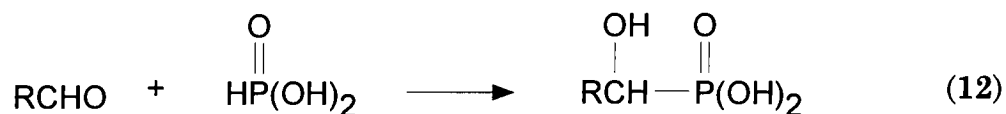


Scheme 78

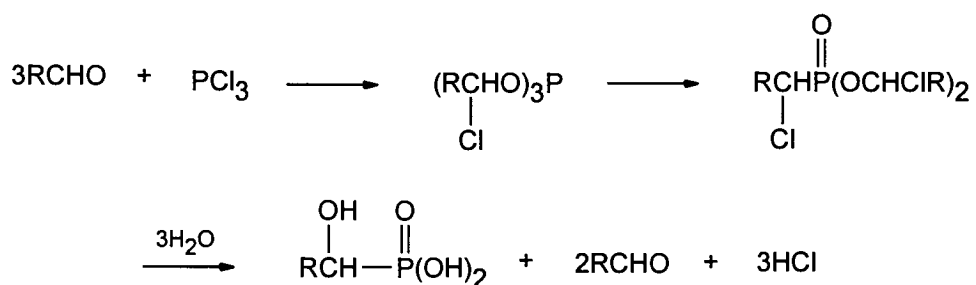
Chloro-, bromo- and iodo-trimethylsilane have all been used to dealkylate esters. As expected, the bromo- and iodo-trimethylsilanes are more reactive than the corresponding chlorotrimethylsilane. Blackburn<sup>102</sup> has found that iodotrimethylsilane is selective for phosphonate esters, whereas bromotrimethylsilane modifies both phosphonate esters and carboxylate esters when both are present within a substrate.

### 7.6.1.6 Reaction of carbonyl compounds with H<sub>3</sub>PO<sub>3</sub> or PCl<sub>3</sub>

Phosphorous acid reacts with carbonyl compounds like aldehydes at elevated temperatures to give  $\alpha$ -hydroxyalkyl phosphonic acids according to equation (12), but due to low yields obtained, this reaction does not have much practical value<sup>89</sup>. However, the reaction of PCl<sub>3</sub> with carbonyl



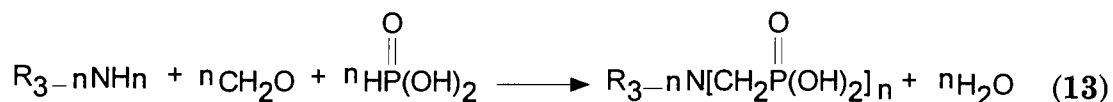
compounds is of more practical importance. Thus, Fossek<sup>103</sup> found that 3 moles of aldehyde reacted with PCl<sub>3</sub> to bring about the formation of such phosphonic acids, and later, Kabachnik<sup>104</sup> proposed the mechanism outlined in Scheme 79. It is worth noting that if  $\alpha$ -hydroxymethylenephosphonic acid itself is required then paraformaldehyde reacts with PCl<sub>3</sub> in high yields<sup>105</sup>.



Scheme 79

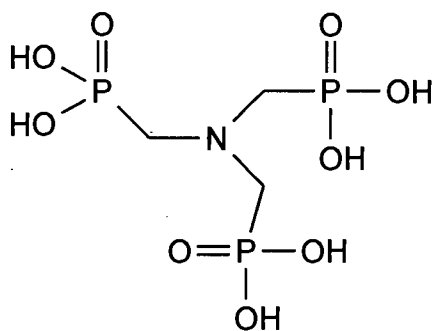


Mannich condensation to form aminomethylenephosphonic acids<sup>94</sup> according to equation (13). Products are generally obtained, in which all

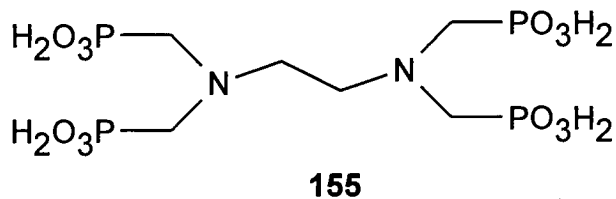


the N-H bonds of the starting amine have been phosphonomethylated. The reaction is well suited for the preparation of, for example, amino-tris(methylenephosphonic acid)<sup>107</sup> **154** from NH<sub>3</sub>, but is not suitable for amino-*bis* or -*mono*(methylenephosphonic acid).

Polyamines and functionally substituted amines, or their hydrochlorides, react in a similar manner, *e.g.* with ethylenediamine, and as a result, ethylenediamine tetrakis(methylenephosphonic acid) **155** is obtained<sup>107</sup>.



**154**

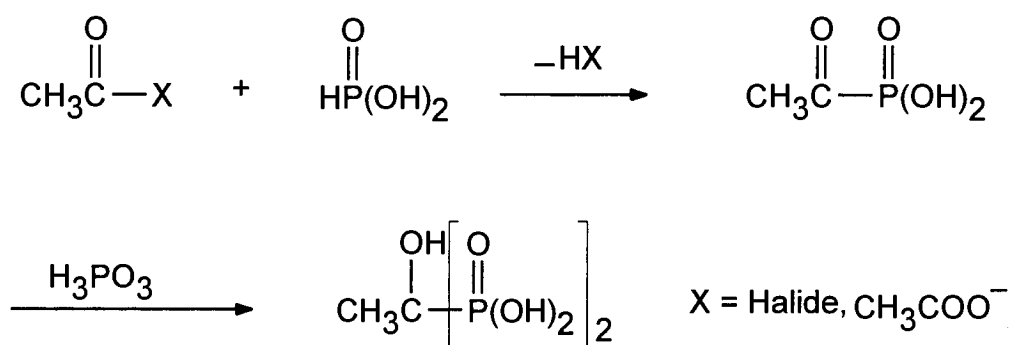


The general method normally involves the slow addition of formaldehyde to a mixture of the phosphorous acid and amine at a temperature above 85°C. The pH of the reaction medium has an important influence upon the rate of reaction, and consequently a conventional acid may be added to keep the pH below 4, and ideally about pH 2<sup>108</sup>. A catalytic amount of halide ions is also required and is found to inhibit the oxidation of the orthophosphorous acid to orthophosphoric acid<sup>108</sup>. Finally, some water is also required to be added to the reaction mixture and contributes to factors such as keeping the reactants in solution, ease of handling of the reaction medium, ease of maintaining the reaction temperature by heating under reflux, and by decreasing the viscosity of the reaction products<sup>108</sup>.

As will be seen later in section 7.6.3 and 7.6.4, this reaction has been one of the most frequently employed methods for producing phosphonate scale inhibitors, particularly those that are presently being used in the oil-fields of the North Sea.

### 7.6.1.8 Direct synthesis of hydroxyalkane-1,1-diphosphonic acids

The reaction of acylating compounds with  $\text{H}_3\text{PO}_3$  results in the formation of complex reaction mixtures. If these are submitted subsequently to steam distillation until the distillate is no longer acidic, hydroxyethane-1,1-diphosphonic acid (HEDP) may be isolated in up to 97% yield<sup>109</sup>. The process involved is outlined in Scheme 81. It is worth



Scheme 81

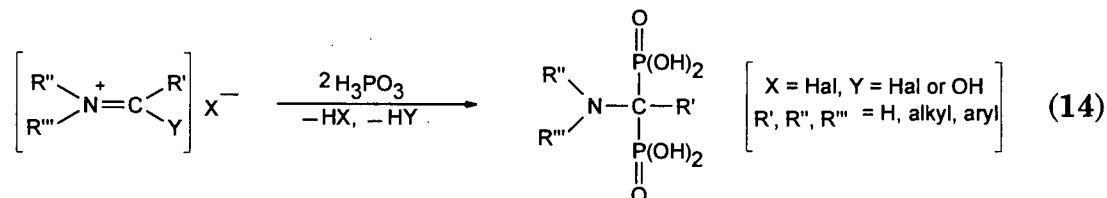
noting that the acylating reagents may lead to further condensation reactions and the formation of reaction mixtures containing acylation products of HEDP, as well as the HEDP condensed dimer. However, upon steam distillation, such side-products are hydrolysed to HEDP, thus explaining the 97% yield.

HEDP is a common industrial scale inhibitor produced by Monsanto (section 7.6.3) and can be made by reacting acetic acid with

PBr<sub>3</sub> (or PCl<sub>3</sub>) instead of phosphorous acid<sup>110</sup>. Other hydroxyalkane-1,1-diphosphonic acids may be prepared by a variety of different methods<sup>89</sup>, including the reaction between acyl chlorides and H<sub>3</sub>PO<sub>3</sub>, carboxylic acid anhydrides and H<sub>3</sub>PO<sub>3</sub>, carboxylic acids and defined amounts of H<sub>2</sub>O and PCl<sub>3</sub>, carboxylic acids and P<sub>4</sub>O<sub>6</sub>, and finally, carboxylic acids and H<sub>3</sub>PO<sub>3</sub>/P<sub>2</sub>O<sub>5</sub>.

### 7.6.1.9 Direct synthesis of aminoalkane-1,1-diphosphonic acids

There are a number of reactions known for the direct synthesis of aminoalkane-1,1-diphosphonic acids, all of which proceed *via* the key intermediate depicted in equation (14).



The following procedures have been reported<sup>89</sup>:

(i) *via* nitrile, PX<sub>3</sub> and hydrolysing agent. Notably, most nitriles undergo this reaction and PBr<sub>3</sub> gives better yields than PCl<sub>3</sub>.

(ii) *via* *N*-unsubstituted carboxylic acid amide dihalogenides and H<sub>3</sub>PO<sub>3</sub>.

The carboxylic acid amide dihalogenides are not normally isolated and it

is sufficient to conduct a stream of HCl or HBr gas into the molten mixture of nitrile and  $\text{H}_3\text{PO}_3$ .

(iii) *via* *N,N*-disubstituted carboxylic acid amide dihalogenides and  $\text{H}_3\text{PO}_3$ . The dihalogenides are produced by the reaction of the corresponding amide with  $\text{PCl}_5$ , oxalyl chloride, *etc.*

(iv) *via* carboxylic acid amide hydrohalogenides and  $\text{H}_3\text{PO}_3$ . Again the carboxylic acid amide hydrohalogenides are not isolated and it is sufficient to react a mixture of carboxylic acid amide and phosphorous acid with HCl or HBr at 130-160°C.

### 7.6.2 Main methods of phosphonic acid ester synthesis

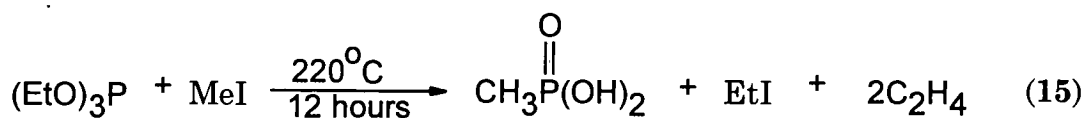
This section will give a brief overview of the main methods, with respect to scale inhibitors, in which phosphonic acid diesters have been synthesised. In fact, in any general synthetic scheme in which a phosphonic acid diester is a target compound, the preferred route is almost certainly to be chosen from one of these methods.

Although the majority of phosphonate scale inhibitors are preferred as phosphonic acids, or salts of the acids, the esters can also be used as effective scale inhibitors in circumstances where they have a good enough performance. The main reason for needing to understand the synthesis of the phosphonic diesters is that many of the phosphonic acids used as scale inhibitors are synthesised *via* hydrolysis or hydrogenation of the corresponding esters. This section will deal with the following

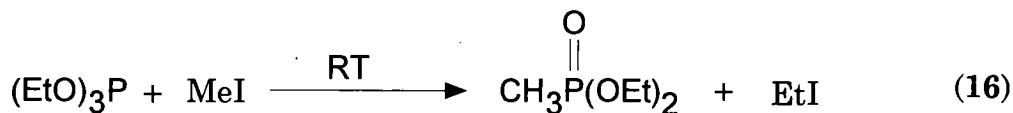
methods of phosphonic acid diester synthesis: (i) the Michaelis-Arbuzov reaction, (ii) the Michaelis-Becker reaction, (iii) the addition of phosphites to carbonyl compounds, and (iv) the condensation of aldehydes or ketones with amines and dialkyl phosphites.

### 7.6.2.1 The Michaelis-Arbuzov reaction

This reaction is one of the most important and commonly used reactions for the preparation of phosphonic acid diesters. The reaction was first observed in 1898 by Michaelis and Kaehne<sup>99</sup> who found that when triethyl phosphite was reacted with methyl iodide at 220°C for 12 hours, methylphosphonic acid was obtained [equation (15)]. In 1905,

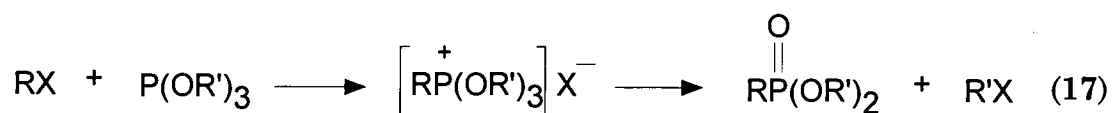


Arbuzov<sup>111</sup> developed this reaction further and found that at room temperature, triethyl phosphite readily condensed with methyl iodide to form methylphosphonic acid diester [equation (16)]. Clearly, at the high



temperatures that Michaelis had carried out the reaction, pyrolysis of the diethyl ester occurred (see section 7.6.1.4) with the elimination of ethylene to form methylphosphonic acid.

The general reaction that is now widely utilised involves the direct condensation of alkyl halides with trialkyl phosphites to form phosphonic acid diesters<sup>112</sup>. Later it was found that other alkylating agents and acylating agents may be used in the reaction and the general process is shown in equation (17).

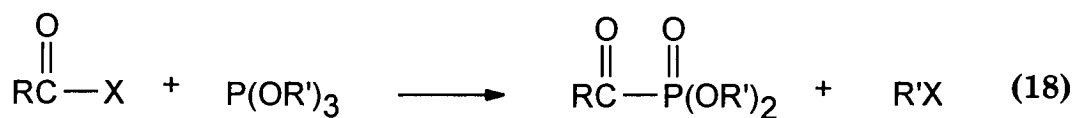


The mechanism of the Arbuzov reaction proceeds *via* a phosphonium ion intermediate, which in most cases cannot be isolated, although in reactions with carbocation salts, such as triphenylmethyl tetrafluoroborate, the depicted intermediate can be isolated.

Complications can arise due to the self-alkylating ability of trialkyl phosphites. For example, phosphonic acid esters are formed upon heating of trialkyl phosphites, especially when catalytic amounts of alkyl halides are present. For the preparation of phosphonic acid esters with the same

alkyl group attached to both *P* and *O*, it is simply necessary to treat the trialkyl phosphite with catalytic amounts of alkyl halide. If the alkyl groups are preferred to be different, then at least stoichiometric amounts of the alkyl halide are required.

With acyl halides, trialkyl phosphites react readily to produce  $\alpha$ -ketophosphonic acid esters as shown in equation (18).

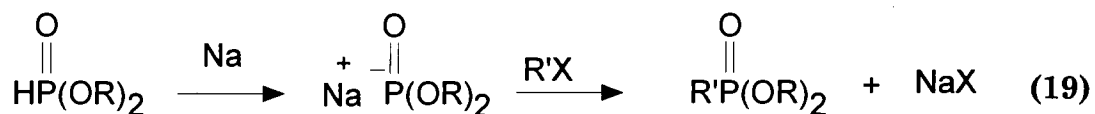


Other alkylating reagents also react with trialkyl phosphites according to the Michaelis-Arbuzov scheme<sup>112</sup>. These include, in addition to alkyl- and acyl- halides, sulfonic acid esters, carboxylic acid anhydrides and salts of Mannich bases.

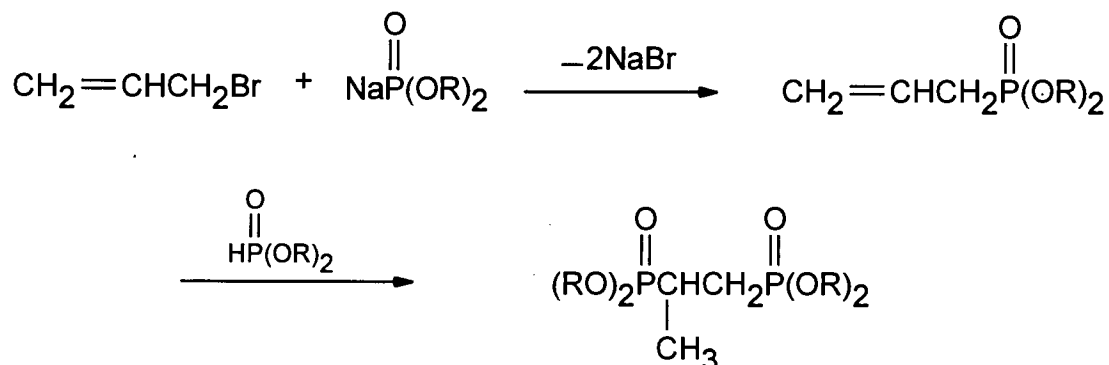
#### 7.6.2.2 The Michaelis-Becker reaction

This reaction of salts of dialkylphosphites and alkylhalides was discovered by Michaelis and Becker<sup>113</sup> in 1897. Normally, sodium salts of the dialkyl phosphites are used, although the alkali salts may be substituted by mixtures of dialkyl phosphites and tertiary amines. Instead of alkyl halides, other alkylating agents and acylating agents, as

in the Michaelis-Arbuzov reaction, may be used<sup>89</sup>. The reaction proceeds according to equation (19).



