SYNTHESIS AND REACTIVITY

OF

SOME β - SUBSTITUTED ALKYLPHOSPHONATES

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by

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to my family

ABSTRACT

The ability of the β-trimethylammonioethylphosphonic acid dianion to undergo fragmentation in alkaline conditions to produce trimethylamine, ethylene and metaphosphate was investigated. The results obtained were to give an indication of the susceptibility of $(C_6H_3Cl_2)OCH_2CH_2N^+R_2CH_2CH_2P(OR')O_2^-$ to analogous fragmentation to release 2-(3,4-dichlorophenoxy)ethyldialkylamine and ethylene, both well documented plant growth regulating hormones.

Since the trimethylammonioethyl-substituted species was found to be stable to fragmentation, studies were embarked upon to convert this molecule into one which would react as required. The substitution of an alkyl group at the β-position of such a β-substituted alkylphosphonate is reported to accelerate the rate of fragmentation. β-trimethylammoniopentylphosphonate was therefore expected to fragment where its ethyl analogue did not.

Attempts at its synthesis were made by various approaches. 2-chloropentylphosphonic acid, a precursor, was successfully prepared and esterified (in order to protect the acid from premature fragmentation) so that it might be reacted with trimethylamine (a nucleophile), to produce diethyl β-trimethylammoniopentylphosphonate, which was then to be hydrolysed to the phosphonic acid form. Instead of the required substitution of Cl by Me_3N, the action of base on the ester produced diethyl 1-pentenylphosphonate. Only traces of the substitution product were observed.

It was thought that the replacement of chlorine by a better leaving group such as bromine or iodine would favour the substitution product over the elimination product.

Attempts at the synthesis of diethyl 2-iodopentylphosphonate and diethyl 2-bromopentylphosphonate by various means are described, but no satisfactory syntheses have been achieved, since once again the dehydrohalogenation product predominates.

During an attempted synthesis of diethyl 2-iodopentylphosphonate by reaction of diethyl 2