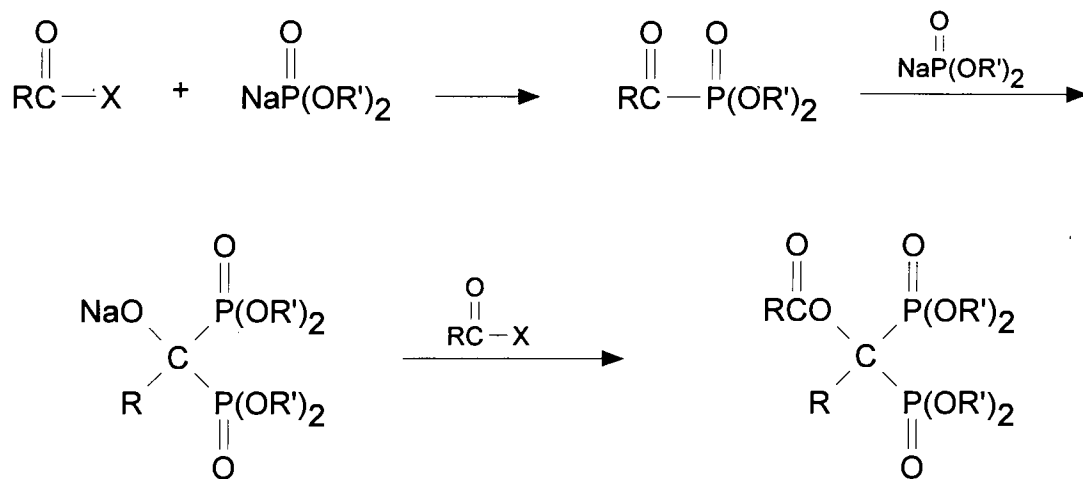
Unsaturated alkyl halides may also be used, although these reactions are often accompanied by addition to the double bond (Scheme 82).



Scheme 82

Acyl halides also undergo the Michaelis-Becker reaction, although, the reaction does not stop at the  $\alpha$ -oxophosphonic acid ester stage, but

undergoes further reaction with the phosphite salt, and subsequently with the acyl halide (Scheme 83).

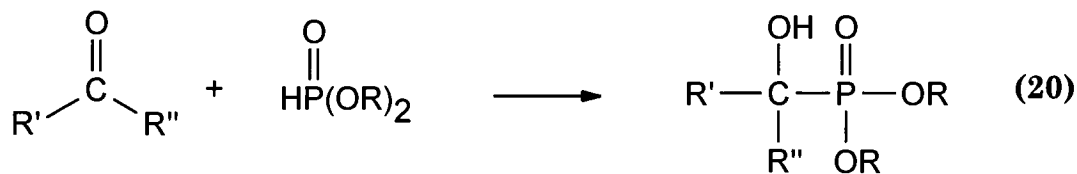


Scheme 83

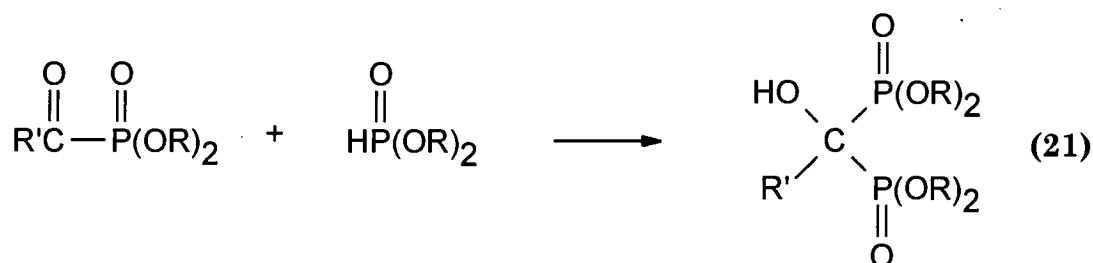
Other alkylating agents that react with dialkylphosphite salts include acid anhydrides, epoxides, carboxylic acid esters and sulfonic acid esters<sup>89</sup>.

### 7.6.2.3 Addition of phosphites to carbonyl groups

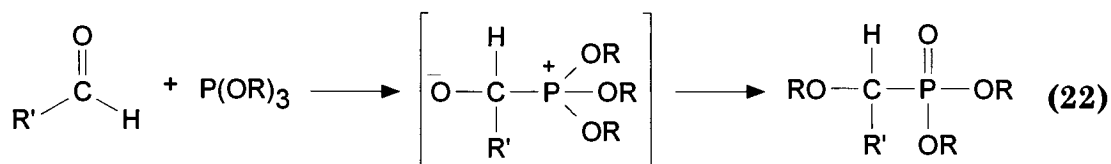
With the exception of  $\alpha,\beta$ -unsaturated ketones, dialkylphosphites add to the carbonyl group of ketones and aldehydes<sup>89</sup> according to equation (20). It is possible to reverse the reaction with aqueous base which cleaves the *P-C* bond of the  $\alpha$ -hydroxy phosphonic acid diester.



Similar to the direct synthesis of hydroxyalkane-1,1-diphosphonic acids (see section 7.6.1.8), dialkylphosphites react with  $\alpha$ -oxo-alkane-phosphonic acid esters to give hydroxyalkane-1,1-diphosphonic acid esters as shown in equation (21).

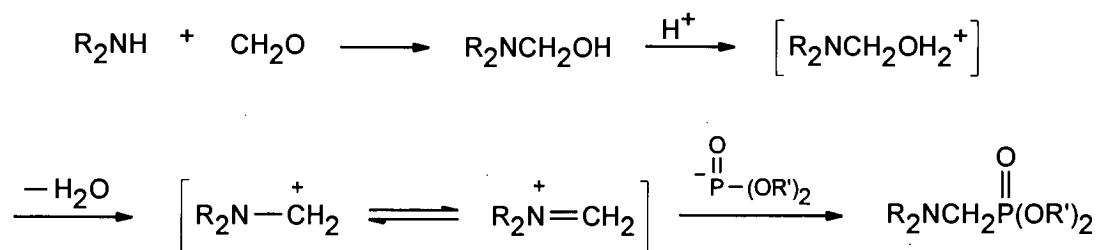


Trialkyl phosphites add to aldehydes only at elevated temperatures and under pressure with subsequent alkylation on oxygen<sup>89</sup> (equation 22).



#### 7.6.2.4 Condensation of aldehydes or ketones with amines and dialkylphosphites

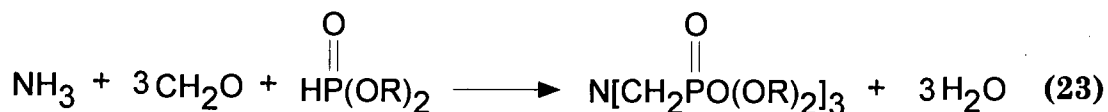
Aldehydes and ketones react with primary or secondary amines and dialkyl phosphites to form  $\alpha$ -amino-alkyl phosphonic acid diesters<sup>89</sup>. The mechanism is similar to the Mannich reaction since the adduct formed in the initial reaction of the amine with the aldehyde or ketone goes on to react further with dialkyl phosphites to form the  $\alpha$ -amino-alkyl phosphonic acid esters<sup>114</sup>. When initial formation of  $\alpha$ -hydroxy phosphonic acid esters is carried out, there is no further reaction with amines to yield the  $\alpha$ -aminoalkyl phosphonic acid esters. The mechanism for formaldehyde is depicted in scheme 84.



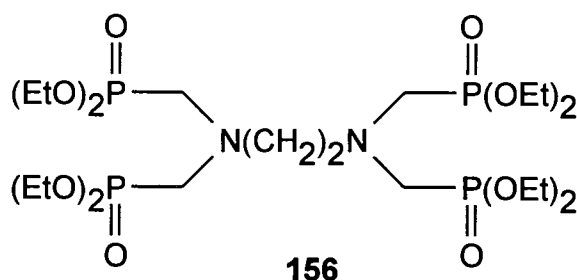
Scheme 84

When secondary amines are employed in this reaction, only mono-phosphonic acid esters are obtained. However for primary amines, all N-

H bonds are phosphonomethylated provided sufficient reactants are present. For example, the use of ammonia and subsequent formation of amino-tris(methylenephosphonic acid esters)<sup>89</sup> is shown in equation (23).



Poly(amino) compounds and their condensation products with aldehydes or ketones and dialkyl phosphites react in a similar manner to mono-amino compounds. When subsequent molar ratios of reactants are present, the reaction proceeds with substitution at all nitrogen atoms. For example, with ethylenediamine, formaldehyde and diethylphosphite, the bis-phosphonic ester **156** is formed.



### **7.6.3 Dequest phosphonates prepared by the Monsanto company<sup>85</sup>**

Since 1960, the Monsanto company has been the leading player in the synthesis and production of phosphonates as scale inhibitors. The phosphonates produced have been marketed under Monsanto's registered trademark of Dequest. The structure and chemical and trade names of these phosphonates are outlined in section 7.6.3.1.

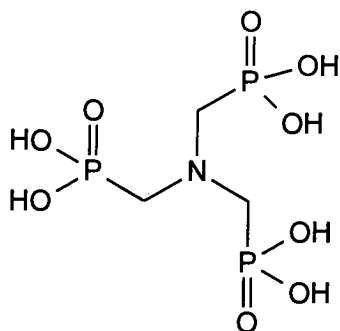
The Dequest phosphonates have been used as scale-inhibitors not only in the field of oil recovery but also in a wide variety of markets including cooling-water treatment, industrial cleaning and detergents.

In the field of oil recovery, Dequest phosphonates offer a combination of properties, including threshold scale-inhibition on a range of scale-forming minerals (section 7.6.3.2), thermal and hydrolytic stability and a compatibility with most other common oil-field treatment chemicals, *e.g.* corrosion inhibitors, demulsifiers, surfactants. In addition, their presence in water can be detected down to ppm levels either by thorium chelometric titration, or by colorimetric measurement of phosphorus after persulfate digestion. Due to their properties these phosphonates are the most extensively used scale-inhibitors in the oil industry.

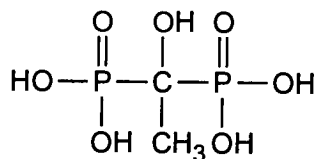
#### **7.6.3.1 Structure and chemical/trade names of Dequest phosphonates**

All the phosphonates shown below, with the exception of Dequest 2010, have been synthesised by the condensation of phosphorous acid with

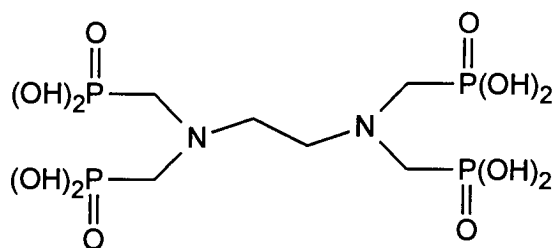
formaldehyde and the relevant amine<sup>94</sup> (section 7.6.1.7). Dequest 2010 was synthesised by the reaction of acylating agents with phosphorous acid<sup>109</sup> (section 7.6.1.8)



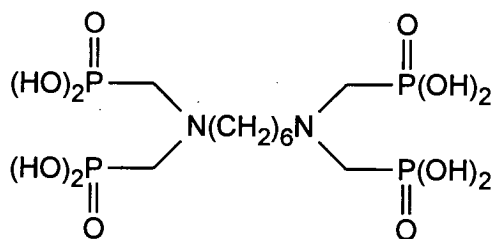
Dequest 2000  
[Amino-tris(methylenephosphonic acid)]



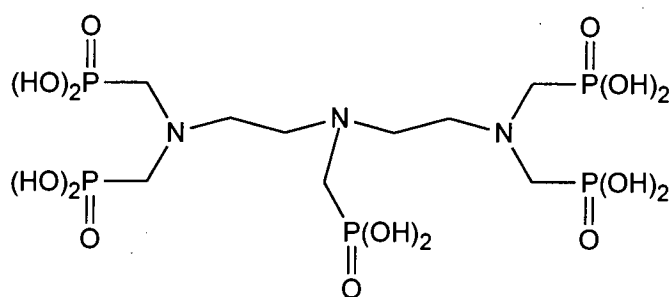
Dequest 2010  
[1-Hydroxyethane-1,1-bis-phosphonic acid]



Dequest 2041  
[Ethylenediaminetetra(methylenebisphosphonic acid)]



Dequest 2051  
[Hexamethylenediaminetetra(methylenephosphonic acid)]



Dequest 2060S  
[Diethylenetriaminepenta(methylenephosphonic acid)]

### 7.6.3.2 Performance evaluation of Dequest phosphonates

A great number of experimental results have been obtained by Monsanto regarding the scale inhibition abilities of Dequest phosphonates relative to  $\text{CaCO}_3$ ,  $\text{CaSO}_4$  and  $\text{BaSO}_4$  under various conditions using the static bottle technique (section 7.5.1). Table 6 shows results provided by Monsanto for scale-inhibitors in oil-field production<sup>85</sup>.

For determining which scale inhibitor to use, if more than one is possible, then the inhibitors are judged on a cost/performance basis. On the basis of these results, Monsanto suggested that for calcium carbonate scale, Dequest 2010 should be employed. Dequest 2051 and 2041 are suggested for calcium sulphate scale. On the other hand, Dequest 2010, 2041 and 2061 are most suitable for barium sulphate scale.

**Table 6 : Scale inhibition performance of Dequest phosphonates**

	Test conditions	1	2	3	4	5	6
	Scale type	CaCO <sub>3</sub>	CaCO <sub>3</sub>	CaSO <sub>4</sub>	CaSO <sub>4</sub>	BaSO <sub>4</sub>	BaSO <sub>4</sub>
	NaCl molarity	0	1.95	0	1.95	0	1.95
	Scale concentration	1250ppm	1500ppm	4200ppm	11200ppm	39ppm	611ppm
	Temperature	94°C	94°C	93°C	93°C	95°C	95°C
	Time	5 hours	5 hours	5 hours	5 hours	5 hours	5 hours
	Supersaturation *	3.8	3.8	3.6	3.6	10	10
Inhibitor series	ppm inhibitor	% scale inhibition	% scale inhibition	% scale inhibition	% scale inhibition	% scale inhibition	% scale inhibition
Dequest 2000	2	18	87	11	16	82	0
	8	38	100	100	66	78	0
	20	58	100	100	100	100	0
Dequest 2010	2	18	97	0	16	71	0
	8	38	97	66	25	81	45
	20	31	90	100	33	100	54
Dequest 2041	2	6	100	11	16	100	22
	8	28	100	100	100	89	74
	20	66	90	100	100	100	80
Dequest 2050	2	30	100	11	16	82	0
	8	49	100	100	100	100	27
	20	61	90	100	100	100	59
Dequest 2060	2	15	0	0	33	99	26
	8	36	100	100	100	94	74
	20	75	84	100	100	100	80

\* Ratio of actual concentration of the scaling compound relative to its concentration at thermodynamic equilibrium.

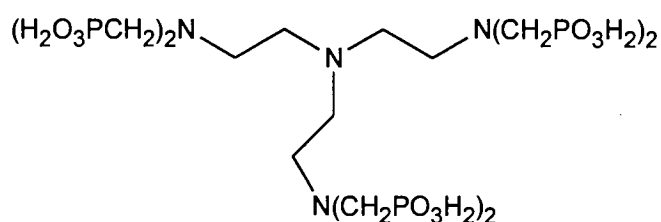
#### 7.6.4 Scale inhibitors in the patented literature

The following is an illustrative list of phosphonates, which in addition to the Dequest phosphonates, have been reported as having scale inhibition properties. The list is only a very small percentage of potential scale inhibitors, and consequently is by no means exhaustive. The

examples are only intended to give the reader a flavour of the types of scale inhibitors available and their synthesis.

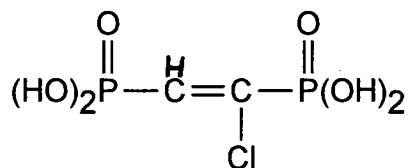
### 1. Triethylenetetraminehexa(methylenephosphonic acid)<sup>115</sup>

**Synthesis :** Condensation of phosphorous acid, triamine and formaldehyde.



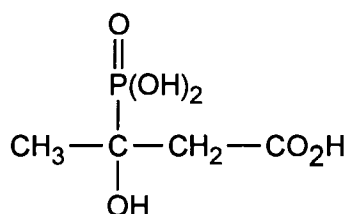
### 2. Chlorovinyl-1,2-bis(phosphonic acid)<sup>116</sup>

**Synthesis :** Arbuzov reaction of triethyl phosphite with 1,2-dichloroethyne yields ethyne-1,2-bis(phosphonic acid diethyl ester) which upon hydrolysis with hydrochloric acid yields the target compound.



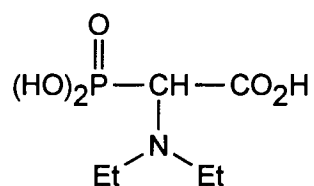
### 3. 3-Hydroxy-3-phosphonobutanoic acid<sup>92</sup>

**Synthesis :** (a) Reaction of a dialkyl phosphite with ethyl acetoacetate followed by hydrolysis, or (b) phosphorous trichloride with ethyl acetoacetate, and subsequent conversion into the phosphonic acid by addition of acetic acid.



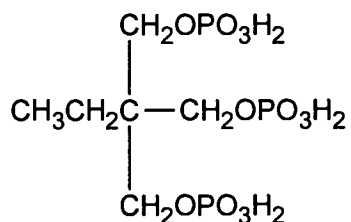
### 4. 2-Diethylamino-2-phosphonoacetic acid<sup>117</sup>

**Synthesis :** Mannich-type reaction of diethylamine hydrochloride, phosphorus acid and glyoxylic acid



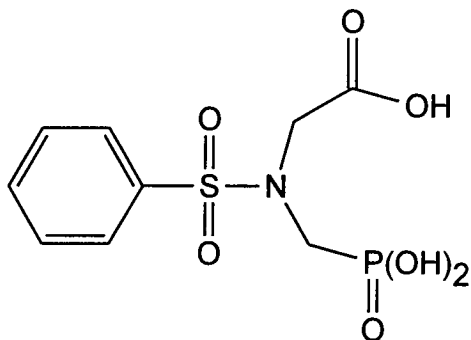
### 5. Trimethylol propane triphosphate<sup>118</sup>

**Synthesis :** Reaction of trimethylol propane with polyphosphoric acid



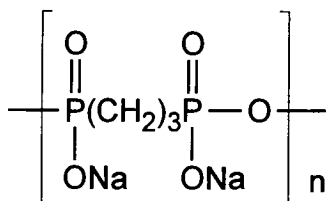
**6 . *N*-phenylsulfonamido-*N*-phosphonomethylglycine<sup>119</sup>**

**Synthesis :** By reaction of *N*-phosphonomethylglycine with phenylsulfonyl chloride.



**7. Polymeric propylenephosphonate<sup>120</sup>**

**Synthesis :** By heating disodium propane-1,3-diphosphonate at 290-335°C for 1-3 hours under nitrogen.

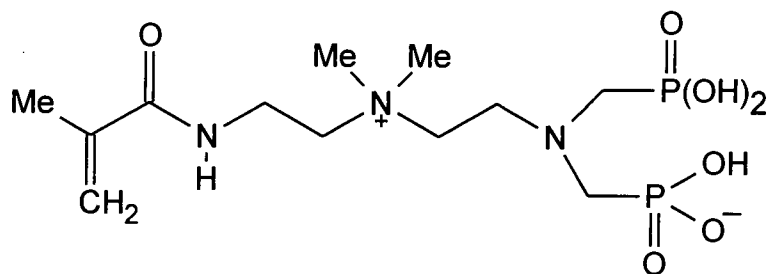


**8 a)**  $\alpha$ -Aminomethylphosphonate betaines<sup>121</sup>

**Synthesis :** Dimethylaminopropylmethacrylamide added slowly to 2-chloro ethylaminomethylenediphosphonic acid, followed by treatment with NaOH/H<sub>2</sub>O.

**b)** Polymers and co-polymers of  $\alpha$ -aminomethylenephosphonate betaines<sup>122</sup>.

**Synthesis :** Conventional free-radical polymerisation using a peroxide or an azo compound initiator



# **Chapter Eight**

## **Results and Discussion**

# Chapter Eight

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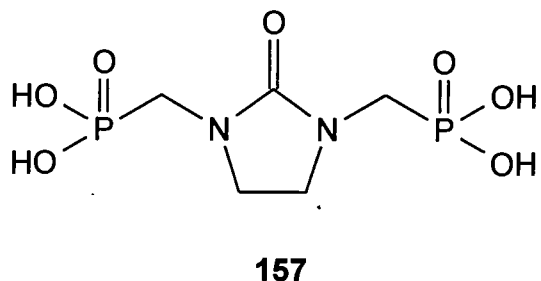
## 8.1 Introduction

The project to synthesis novel phosphorus-containing scale inhibitors for use in oil-field operations was partially funded by British Petroleum, who was interested in these compounds specifically for their oil-fields in the North Sea, which are renowned for their problems with barium and strontium scales. B.P. found that the scale inhibitors available from Monsanto (section 7.6.3), which were the most widely used in the North Sea oil-fields, worked well for most water systems, but their efficiency fell below the desired levels when the pH of these systems dropped to around pH 4. The aim of this project therefore, was to synthesis novel phosphonate scale inhibitors, specifically those which can perform well on barium and strontium scales at low pH values. These new compounds would then be evaluated for their scale inhibition abilities at the company's Sunbury Research Centre.

During this project a free reign was given on the type of phosphonates to be synthesised, the only criteria being that they had in fact to be organic phosphonates. The reason for this latitude was that there was no evidence as to why one particular inhibitor worked better than others at a low pH. For instance, it perhaps would be thought that an inhibitor with say 3 or 4 phosphonic acid groupings would perform better than an inhibitor with only 2 or 3, but this is not always the case. As a result, B.P. were interested in screening any phosphonate inhibitor that could be synthesised with the desirable *N-C-P* linkage found in other inhibitors<sup>85</sup>.

## 8.2 Phosphonates derived from 2-imidazolidinone

Based on the foregoing considerations, the first compound whose synthesis was attempted was 1,3-bis(methylenephosphonic acid)-2-imidazolidinone **157**. This choice seemed an appropriate compound to use

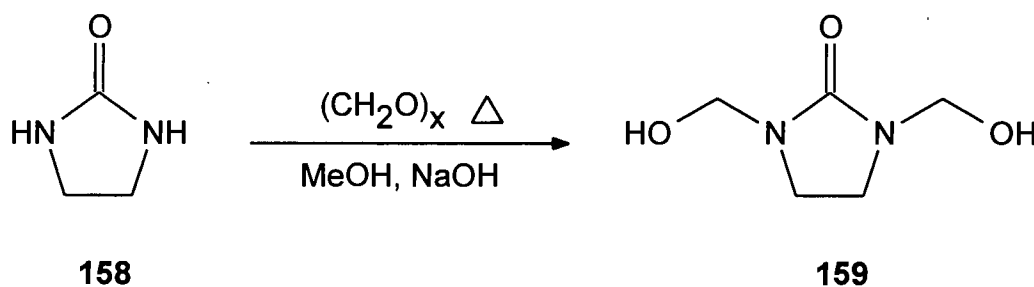


as a starting point since it contained, (i) the desired phosphonic acid groupings, (ii) N-C-P linkages as found in other inhibitors<sup>85</sup> and (iii) two nitrogens bridged by two methylene groups also found in other inhibitors<sup>85</sup>.

The most common route used so far to synthesise methylenephosphonic acids directly bonded to nitrogen is *via* a method by Moedritzer<sup>94</sup> which involved reaction of formaldehyde and phosphorous acid with the nitrogen-bearing component. Unfortunately, this reaction only occurs with primary and secondary amines, whereas the synthesis of **157** would be starting from 2-imidazolidinone **158**, which is of course an amide.

An alternative route to **157** involves the synthesis of the bis-hydroxymethyl compound from 2-imidazolidinone, followed by reaction with  $\text{PCl}_3$  to yield a bis-phosphoryl dichloride which upon hydrolysis would lead to **157**. This route is analogous to that described in section 7.6.1.1 (Scheme 74) to form aminomethylene phosphonic acids.

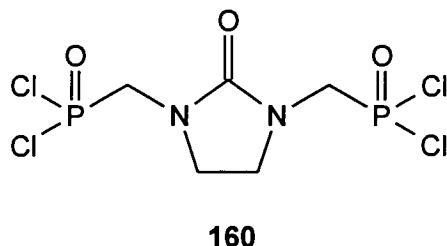
The synthesis of the key diol, 1,3-bis(hydroxymethyl)-2-imidazolidinone **159**, was successfully achieved by the reaction of **158** with paraformaldehyde in the presence of sodium hydroxide<sup>123</sup> (Scheme 85).



Scheme 85. Synthesis of 1,3-bis(hydroxymethyl)-2-imidazolidinone **159**.

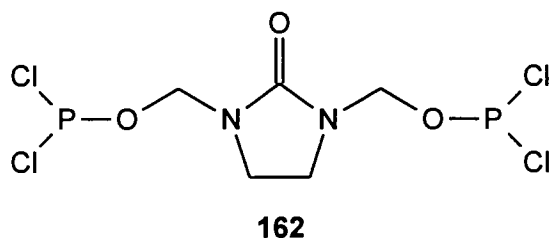
The diol was then treated with two equivalents of phosphorus trichloride in dry DME and the reaction monitored by  $^{31}\text{P}$  NMR spectroscopy. After heating the reaction under reflux for two hours the reaction mixture was shown to consist of a single phosphorus-containing product at 40.5 ppm which was consistent with the formation of phosphoryl dichloride

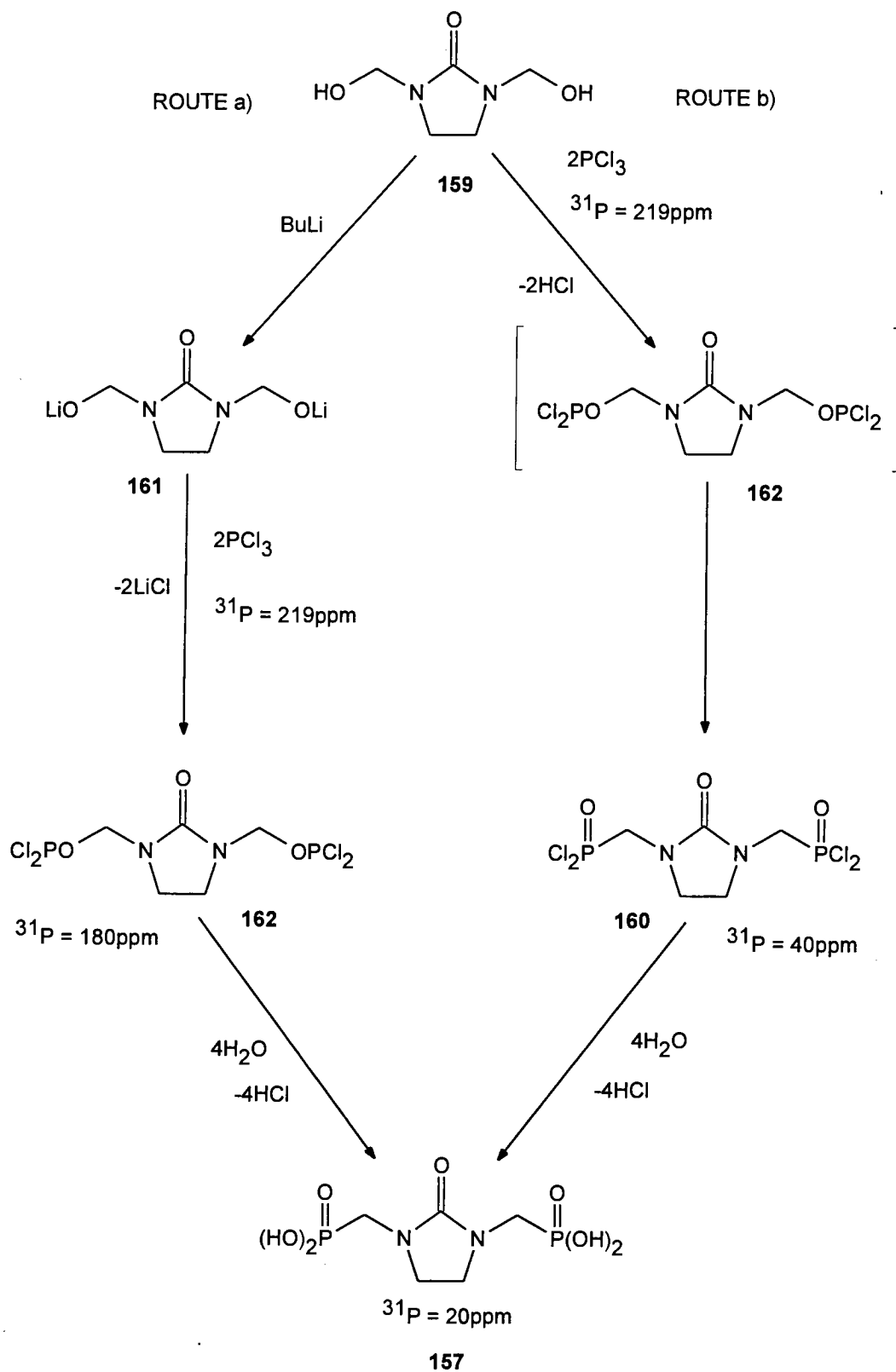
**160.** However, subsequent hydrolysis of **160** by the addition of water resulted in two



major products being formed, resonating at  $\delta$  19 and 3 ppm. The former was assigned to the desired product **157**, while the latter was assigned to phosphorous acid, an assignment proven by peak enhancement with an authentic sample.

The synthesis of **157** was also attempted by reacting the lithium salt of diol **161** with two equivalents of phosphorus trichloride. On this occasion, after heating for two hours under reflux, a signal at 180 ppm in the  $^{31}\text{P}$  NMR spectrum appeared and was attributed to the dichlorophosphite **162**. Subsequent hydrolysis of **162** by addition of water produced two major products, which were again the desired acid **157** and phosphorous acid.

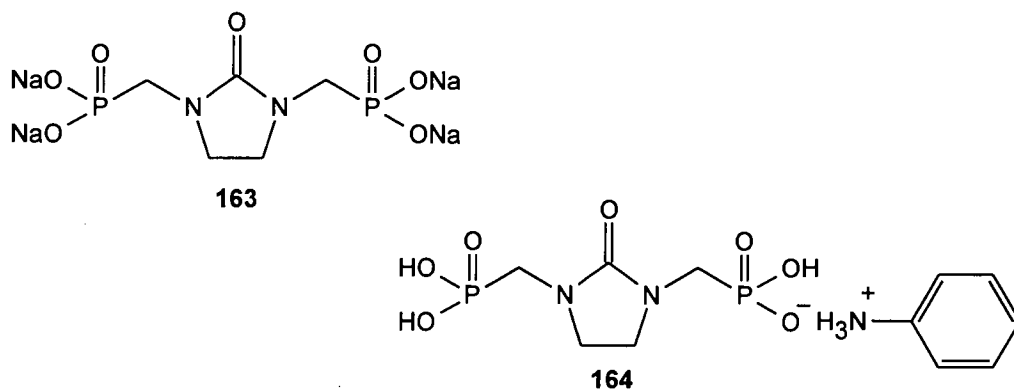




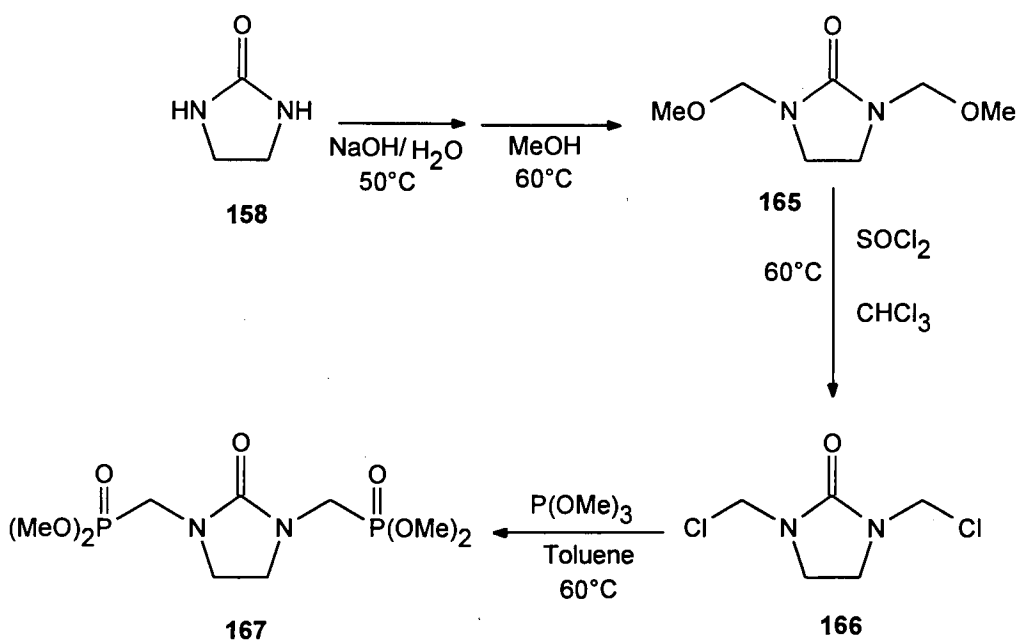
Scheme 86. Reaction pathways to compound 157

The reaction pathways involved in these reactions are shown in Scheme 86. The pertinent difference between the two reaction pathways is that in one instance dichlorophosphite **162** is stable and can be observed by  $^{31}\text{P}$  NMR spectroscopy, whereas in the other, it immediately undergoes rearrangement to the phosphoryl dichloride **160**. It is believed that this rearrangement is acid-catalysed since hydrochloric acid is present when **162** does rearrange to **160** (route b), but is absent when **162** is formed in route a, and consequently is stable. Furthermore, when **162** is hydrolysed, hydrochloric acid is liberated, which causes rearrangement to the acid **157**.

The desired compound, 1,3-bis(methylenephosphonic acid)-2-imidazolidinone **157**, was eventually synthesised and isolated as a single product by changing the reaction conditions. This was achieved by cooling neat phosphorous trichloride to  $0^{\circ}\text{C}$  and carefully adding the diol **159** portionwise. Subsequent heating of the mixture under reflux for ten minutes caused the formation of the phosphoryl dichloride **160**, which was then cooled to  $0^{\circ}\text{C}$ , and treated with ice water to yield the desired acid **157**. The latter was also isolated as the sodium salt **163** by treatment with sodium hydroxide, and as the anilinium salt **164** by addition of aniline to an ethanolic solution of the acid.

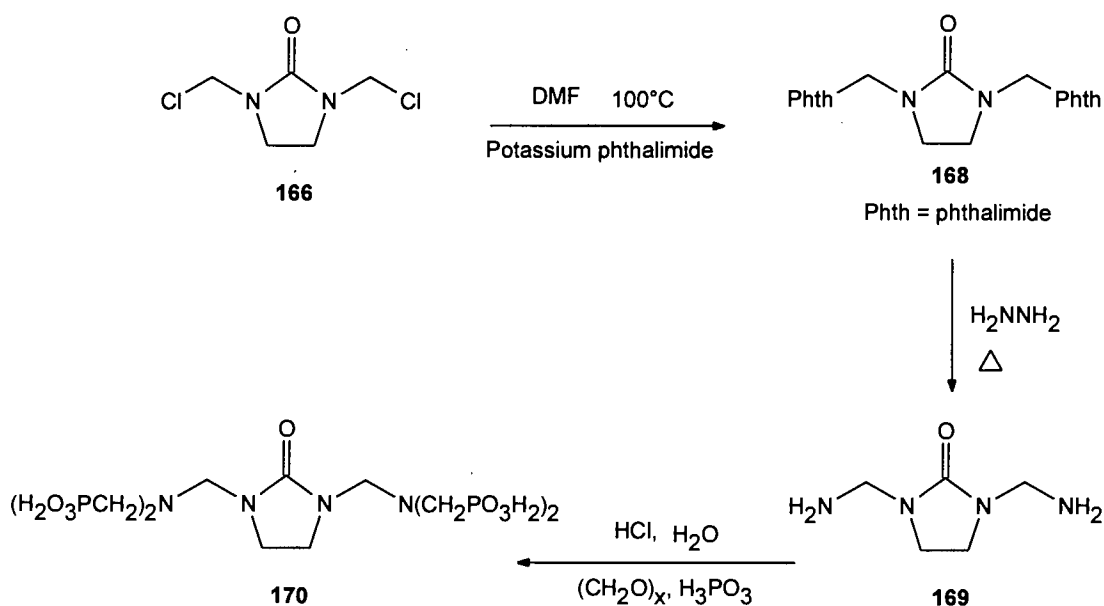


The tetra-methyl ester of bis-phosphonic acid **157** was also successfully synthesised by the means of an Arbuzov reaction<sup>112</sup> as outlined in Scheme 87. This approach first required the synthesis of the appropriate alkyl halide, 1,3-bis(chloromethyl)-2-imidazolidinone<sup>124</sup> **166** by a two-step procedure from 2-imidazolidinone **157**.



Scheme 87. Synthesis of the methyl ester **167**.

In an attempt to extend the phosphorous-containing side-chains in **167**, the alkyl halide **166** was also reacted with two equivalents of potassium phthalimide in the manner of a Gabriel synthesis<sup>125</sup> to produce 1,3-bis(phthalimidomethyl)-2-imidazolidinone **168** (Scheme 88). It was



Scheme 88. Proposed synthesis of 1,3-bis (aminomethyl)-2-imidazolidinone-tetra(methylenephosphonic acid) **170**.

envisaged that treatment of **168** with hydrazine would lead to the diamine **169**, subsequent treatment of which with phosphorous acid and formaldehyde, would give access to the desired compound, 1,3-bis(aminomethyl)-2-imidazolidinone-tetra(methylenephosphonic acid) **170**. Unfortunately, the reaction step involving treatment of **168** with

hydrazine failed. The residue from the reaction with hydrazine was analysed by both CI and FAB mass spectroscopy, but both techniques showed only breakdown products of the phthalimido derivative **168** to be present. TLC of the residue indicated a plethora of products to have been formed in the reaction, and separation by flash column chromatography afforded only four products, two of which were obtained in sufficient quantities to be analysed by  $^1\text{H}$  NMR spectroscopy. The conclusion drawn from the  $^1\text{H}$  NMR and mass spectroscopy data was that the desired bis-diamine **169** was probably too unstable to exist under the conditions used, and that the reaction produced only breakdown products of **168**, some of which were tentatively attributed to those compounds shown in Figure 19.

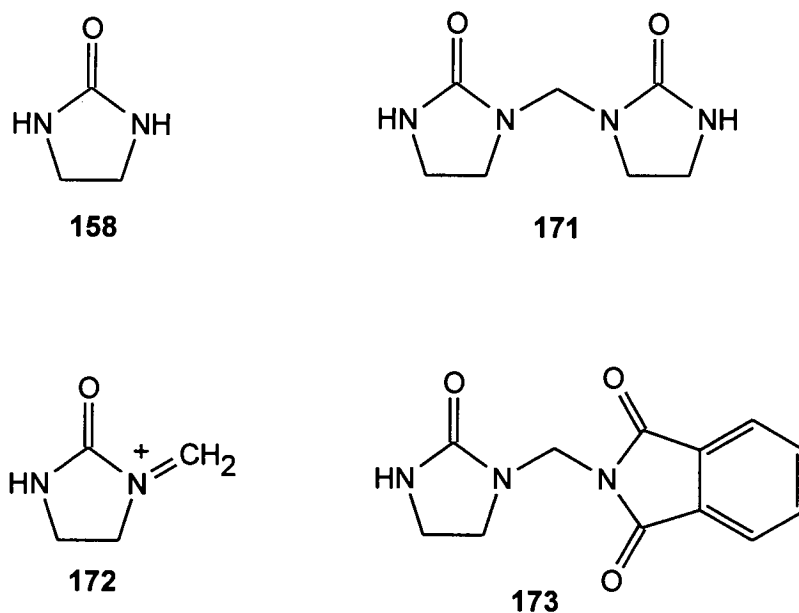
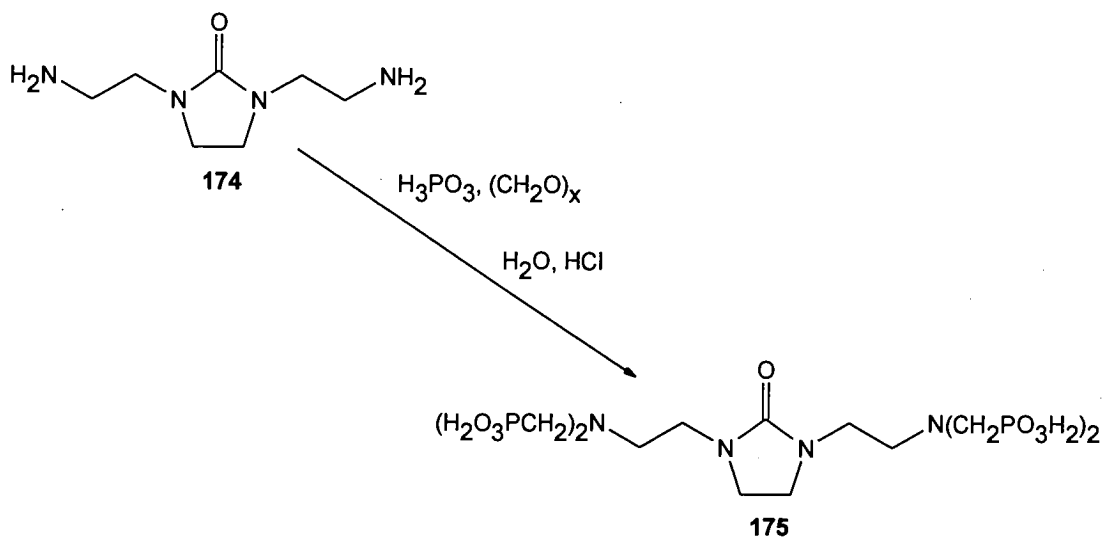


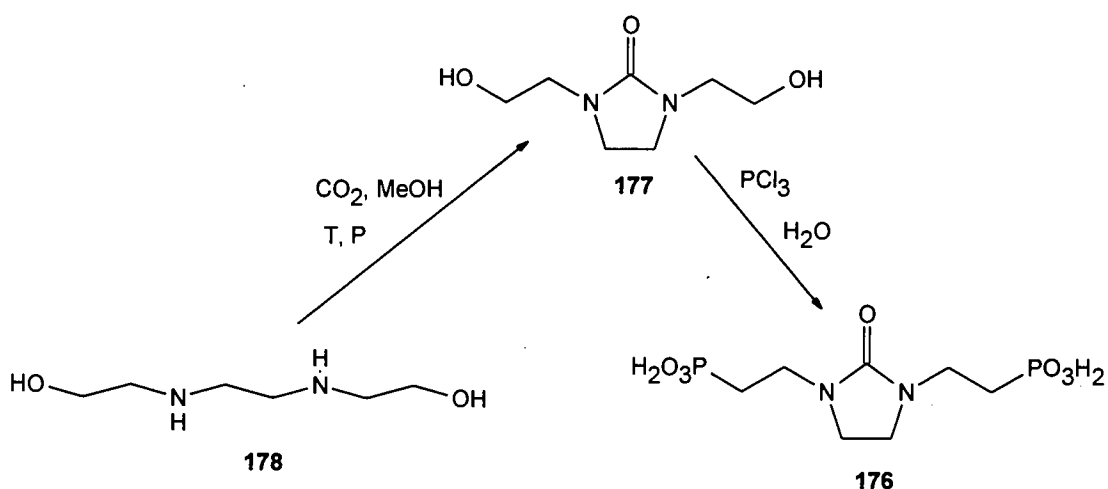
Figure 19. Products from the treatment of **168** with hydrazine.

The next compounds to be synthesised from 2-imidazolidinone were to be similar to those already discussed apart from having an ethylene group rather than a methylene extending directly from both nitrogens. The first to be synthesised was 1,3-bis(aminoethyl)-2-imidazolidinone-tetra(methylenephosphonic acid) **175**. This was synthesised by the method of Moedritzer<sup>94</sup> which involved condensing the diamine **174** with formalin and phosphorous acid. This is the method which was used to synthesise most of the inhibitors available from Monsanto (section 7.6.3). The starting diamine 1,3-bis(aminoethyl)-2-imidazolidinone **174** was provided by B.P. chemicals in Hull. The synthesis of **175** is shown in Scheme 89.



Scheme 89. Synthesis of 1,3-bis(aminoethyl)-2-imidazolidinone-tetra(methylenephosphonic acid) **175**.

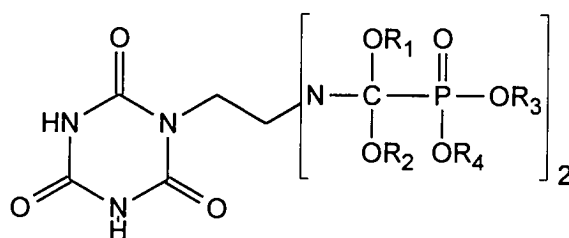
The synthesis of compound **176**, 1,3-bis(ethylenephosphonic acid)-2-imidazolidinone, was also attempted, but the final stage of its proposed synthesis is as yet uncompleted. As with compound **157**, it is believed that reaction of the diol **177** with phosphorus trichloride followed by hydrolysis would lead to the acid **176** (Scheme 90). The diol precursor to the desired acid was synthesised from *N,N*-bis(2-hydroxyethyl)ethylenediamine **178** by reaction in a Rothbomb pressure vessel with carbon dioxide (dry ice) at a temperature of 185°C at an initial pressure of 67 bar. The product was formed in 25% yield (unoptimised) along with unreacted starting material which could be recycled.



Scheme 90. Proposed synthesis of 1,3-bis(ethylenephosphonic acid)-2-imidazolidinone **176**.

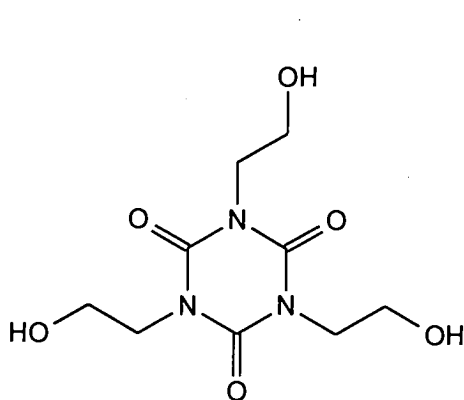
### 8.3 Phosphonates derived from cyanuric acid

As part of the programme of work, several attempts were made to synthesise inhibitors derived from cyanuric acid **179** due to a patent filed by the Monsanto Chemical Company<sup>126</sup> which claimed scale inhibition properties for **180** where  $R_3$  and  $R_4$  are H or metal ions, and  $R_1$  and  $R_2$

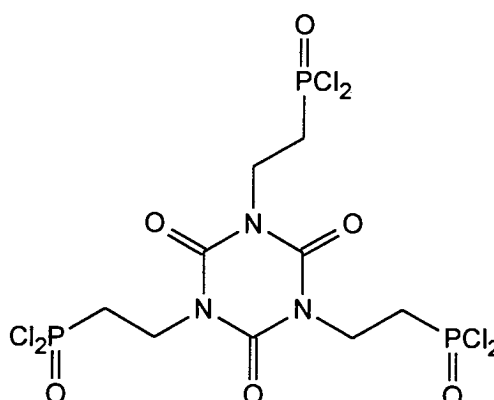


**180**

are H or organic radicals. It was envisaged that phosphorylation of each acidic *N-H* site of the cyanuric acid structure by alkyl phosphonic acid groupings would perhaps lead to an enhancement of the scale inhibition properties of **180**.

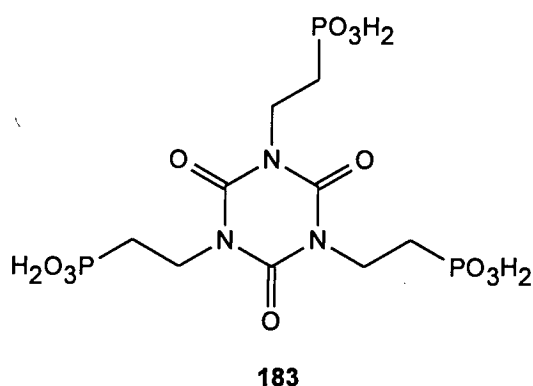


**181**



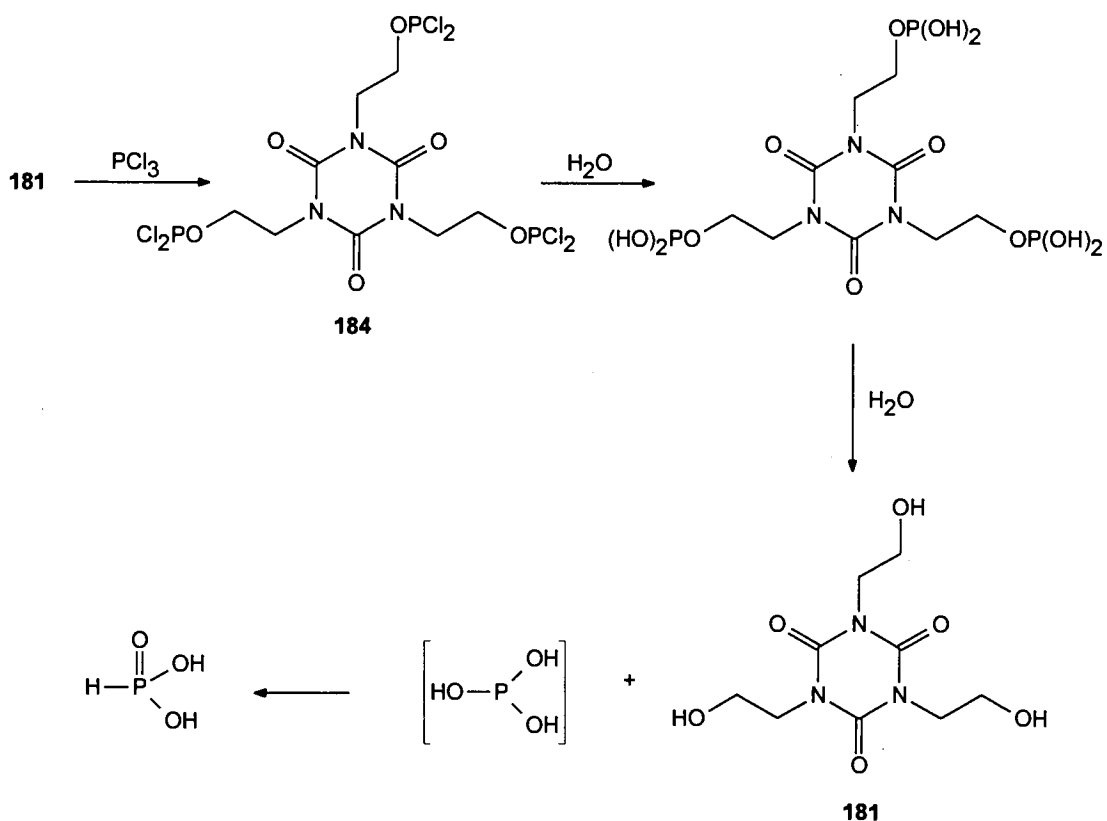
**182**

The initial work involving the cyanuric acid structure focussed on attempts to phosphorylate the commercially available triol, tris(hydroxyethyl)cyanuric acid **181**. Based on the work described in the previous section (8.2) concerning the diol derived from 2-imidazolidinone **159**, it was believed that treatment of **181** with phosphorous trichloride would produce the tris-phosphoryl dichloride **182**, whose subsequent hydrolysis would yield the novel acid **183**. However, when this process



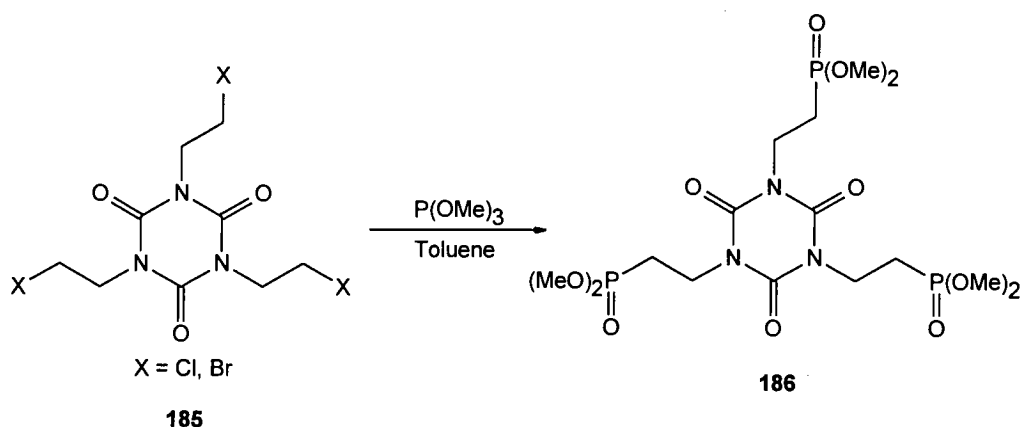
was attempted the only phosphorus signal present in the  $^{31}\text{P}$  NMR spectrum of the reaction mixture was at 4.9 ppm, which was proven to be phosphorous acid ( $\text{H}_3\text{PO}_3$ ) by peak enhancement experiments. Moreover, after removal of solvents the reaction residue also consisted of the starting triol **181**. The recovery of the triol was unexpected since it would certainly have reacted during the initial heating with neat phosphorus trichloride under reflux. In order to prove this point, the reaction was carried out in DME as solvent with stoichiometric amounts of phosphorus

trichloride and the process followed by  $^{31}\text{P}$  NMR spectroscopy. The outcome was unexpected; in fact, the phosphoryl dichloride **182** had not been formed but, instead the dichlorophosphite **184** was present as shown by the appearance of a signal at 178 ppm. Consequently, when water was added only phosphorous acid was formed. These observations can be explained by the reaction pathway shown in Scheme 91, whereby the synthesis of the acid **183** failed due to the lack of the desired rearrangement of **184** to the phosphoryl dichloride **182** (cf. Scheme 86; **162**  $\rightarrow$  **160**).



Scheme 91. Proposed pathway of the reaction of the triol **181** with phosphorus trichloride followed by hydrolysis.

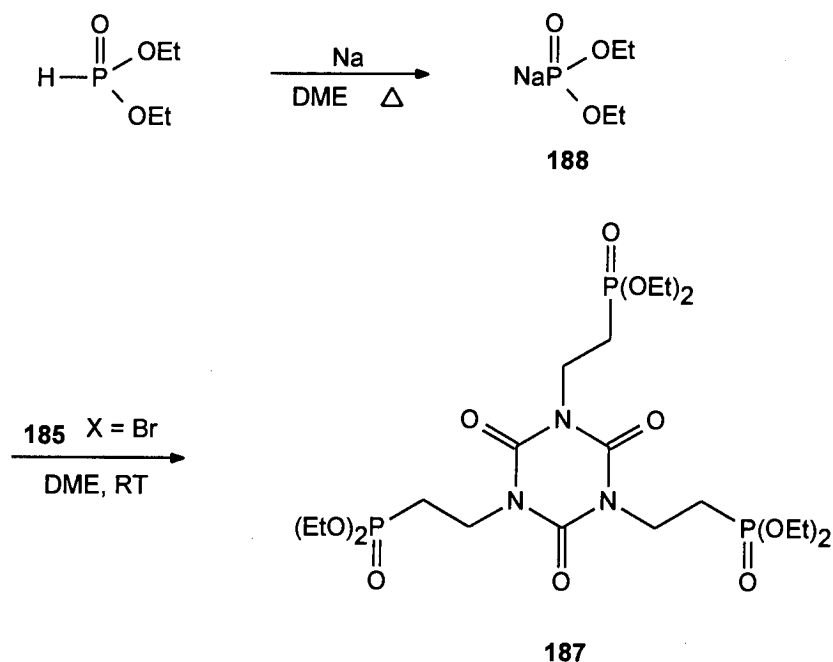
Other attempts to synthesise the acid **183** were also carried out, including conversion of the triol **181** into the alkyl halide **185** followed by an Arbuzov reaction using trimethylphosphite (Scheme 92). It was envisaged



Scheme 92. Proposed Arbuzov synthesis of the ester **186**.

that the methyl groups of the ester **186**, whose potential as a scale inhibitor would also be investigated, could be cleaved by methods described in section 7.6.1 to produce the desired acid **183**. However, despite varying reaction temperatures (80-110°C), as well as reaction times (7 hrs-5 days), by using excess trimethylphosphite and by using the more reactive alkyl bromide, all attempts to synthesise **186** failed. Each attempt after work-up and column chromatography gave around 80% recovery of the starting halide. We are unable at present to give an

explanation for the failure of this reaction, but it is of interest to note that the synthesis of the corresponding ethyl ester **187** was successfully accomplished by the Michaelis-Becker reaction (section 7.6.2.2) as shown in Scheme 93. The route involved formation of the sodium salt **188** of

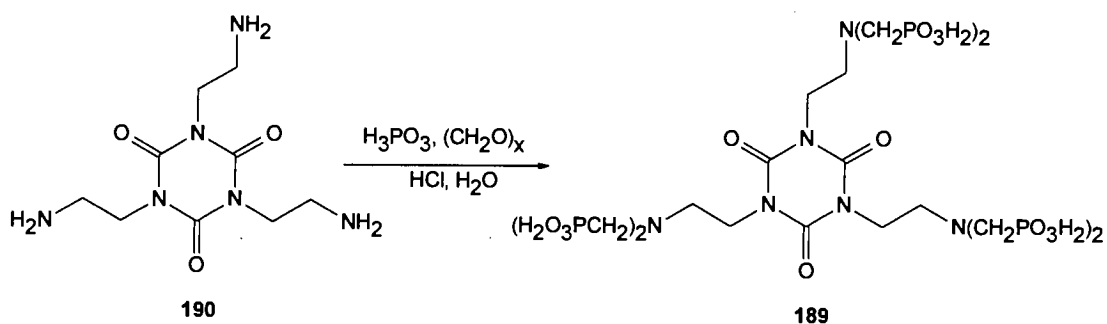


Scheme 93. Synthesis of the ethyl ester **187**.

diethyl phosphite by boiling the latter with sodium metal under reflux in dry DME until all the metal had reacted. The alkyl bromide **185** was then added, and the solution stirred at room temperature for 48 hours after which time  $^{31}\text{P}$  NMR spectroscopy showed the presence of the *tris-*

ester **187** as a single peak at 26.3 ppm. The product was isolated and purified by column chromatography (yield 50%), but hitherto, attempts to cleave the ethyl groups to form the free acid have not been carried out.

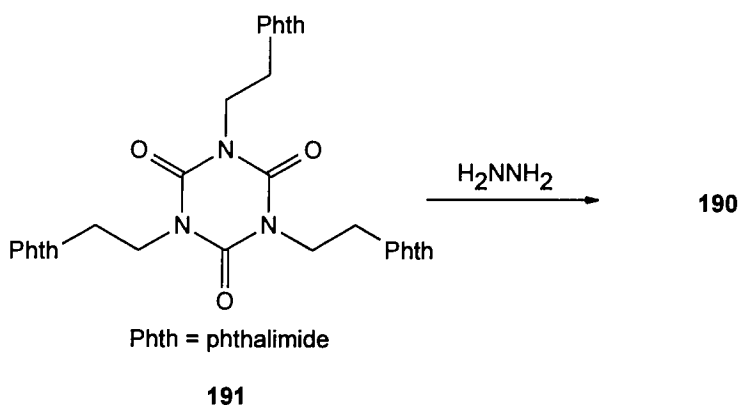
The synthesis of acid **189** was also planned to be attempted by a simple one-pot reaction of the tris-amine **190** with formalin and phosphorus acid (Scheme 94). Unfortunately, the synthesis of the acid



Scheme 94. Proposed synthesis of the acid **189**.

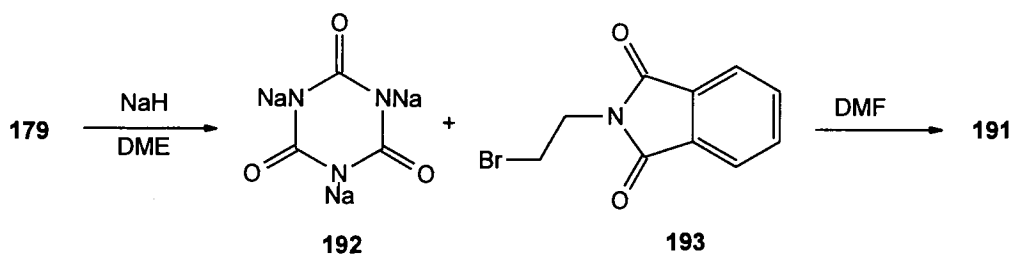
was not achieved due to the failure in preparing the tris-amine **190**. Several different methods were attempted, the first being a Gabriel synthesis whereby the alkyl halide **185** was reacted with potassium phthalimide to give **191**, followed by treatment with hydrazine (Scheme 95). However, the product from the first step was shown by a combination of mass spectroscopy and NMR spectroscopy to consist of a

mixture of mono-, bis- and tris-(phthalimidoethyl)cyanuric acid, which proved difficult to separate by column chromatography.



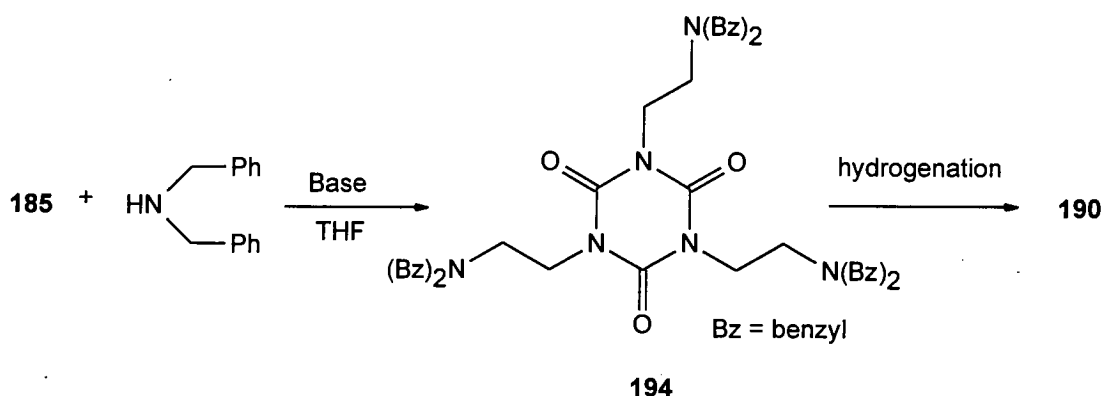
Scheme 95. Proposed synthesis of the tris-amine **190**.

As an alternative route to phthalimido derivative **191**, the sodium salt of cyanuric acid **192** was reacted with bromoethyl phthalimide **193** as shown in Scheme 96. Once again, however, the method failed with almost complete recovery of the starting phthalimide **193** after work-up.



Scheme 96. Proposed synthesis of the phthalimido compound **191**.

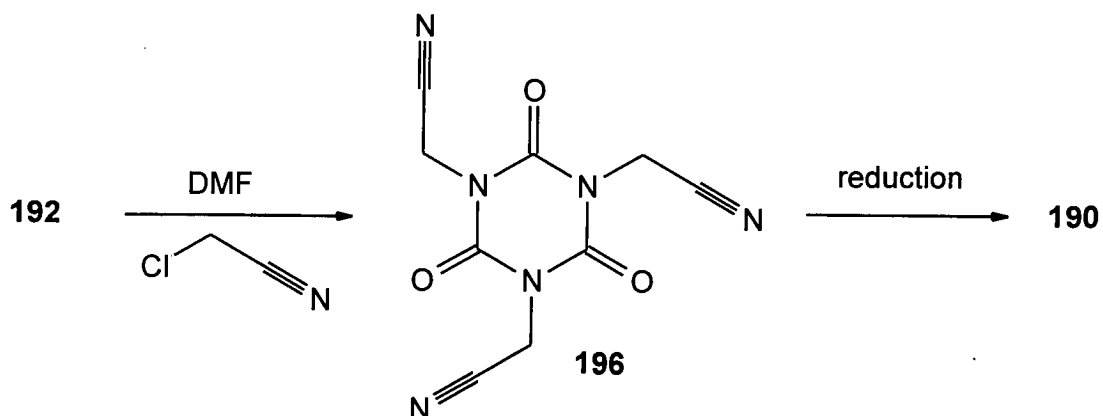
In a further approach to the tris-amine **190**, halide **185** was reacted with dibenzylamine in an attempt to prepare *tris*-(*N,N*-dibenzylaminoethyl)cyanuric acid **194** (Scheme 97). It was assumed that straightforward hydrogenation would cleave the benzyl groups to yield the desired compound. Two different bases were used, the first being



Scheme 97. Proposed synthesis of the triamine **190**.

triethylamine, which after three hours heating under reflux led to no reaction. By comparison, with the more powerful butyllithium, after one hour at room temperature, the reaction showed a plethora of products by TLC. Nonetheless, it is believed that this reaction may be made to be successful if more time was spent on varying the reaction conditions.

The third attempt to synthesis the *tris*-amine **190** focussed on the synthesis of the *tris*-nitrilo compound **196**, reduction of which should result in the formation of **190** as shown in Scheme 98. The synthesis of **196** was achieved successfully by a literature method<sup>127</sup> involving the



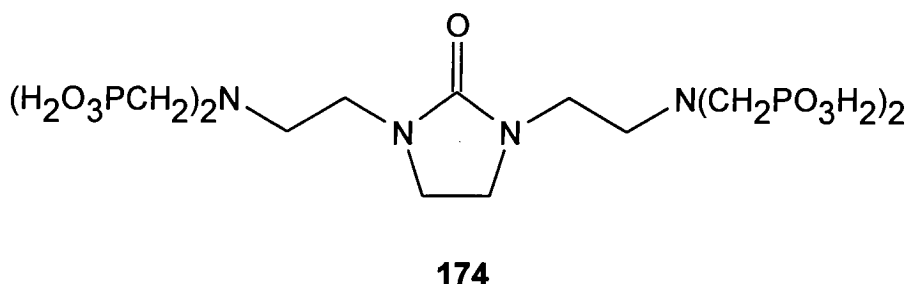
Scheme 98. Proposed synthesis of the triamine **190**.

reaction of the tri-sodium salt **192** with chloroacetonitrile. However, at this stage reduction of **196** has not yet been carried out due to termination of this aspect of the project. Hydride-based reducing agents would normally be a possibility, but in this case would almost certainly affect the imide carbonyls. Catalytic hydrogenation is another alternative, but hydrogenation of nitriles is complicated by the formation of secondary amines, although there are methods to combat this

drawback as well as the long reaction times and low yields. These difficulties leave the task of the hydrogenation of **196** to be explored with caution.

#### 8.4 Testing of the novel inhibitors

Although a few novel inhibitors were synthesised, hitherto only one has yet been tested for its inhibition properties. The compound concerned is 1,3-bis(aminoethyl)-2-imidazolidinone-tetra(methylenephosphonic acid) **174**, which was tested at Sunbury Research Centre using the “static



bottle test” as described in section 7.5.1. The results of these tests are given in Table 7, from which it is evident that compound **174** is an unsatisfactory inhibitor under the conditions of testing due to its inability to combat barium scale formation with increasing seawater breakthrough. However, such results are typical of many inhibitors tested under these conditions, including commercially available

inhibitors, and compound 174 may be suitable as an inhibitor for water systems with less harsh conditions, *i.e.* higher pH and lower barium ion concentrations.

**Table 7.** Scale inhibition performance of compound 174

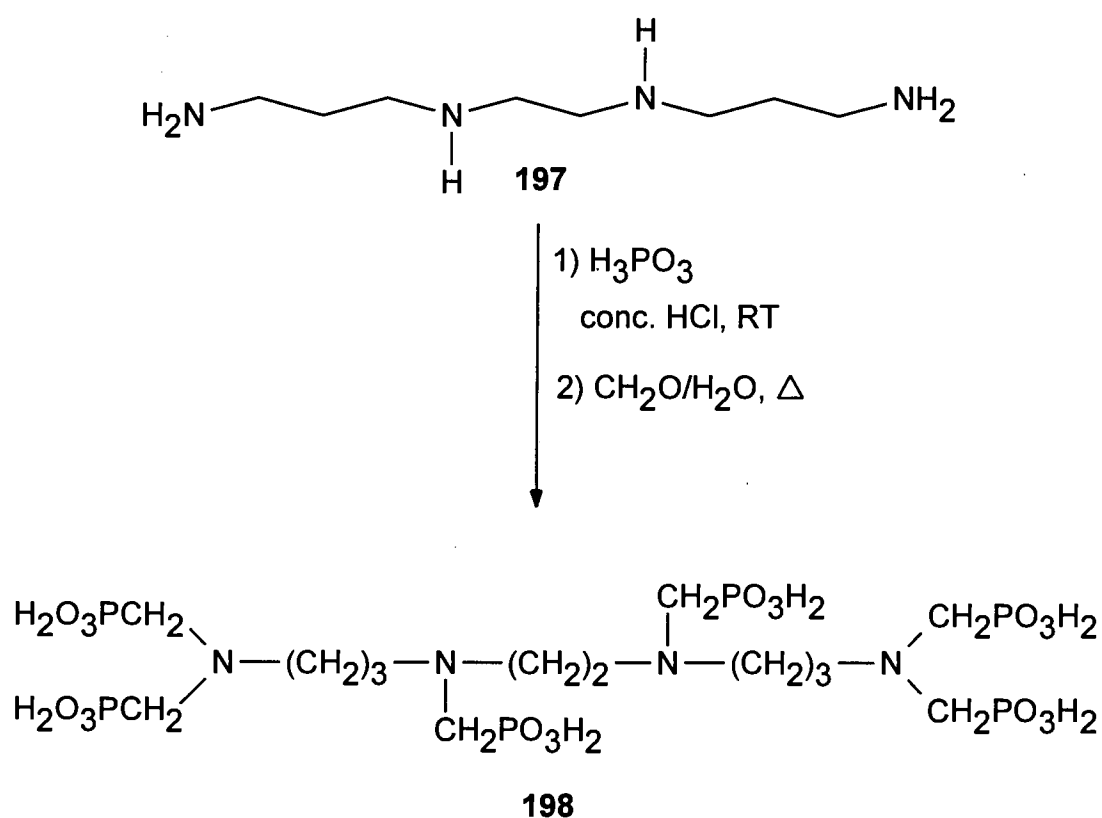
Scale type	Ca	Ca	Ba	Ba	Sr	Sr
SW/FW ratio	20/80	60/40	20/80	60/40	20/80	60/40
ppm inhibitor	% inhibition	% inhibition	% inhibition	% inhibition	% inhibition	% inhibition
100	94	4	40	3	68	59
200	69	0	91	6	93	72

## 8.5 Conclusion

From the discussion, it is evident that much of the work carried out appears incomplete, *i.e.* some syntheses have only progressed part-way whilst only one of the compounds synthesised was actually tested for its inhibition properties. This situation arose due to the discovery of a scale inhibitor for severe water *i.e.* high barium content and low pH, by B.P. Research in house, a year or so into the CASE award. Furthermore, at this stage many of the key aspects of the Research Centre at Sunbury were closed with the consequent loss of scientific personnel, including my

industrial supervisor. Consequently, this scale inhibitor project was shelved at its present stage, and permission was given by B.P. to turn attention to the generation of alkyl metaphosphates in solution, as described in Part I of this thesis.

The synthesis of the phosphonate **198** which eventually solved the problem of severe water conditions<sup>87,130</sup> is shown in Scheme 99. The



Scheme 99. Synthesis of phosphonate **198**

procedure follows a simple one-pot method by Moedritzer<sup>94</sup>, which involves drop-wise addition of the commercially available *N,N*-bis(3-aminopropyl)ethylenediamine 197 to phosphorus acid dissolved in conc. HCl under an N<sub>2</sub> atmosphere. When addition was complete, the reaction was heated under reflux and formaldehyde 37 wt% solution added slowly. The product was isolated by cooling the reaction mixture and then pouring it into ethanol to yield crude 198.

The results<sup>87,130</sup> of "static bottle" tests on phosphonate 198 established that, at high barium content and low pH, it out-performed all of the commercially available scale-inhibitors commonly used under such conditions. The results are shown in Table 8. As can be seen phosphonate 198 provides almost 100% inhibition of scale at a very low dosage.

**Table 8.** Scale inhibition performance of phosphonate 198

SCALE INHIBITOR	CONC mg/l	INHIBITOR EFFICIENCY					
		FW:SW 80:20			FW:SW 40:60		
		pH 4.5	5.2	6.0	4.5	5.2	6.0
(1)	30	62					
	50	95					
	75	98			30		
	100				80	80	16
	150				87		
	200				95	47	22

Figure 20 also shows the efficiency of **198** compared to commercially available scale-inhibitors S40 supplied by Ciba Geigy which has been widely used in the North Sea for controlling BaSO<sub>4</sub> scale. In the figure the plots of compound **198** are represented by A and those of S40 by B. The figure clearly shows compound **198** to have a greater efficiency over a wide range of concentrations and sea-water/formation water mixtures than the conventional scale inhibitor.

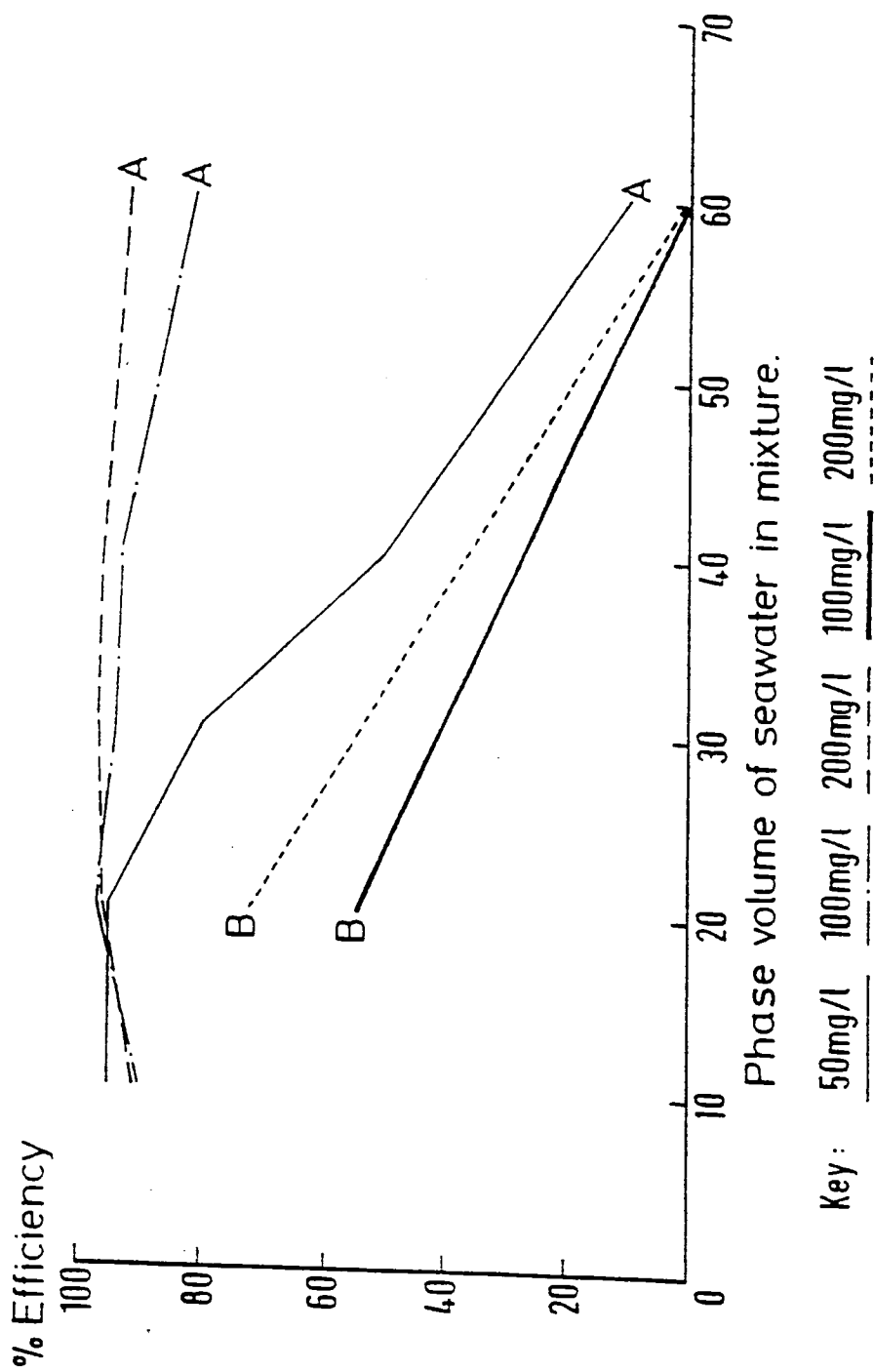


Figure 20. Scale inhibition efficiency of compound 198 compared to commercially available S40 supplied by Ciba Geigy

# **Chapter Nine**

## **EXPERIMENTAL**

# Chapter Nine

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## 9.1 Instrumentation and General Techniques

The instrumentation and general techniques used were identical to those described in 6.1..

## 9.2 Reactions deriving from 2-imidazolidinone

### 9.2.1 Attempted preparation of 1,3-bis(hydroxymethyl)-2-imidazolidinone (159).

To a solution of 2-imidazolidinone **158** (0.63g, 7.3 mmol) and paraformaldehyde (0.44g, 14.6 mmol, 2eqv) in DME (30ml) was added potassium carbonate (0.026g, catalytic amount) and the reaction heated under reflux for two hours. The resultant solution was then evaporated to dryness to yield a colourless solid. On analysis by  $^1\text{H}$  NMR spectroscopy the solid proved to be only starting 2-imidazolidinone and therefore no reaction had occurred.

### 9.2.2 Preparation of 1,3-bis(hydroxymethyl)-2-imidazolidinone (159)

From a literature method by Simkover<sup>123</sup>

To a solution of 2-imidazolidinone (4.15g, 0.048 mol) in methanol (30ml) was added a solution of paraformaldehyde (3.32g, 0.110 mol, 2eqv) and sodium hydroxide (0.088g, 2.2 mmol) in methanol (20ml). After heating under reflux for two hours the solution was allowed to cool and the solvent then removed in vacuo to produce a viscous, colourless oil which quickly crystallised on standing. This was recrystallised from ethanol to afford 1,3-

bis(hydroxymethyl)-2-imidazolidinone **159** as a colourless solid (5.28g, 83%); **Mp** = 101-103°C (lit.<sup>123</sup> = 101-103°C); **<sup>1</sup>H NMR** (60 MHz, d<sub>6</sub>-DMSO) δ 5.35 (2H, s, OH), 4.56 (4H, s, CH<sub>2</sub>), 3.36 (4H, s, CH<sub>2</sub>) ppm; **<sup>13</sup>C NMR** (50.3 MHz, d<sub>6</sub>-DMSO) δ 159.34 (C=O), 66.92 (CH<sub>2</sub>), 40.14 (CH<sub>2</sub>) ppm; **IR** (KBr disc)  $\nu_{\max}$  3359, 3239 (OH), 1674 (C=O) cm<sup>-1</sup>; **MS** (FAB) m/z 147 (M+1)<sup>+</sup>.

### 9.2.3 Attempted preparation of 1,3-bis(methylenephosphonic acid)-2-imidazolidinone (**157**)

a) Phosphorus trichloride (1.035g, 7.54 mmol) was slowly added to a stirred suspension of 1,3-bis(hydroxymethyl)-2-imidazolidinone **159** (0.55g, 3.77 mmol) in dry DME (15ml) at 0°C under an argon atmosphere. The reaction was stirred for 30 minutes at room temperature and then heated under reflux for two hours. After this time <sup>31</sup>P NMR spectroscopy showed the reaction to consist of a single phosphorous containing product at 40.5 ppm which was assigned to the phosphoryl dichloride **160**. Water (5ml) was then added and the reaction stirred for a further 30 minutes. <sup>31</sup>P NMR spectroscopy showed the reaction to consist of a signal at 18.98 ppm assigned to the desired acid **157** and a signal at 2.83 ppm assigned to, and proven to be phosphorous acid by peak enhancement experiments.

b) Butyllithium solution (hex., 1.6M, 2.9ml) was added slowly to a stirred suspension of the diol **159** (0.341g, 2.33 mmol) in dry DME (10ml) at 0°C under an argon atmosphere and stirred for 30 minutes.

Phosphorus trichloride (0.641g, 4.66 mmol) was then added and the reactants heated under reflux for two hours which produced a signal in the  $^{31}\text{P}$  NMR spectrum at 180 ppm, assigned to the dichlorophosphite **162**. As above (part a) addition of water (5ml) produced both the desired acid **157** and phosphorous acid

#### 9.2.4 Preparation of 1,3-bis(methylenephosphonic acid)-2-imidazolidinone (**157**)

Phosphorous trichloride (10ml) was cooled to 0°C and then carefully treated portionwise with 1,3-bis(hydroxymethyl)-2-imidazolidinone **159** (0.71g, 4.86 mmol). Once the addition was complete the reaction mixture was heated under reflux for 10 minutes, after which time excess phosphorous trichloride was removed under vacuum. The residue was cooled to 0°C and then carefully treated with ice water (10ml) and the reaction stirred for a further 10 minutes. Excess water and volatiles were then removed to yield crude 1,3-bis(methylenephosphonic acid)-2-imidazolidinone **157** as an orange coloured solid (0.96g, 72%);  $^1\text{H}$  NMR (200MHz,  $\text{d}^6\text{-DMSO}$ )  $\delta$  8.83 (4H, s, OH), 3.48 (4H, s,  $\text{CH}_2$ ), 3.40 (4H, d,  $J = 10.4$  Hz,  $\text{CH}_2$ ) ppm;  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{d}^6\text{-DMSO}$ )  $\delta$  166.4 (C=O), 52.5 ( $\text{CH}_2$ ), 39.3 ( $\text{CH}_2$ ) ppm;  $^{31}\text{P}$  NMR (36.23 MHz,  $\text{d}^6\text{-DMSO}$ )  $\delta$  18.91 (t,  $J = 10.4$  Hz) ppm; IR (thin film)  $\nu_{\text{max}}$  3500-2300 (P-OH), 1700 (C=O), 1260 (P-O)  $\text{cm}^{-1}$ ; MS (FAB)  $m/z$  275 ( $\text{M}+1$ )<sup>+</sup>

### 9.2.5 Preparation of the sodium salt (163) of 1,3-bis(methylenephosphonic acid)-2-imidazolidinone (157)

A solution of the acid 157 (1.9g, 6.93mmol) in water (20ml) at 0°C was treated dropwise with sodium hydroxide (4.44g, 0.0278mol, 4eqv) in water (20ml) and the resultant reaction mixture stirred at room temperature for one hour. The reaction mixture was then poured into dichloromethane (50ml), the aqueous layer separated and then concentrated to yield crude 1,3-bis(methylenephosphonic acid)-2-imidazolidinone, tetra sodium salt 163 (1.95g, 78%); <sup>31</sup>P NMR (36.23 MHz, D<sub>2</sub>O) δ 14.39 (t, J = 10.38 Hz) ppm; MS (FAB) m/z 363 (M+1)<sup>+</sup>; Flame test, positive yellow colour for the presence of sodium.

### 9.2.6 Preparation of the anilinium salt (164) of 1,3-bis(methylenephosphonic acid)-2-imidazolidinone (157)

1,3-bis(methylenephosphonic acid)-2-imidazolidinone 157 (4.30g, 0.0157mol) was dissolved in an ethanol/methanol solution (24ml/6ml), cooled to 0°C and then treated with freshly distilled aniline (1.46g, 0.0157mol). After stirring for 10 minutes the precipitated product was filtered and dried under vacuo to yield the anilinium salt 164 as a colourless solid (2.30g, 40%). Upon standing for seven days the filtrate produced a second crop of product crystals (1.10g, 19%); <sup>1</sup>H NMR (200MHz, d<sup>6</sup>-DMSO) δ 9.44 (6H, bs, OH, NH<sub>2</sub>), 7.24-6.12 (5H, dm, Ar CH), 3.48-3.27 (8H, cm, CH<sub>2</sub>) ppm; <sup>13</sup>C NMR (50.3MHz, d<sup>6</sup>-DMSO) δ 160.6 (C=O), 141.7 (Ar quat C), 129.4 (Ar CH), 121.2

(Ar, CH), 118.2 (Ar CH), 56.3 (CH<sub>2</sub>), 43.6 (CH<sub>2</sub>) ppm; <sup>31</sup>P NMR (36.23 MHz, D<sub>2</sub>O) δ 17.46 (t, J = 9.46 Hz) ppm - the addition of 4-5 drops of trifluoroacetic acid resulted in the formation of the free phosphonic acid **157** and the <sup>31</sup>P NMR signal shifted to 20.73 ppm; **Accurate mass (FAB)**, Found: 368.07769; C<sub>11</sub>H<sub>19</sub>N<sub>3</sub>O<sub>7</sub>P<sub>2</sub> requires 368.07764.

### 9.2.7 Preparation of 1,3-bis(methoxymethyl)-2-imidazolidinone (**165**)

From a literature method by Peterson<sup>124</sup>

To a solution of 2-imidazolidinone (14.33g, 0.166 mol) and formalin (37% solution, 27.10g, 0.334 mole, 2eqv) was added sodium hydroxide (40% solution, 0.3mls) and the mixture heated at 50°C for two hours. The solution was then neutralised with dilute hydrochloric acid and the water removed in vacuo at 50°C. The residual oil was taken up in methanol (60ml), oxalic acid (0.5g, catalytic amount) added and the solution heated for one and a half hours at 60°C. The solution was then neutralised with concentrated sodium hydroxide solution and the resultant precipitate removed by filtration. The filtrate was then evaporated to yield an oil which was purified by Kugelrohr distillation to yield 1,3-bis(methoxymethyl)-2-imidazolidinone **165** as a colourless oil (22.33g, 77%); **Bp** = 85°C/0.15 mmHg (lit.<sup>124</sup> = 116-120°C/3 mmHg); <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>) δ 4.77 (4H, s, CH<sub>2</sub>), 3.60 (4H, s, CH<sub>2</sub>), 3.38 (6H, s, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>) δ 159.05 (C=O), 74.71 (CH<sub>2</sub>), 54.69 (CH<sub>3</sub>), 39.85 (CH<sub>2</sub>) ppm; **IR** (thin film) ν<sub>max</sub> 1668 (C=O) cm<sup>-1</sup>; **MS** (FAB) m/z 159 (M-CH<sub>3</sub>)<sup>+</sup>, 143 (M-OCH<sub>3</sub>)<sup>+</sup>, 129 (M-CH<sub>2</sub>OCH<sub>3</sub>)<sup>+</sup>.

### 9.2.8 Preparation of 1,3-bis(chloromethyl)-2-imidazolidinone (166)

From a literature method by Peterson<sup>124</sup>

1,3-bis(methoxymethyl)-2-imidazolidinone **158** (6g, 0.034 mol) was dissolved in chloroform (10ml) and was added dropwise to a solution of thionyl chloride (8.62g, 0.072 mol, 2eqv) in chloroform (10ml) at 60°C. After heating at 60°C for two hours the solvents were removed in vacuo and the residue taken up in ether (10ml) to yield the crude product. Recrystallisation from chloroform gave 1,3-bis(chloromethyl)-2-imidazolidinone **166** as a light yellow coloured solid (5.24g, 83%); **Mp** = 85-87°C, (lit.<sup>124</sup> = 87-88°C); <sup>1</sup>H NMR (60 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ 4.97 (4H, s, CH<sub>2</sub>), 3.17 (4H, s, CH<sub>2</sub>) ppm; <sup>13</sup>C NMR (50.3 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) δ 156.66 (C=O), 56.62 (CH<sub>2</sub>), 39.73 (CH<sub>2</sub>) ppm; IR (KBr disc) ν<sub>max</sub> 1685 (C=O) cm<sup>-1</sup>; MS (FAB) m/z 147 (M-Cl-1)<sup>+</sup>.

### 9.2.9 Preparation of 1,3-bis(dimethylphosphorylmethyl)-2-imidazolidinone (167)

To a solution of 1,3-bis(chloromethyl)-2-imidazolidinone **166** (1.50g, 8.19mmol) in toluene (10ml) at room temperature was added trimethyl phosphite (2.03g, 0.016mol) in toluene (3ml) and the resultant mixture heated at 60°C for 45 minutes. The reaction mixture was then cooled upon which precipitation occurred. Recrystallisation from ethyl acetate yielded 1,3-bis(dimethylphosphorylmethyl)-2-imidazolidinone **167** as a colourless solid (2.09g, 77%); **Mp** = 77-79°C; <sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>) δ 3.57 (12H, d, J = 10.7 Hz, CH<sub>3</sub>), 3.44 (4H, d, J = 9.36 Hz, CH<sub>2</sub>), 3.34 (4H, s, CH<sub>2</sub>) ppm; <sup>13</sup>C

**NMR** (50.3MHz, CDCl<sub>3</sub>)  $\delta$  159.2 (C=O), 52.3 (d, J = 6.8 Hz, CH<sub>3</sub>), 38.8 (d, J = 161.4 Hz, CH<sub>2</sub>) ppm; **<sup>31</sup>P NMR** (36.23 MHz, CDCl<sub>3</sub>)  $\delta$  24.8 ppm; **MS (FAB)** m/z 331 (M+1)<sup>+</sup>

### 9.2.10 Preparation of 1,3-bis(phthalimidomethyl)-2-imidazolidinone (168)

From a procedure by Shapiro and Evans<sup>125</sup>

To a solution of 1,3-bis(chloromethyl)-2-imidazolidinone **166** (2.0g, 0.01mol) in dimethylformamide (15ml) was added potassium phthalimide (4.3g, 0.023mol, 2eqv) in dimethylformamide (10ml). The resulting solution was heated at 100°C for three hours. Once the solution had cooled, dichloromethane (50ml) was added, the mixture then poured into water (50ml) and the aqueous layer extracted with dichloromethane (2x30ml). The combined organic extracts were then washed with sodium hydroxide solution (0.25M, 50ml) followed by water (50ml) and then dried over anhydrous sodium sulphate. After filtration the filtrate was then evaporated to yield a colourless solid (3.00g, 68% crude). The product was purified by flash chromatography (30g, SiO<sub>2</sub>) using gradient elution with n-hexane:ethyl acetate 100:0 to 0:100 yielding 1,3-bis-(phthalimidomethyl)-2-imidazolidinone **168** (1.8g, 41%) as a colourless solid; **Mp** = 219-221°C; **<sup>1</sup>H NMR** (200MHz, CDCl<sub>3</sub>)  $\delta$  7.54-7.13 (8H, dm, Ar CH), 5.16 (4H, s, CH<sub>2</sub>), 3.47 (4H, s, CH<sub>2</sub>) ppm; **<sup>13</sup>C NMR** (50.3 MHz, CDCl<sub>3</sub>)  $\delta$  167.56 (C=O), 157.90 (C=O), 134.17 (Ar CH), 131.66 (Ar quat C),

123.51 (Ar CH), 46.72 (CH<sub>2</sub>), 42.31 (CH<sub>2</sub>) ppm; IR (KBr disc)  $\nu_{\max}$  1720 (C=O), 1695 (C=O) cm<sup>-1</sup>; MS (FAB) m/z 405 (M+1)<sup>+</sup>.

### 9.2.11 Attempted formation of 1,3-bis(aminomethyl)-2-imidazolidinone (169).

To a solution of 1,3-bis(phthalimidomethyl)-2-imidazolidinone 168 (0.79g, 1.95 mmol) in methanol (25ml) was added hydrazine hydrate (0.21g, 4.2 mmol, 2.1eqv) in methanol (5ml) and the resultant mixture heated under reflux for 5 hours. Solvents were then removed in vacuo, the residue taken up in dichloromethane (50ml) and shaken for fifteen minutes with ammonium hydroxide solution (4N, 30ml). The ammonical layer was then extracted with dichloromethane (3x30ml), the organic extracts combined and solvents removed in vacuo to yield a green pasty residue. TLC of the residue showed some starting material still present as well as a plethora of products. Separation by flash chromatography (20g, silica) using gradient elution with dichloromethane:ethanol:ammonia (500:8:1 to 50:8:1) afforded only four products, two of which were obtained in sufficient amounts to be analysed by <sup>1</sup>H nmr spectroscopy. However, the <sup>1</sup>H nmr spectra combined with FAB and EI mass spectra data of the crude residue showed that none of the desired product had been formed with only breakdown products of the starting material being produced.

### 9.2.12 Isolation of 1,3-bis(aminoethyl)-2-imidazolidinone (190).

1,3-bis(aminoethyl)-2-imidazolidinone **190** was supplied by B.P.Chemicals, Hull. After purification by fractional distillation and then Kugelrohr distillation of the main fraction, 1,3-bis(aminoethyl)-2-imidazolidinone **190** was obtained as a colourless oil; **Bp** = 160°C/0.325mmHg; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 3.06 (4H, s, CH<sub>2</sub>), 2.93 (4H, t, J = 6.24 Hz, CH<sub>2</sub>), 2.50 (4H, t, J = 6.24 Hz, CH<sub>2</sub>), 1.09 (4H, s, NH<sub>2</sub>) ppm; <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>) δ 161.43 (C=O), 46.96 (CH<sub>2</sub>), 42.47 (CH<sub>2</sub>), 39.38 (CH<sub>2</sub>) ppm; IR (thin film) ν<sub>max</sub> 3294, 3258 (NH<sub>2</sub>), 1690 (C=O) cm<sup>-1</sup>; MS (FAB) m/z 173 (M+1)<sup>+</sup>.

### 9.2.13 Preparation of 1,3-bis(aminoethyl)-2-imidazolidinone-tetra(methylenephosphonic acid) (175)

Adapted from a literature report by Moedritzer<sup>94</sup>

Hydrochloric acid (17ml, 35% solution) was added to phosphorous acid (13.3g, 0.16 mol), with cooling and stirring, until all of the phosphorous acid had dissolved, after which time 1,3-bis(aminoethyl)-2-imidazolidinone **174** (4.0g, 0.023 mol) was slowly added. The solution was heated to 135°C and formaldehyde (37% solution, 15g, 8 eqv) was added over a 40 minute period and then the solution heated for 4 hours. After the reaction had cooled the solution was poured into cold ethanol (200ml) which produced a gummy solid. The solid was then dissolved in the minimum amount of hot water and again poured into cold ethanol (200ml). This process was repeated one more

time and then the still gummy solid dried under high vacuum at 100°C which yielded 1,3-bis(aminoethyl)-2-imidazolidinone-tetra(methylenephosphonic acid) **175** as a colourless powder (7.91g, 62%); <sup>1</sup>H NMR (270.05 MHz, D<sub>2</sub>O) δ 3.5-3.3 (20H, m, CH<sub>2</sub>'s) ppm; <sup>13</sup>C NMR (50.3 MHz, D<sub>2</sub>O) δ 163.15 (C=O), 54.56 (CH<sub>2</sub>), 52.63 (CH<sub>2</sub>), 49.89 (CH<sub>2</sub>), 43.16 (CH<sub>2</sub>), 39.40 (CH<sub>2</sub>) ppm; <sup>31</sup>P NMR (36.23 MHz, D<sub>2</sub>O) δ 8.21 (t, J = 10.24 Hz) ppm; IR (KBr disc) ν<sub>max</sub> 3500-2300 (P-OH), 1695 (C=O), 1270 (P-O) cm<sup>-1</sup>; Accurate mass (FAB), Found: 549.06819; C<sub>11</sub>H<sub>29</sub>N<sub>4</sub>O<sub>13</sub>P<sub>4</sub> (M<sup>+</sup>) requires: 549.06815.

#### 9.2.14 Preparation of 1,3-bis(hydroxyethyl)-2-imidazolidinone (**177**)

Note: This reaction was carried out at high pressure and temperatures in a sealed system. Every safety precaution must be thought of in advance and adhered to *e.g.* blast shields and pressure safety valves to prevent excessive build up of pressure.

A Rothbomb pressure vessel (100ml capacity) was charged with 1,3-bis(2-hydroxyethyl)ethylenediamine **176** (5.0g) in methanol (30ml) to which enough dry ice (solid CO<sub>2</sub>, 35g) was added to create an initial pressure of 40 Bar at room temperature. The vessel was then heated to 185°C (silicon oil bath) for 17 hours with the maximum pressure reached being 76 Bar. The heat was then removed, the bomb allowed to cool and the pressure released. The contents of the bomb were emptied and solvent removed in vacuo to yield a brown viscous oil. IR analysis of the oil showed both starting

material and product to be present. To isolate the product the oil was dissolved in dilute hydrochloric acid (20ml) and the acid then exchanged for methanol which precipitated the hydrochloride salt of the starting amine. Once the salt was removed by filtration the filtrate was concentrated to yield a colourless oil which was purified by Kugelrohr distillation to yield 1,3-bis(hydroxyethyl)-2-imidazolidinone **177**.; **Bp** = 195°C/0.15 mmHg; **<sup>1</sup>H NMR** (200 MHz, d<sub>6</sub>-DMSO) δ 4.75 (2H, bs, OH), 3.44 (4H, t, J = 5.85 Hz, CH<sub>2</sub>), 3.30 (4H, s, CH<sub>2</sub>), 3.09 (4H, t, J = 5.85 Hz, CH<sub>2</sub>) ppm; **<sup>13</sup>C NMR** (50.3 MHz, d<sub>6</sub>-DMSO) δ 161.23 (C=O), 59.43 (CH<sub>2</sub>), 46.67 (CH<sub>2</sub>), 43.51 (CH<sub>2</sub>) ppm; **IR** (thin film) ν<sub>max</sub> 3360 (OH), 1670 (C=O) cm<sup>-1</sup>; **MS** (FAB) m/z 175 (M+1)<sup>+</sup>.

### 9.3 Reactions deriving from cyanuric acid

#### 9.3.1 Attempted preparation of tris(ethylenephosphonic acid)cyanuric acid (**183**)

Phosphorous trichloride (10ml) was cooled to 0°C and then carefully treated portionwise with tris(hydroxyethyl)cyanuric acid **181** (1.60g, 6.32 mmol). Once the addition was complete the reaction was heated under reflux for 10 minutes, after which time excess phosphorus trichloride was removed under vacuum. The residue was cooled to 0°C and then carefully treated with ice water (10ml) and the reaction stirred for a further 10 minutes. Excess water and volatiles were then removed to yield a yellow syrup which upon analysis by <sup>31</sup>P NMR and mass spectroscopy was proven to be a mixture of phosphorous acid and starting triol.

### 9.3.2 Preparation of tris(chloroethyl)cyanuric acid (185)

Adapted from a literature report by Askew<sup>129</sup>

To a solution of tris(hydroxyethyl)cyanuric acid (10.5g, 0.040 mol) in 1,4-dioxane (30ml) was added thionyl chloride (28.0g, 0.235 mol) in 1,4-dioxane (20ml) dropwise over a 10 minute period. The solution was then heated at 60°C for one and a half hours after which time the solvent was removed in vacuo to produce a yellow solid residue. The residue was dissolved in chloroform (50ml), washed with 0.3M sodium hydroxide solution (3x50ml), the aqueous washings extracted with chloroform (2x50ml) and the combined organics dried over magnesium sulphate. After filtration the filtrate was evaporated to yield a colourless solid. Recrystallisation from petroleum ether 60-80/ethyl acetate (2:1) gave tris(chloroethyl)cyanuric acid **185** as a colourless solid (10.18g, 80%); **Mp** = 192-194°C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 4.21 (6H, t, J = 6.37 Hz, CH<sub>2</sub>), 3.69 (6H, t, J = 6.37 Hz, CH<sub>2</sub>) ppm; <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>) δ 148.17 (C=O), 43.51 (CH<sub>2</sub>), 39.79 (CH<sub>2</sub>) ppm; IR (KBr disc) ν<sub>max</sub> 1695 (C=O) cm<sup>-1</sup>; MS (FAB) m/z 316 (M-1)<sup>+</sup>, 280 (M-Cl-1)<sup>+</sup>; Elemental analysis, Found: 34.4% C, 3.8% H, 13.1% N, 33.9% Cl; C<sub>9</sub>H<sub>12</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>3</sub> requires: C, 34.1; H, 3.8; N, 13.3; Cl, 33.7%.

### 9.3.3 Preparation of tris(bromoethyl)cyanuric acid (185)

From a procedure by Feldman<sup>128</sup>

To tris(hydroxyethyl)cyanuric acid (1.00g, 3.83 mmol) and carbon tetrabromide (5.1g, 15.96 mmol, 40% excess) in freshly distilled acetonitrile

(50ml) at 0°C was added triphenylphosphine (4.0g, 15.25 mmol, 30% excess) over a 10 minute period. The solution was allowed to warm to room temperature and left to stir for 24 hours. The solvent was then removed in vacuo and the residue subjected to flash column chromatography (30g, silica) using n-hexane:ethyl acetate (3:1) as the elution solvent. The main fraction to be eluted was tris(bromoethyl)cyanuric acid **185** as a colourless solid (1.45g, 84%); **Mp** = 215-217 °C; **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ 4.28 (6H, t, J = 6.75 Hz, CH<sub>2</sub>), 3.55 (6H, t, J = 6.75, CH<sub>2</sub>) ppm; **<sup>13</sup>C NMR** (50.3 MHz, CDCl<sub>3</sub>) δ 148.06 (C=O), 43.40 (CH<sub>2</sub>), 27.02 (CH<sub>2</sub>) ppm; **IR** (Kbr disc)  $\nu_{\max}$  1690 cm<sup>-1</sup>; **MS** (FAB) m/z 450 (M<sup>+</sup>).

#### 9.3.4 Attempted preparation of tris-(dimethoxyphosphorylethyl)cyanuric acid (186)

a) To a solution of tris(chloroethyl)cyanuric acid **185** (0.95g, 3.00mmol) in toluene (10ml) at 50°C was added dropwise trimethyl phosphite (1.12g, 9.00mmol, 3eqv) in toluene (10ml). The temperature of the reaction mixture was then increased to 80°C and the reaction stirred at this temperature for seven hours. TLC after this time showed some starting material and three product spots to be present. In an attempt to isolate these products the residue of the reaction mixture, after evaporation of solvents, was subjected to flash chromatography (30g, SiO<sub>2</sub>) using gradient elution with n-hexane : ethyl acetate 100:0 to 0:100. However, the spots from TLC which were thought to be reaction products gave negligible yields after being subjected to

chromatography. The main fraction to be obtained was the recovered starting material, tris(chloroethyl)cyanuric acid **185**, in 85% yield.

b) The procedure used in this attempt to synthesise **186** was identical to that in section a) above, except that a 100% excess of trimethyl phosphite was used, the reaction temperature was increased to 100°C and the reaction time was 67 hours. Again after work-up and subjection to flash chromatography the main fraction to be obtained was recovered starting material, tris(chloroethyl)cyanuric acid **185**, in 61% yield.

c) The procedure used in this attempt to synthesise **186** was identical to that in section a) above, except that the more reactive tris(bromoethyl)cyanuric acid **185** was used, the reaction temperature was increased to 110°C and the reaction time was five days. Again after work-up and subjection to flash chromatography the main fraction to be obtained was recovered starting material, tris(bromoethyl)cyanuric acid **185**, in 79% yield.

### **9.3.5 Preparation of tris(diethoxyphosphorylethyl)cyanuric acid (187)**

To a suspension of sodium (0.39g, 0.017mol) in dry DME (10ml) was slowly added diethyl phosphite (2.30g, 0.017mol) in dry DME (5ml) and the reaction mixture stirred for 30 minutes and then heated under reflux for 30 minutes after which time all the sodium had reacted. The reaction mixture

was cooled to room temperature and then a solution of tris(bromoethyl)cyanuric acid **185** (2.50g, 5.56mmol) in dry DME (10ml) was slowly added which produced the precipitation of a colourless solid, presumably sodium bromide. After stirring of the reaction mixture at room temperature for 48 hours,  $^{31}\text{P}$  NMR spectroscopy showed the reaction to consist mainly of a single phosphorus containing product at 26.3 ppm. The reaction mixture was then filtered, the filtrate concentrated and the residue subjected to flash chromatography (30g,  $\text{SiO}_2$ ) using gradient elution with ethyl acetate:methanol 100:0 to 75:25 to yield tris(diethoxyphosphorylethyl)cyanuric acid **187** as a colourless solid (1.73g, 50%); **Mp** = 178-180°C;  $^1\text{H}$  NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  4.05-3.90 (18H, cm,  $\text{CH}_2$ ), 2.11-1.93 (6H, cm,  $\text{CH}_2$ ), 1.20 (18H, t,  $J = 7.1$  Hz,  $\text{CH}_3$ ) ppm;  $^{13}\text{C}$  NMR (50.3MHz,  $\text{CDCl}_3$ )  $\delta$  147.8 (C=O), 61.5 (d,  $J = 6.1$  Hz,  $\text{CH}_2$ ), 37.0 ( $\text{CH}_2$ ), 23.6 (d,  $J = 139.3$  Hz,  $\text{CH}_2$ ), 16.0 (d,  $J = 5.6$  Hz,  $\text{CH}_3$ ) ppm;  $^{31}\text{P}$  NMR (36.23 MHz,  $\text{CDCl}_3$ )  $\delta$  26.0 ppm; **Accurate mass** (FAB), Found: 622.2068;  $\text{C}_{21}\text{H}_{43}\text{N}_3\text{O}_{12}\text{P}_3$  requires 622.20594

### 9.3.6 Attempted preparation of tris(phthalimidoethyl)cyanuric acid (191)

a) To a solution of tris(chloroethyl)cyanuric acid **185** (1.00g, 3.15mmol) in DMF (20ml) was added potassium phthalimide (1.90g, 0.010mol) in DMF (10ml) and the reaction mixture heated at 100°C for three hours. Once the solution had cooled, chloroform (50ml) was added, the mixture then poured

into water (50ml) and the aqueous layer extracted with chloroform (2x50ml). The combined organic extracts were then washed with sodium hydroxide solution (0.25M, 50ml) followed by water (50ml) and then dried over anhydrous sodium sulphate. After filtration the filtrate was evaporated to yield a colourless solid (1.50g) which was shown by TLC to consist of three UV active products. The residue was subjected to flash chromatography (30g, SiO<sub>2</sub>) using gradient elution with n-hexane:ethyl acetate 100:0 to 0:100 which yielded two main fractions. However, by analysis by mass spectrometry and NMR spectroscopy the two products were shown to consist of a mixture of the mono, bis and tris(phthalimidoethyl)cyanuric acid.

b) To a suspension of sodium hydride (0.60g, 80%) in dry DME (10ml) was added cyanuric acid (0.80g, 6.20mmol) and the resultant mixture heated under reflux for three hours and then left to stir overnight. Methanol (2ml) was added to destroy any unreacted sodium hydride and the solvents then removed in vacuo to yield trisodium cyanurate **192** as a colourless solid residue. The sodium salt was then taken up in dry DME (25ml), treated with bromoethylphthalimide (4.72g, 0.019mol) in DMF (10ml) and then heated at 90°C for four hours. Once the reaction had cooled it was poured into hot water (100ml) and then acetone added which produced a colourless precipitate. Analysis by NMR spectroscopy and TLC showed the precipitate to be recovered starting material, bromoethylphthalimide, in 90% yield.

### 9.3.7 Attempted preparation of tris(N,N-dibenzylaminoethyl)cyanuric acid (194)

a) To a solution of dibenzylamine (3.40g, 0.017mol, 9eqv) in freshly distilled THF (15ml) at room temperature was added dropwise a solution of tris(chloroethyl)cyanuric acid **185** (0.60g, 1.89mmol) in THF (15ml). Once the addition was complete the reaction mixture was heated under reflux for three hours. After this time TLC showed that no reaction had taken place.

b) To a solution of dibenzylamine (1.70g, 8.62mmol) in dry DME (10ml) at 0°C was added butyllithium (1.6M, hex, 5.5ml) which resulted in the formation of a magenta coloured solution. After stirring for 40 minutes, tris(chloroethyl)cyanuric acid **185** (0.30g,  $9.48 \times 10^{-4}$ mol) in dry DME (10ml) was added dropwise and the resultant reaction mixture stirred at room temperature for one hour. After this time TLC showed the reaction mixture to consist of a plethora of products, all of which appeared to be UV active, and so the reaction was discarded.

### 9.3.8 Preparation of tris(cyanomethyl)cyanuric acid (196)

From a literature method by Birdick<sup>127</sup>

To a suspension of sodium hydride (80%, 0.76g, 0.025 mol) in dry DME (20ml) was added cyanuric acid (1.00g, 7.74 mmol) and the resultant mixture heated under reflux for 3 hours and then left to stir overnight. Methanol (2ml) was added to destroy any unreacted sodium hydride and the

solvents then removed in vacuo to yield trisodium cyanurate as a colourless solid residue. The sodium salt was then taken up in dry DMF (25ml), treated dropwise with chloroacetonitrile (3.5g, 0.046 mol) at 50°C over a 20 minute period and then heated at 85°C for a further 3 hours. Once the reaction had cooled it was filtered, the filtrate evaporated to dryness and the residue triturated with boiling water to yield tris(cyanomethyl)cyanuric acid **196** as a brown solid (1.14g, 60%); **Mp** = 232-234°C (lit.<sup>127</sup> = 232-234°C); **<sup>1</sup>H NMR** (60 MHz, d<sub>6</sub>-DMSO) δ 4.86 (6H, CH<sub>2</sub>) ppm; **<sup>13</sup>C NMR** (50.3 MHz, d<sub>6</sub>-DMSO) δ 147.43 (C=O), 114.98 (C≡N), 30.64 (CH<sub>2</sub>) ppm; **IR** (KBr disc)  $\nu_{\max}$  2210 (CN), 1695 (C=O) cm<sup>-1</sup>.

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# Appendix

## FROM GAS PHASE TO CONDENSED PHASE: TOWARDS METAPHOSPHATE GENERATION IN SOLUTION

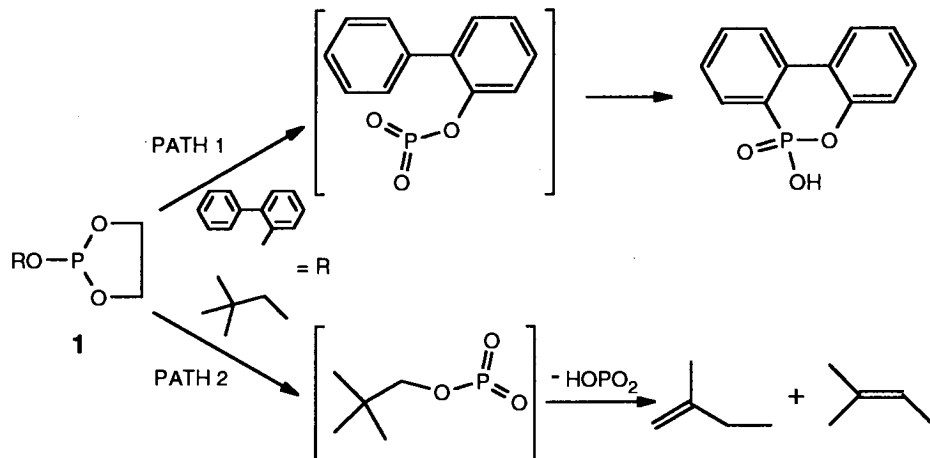
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**Abstract** Based on attempts to generate methyl metaphosphate in solution by thermal fragmentation of a cyclic pyrocarbonate phosphate, it has emerged that reaction of methyl dichlorophosphate with anhydrous potassium hydrogen carbonate serves as an alternative approach as proven by trapping with styrene oxide to form a 1,3,2-dioxaphospholane.

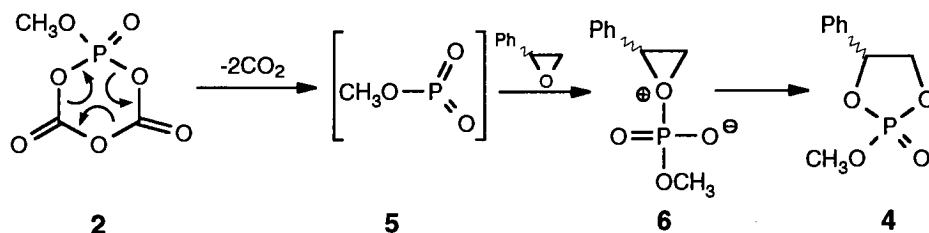
Our previous studies have shown that gas-phase pyrolysis of 2-substituted 1,3,2-dioxaphospholanes **1** generate highly electrophilic metaphosphate species by extrusion of ethylene. Depending upon the nature of the 2-substituent, the metaphosphate follows different reaction pathways, either by electrophilic substitution (path 1)<sup>1</sup> as shown in Scheme 1 or abstraction followed by elimination of metaphosphoric acid (path 2)<sup>2</sup>.



**SCHEME 1**



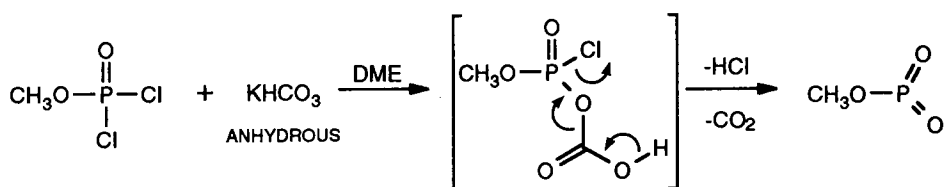
from decomposition of its pyrocarbonate precursor upon warming to room temperature. In an attempt to shed further mechanistic light on the mode of reaction in the final step, the trapping reaction was repeated with optically pure (R)-styrene oxide but the same diastereomeric mixture was obtained. This result ruled out the possibility of rearrangement of **6** to **4** in a *single step* otherwise only the RR-isomer would have been observed. Instead, it pointed to ring-opening *via* a stabilised carbocation with bond rotation, or an entirely different mechanism involving direct attack by the metaphosphate species (in its charge-separated form) on the styrene oxide with inversion of configuration.



SCHEME 3

Initially we attributed the peaks observed at -13 and -1 ppm in our first experiments (Scheme 2) to trimeric and dimeric condensed forms of **5**, but it was recognised that terminal phosphoryl groups in chains appear at about -10 to -12, while signals for phosphoryl units in chains or cycles resonate at about -23 to -26 ppm<sup>5</sup>. The true identity of these products was revealed by comparison with the literature report by Satterthwait and Westheimer<sup>6</sup> on the thermal decomposition of methyl 2-butenylphostonate which extruded butadiene to form *sym*-di-methylpyrophosphate (-13 ppm) and methyl phosphonic acid (-1 ppm), apparently *via* the intermediacy of methyl metaphosphate. The origin of these products clearly requires the involvement of water and this finding led us to re-examine the nature of our supposed precursor pyrocarbonate **2**. These studies established that during its attempted preparation, decomposition of the di-potassium salt occurred *in situ*, despite careful precautions, to afford potassium hydrogen carbonate! Indeed when an anhydrous sample of the latter was condensed with methyl dichlorophosphate in the presence of styrene oxide,

formation of **4** occurred exclusively in keeping with the intermediacy of methyl metaphosphate as shown in Scheme 4 and its subsequent trapping (*vide supra*). Intriguingly, we have now managed to prepare the di-sodium analogue of **3**, [ $\nu_{C=O}$  1610  $\text{cm}^{-1}$ ; FAB-MS ( $M^++1$ ) 150.96199,  $\text{C}_2\text{HNa}_2\text{O}_5$  requires 150.96200] subsequent treatment of which with methyl dichlorophosphate yields the cyclic pyrocarbonate phosphate **2** (-17 ppm) whose chemistry will be described later.



SCHEME 4

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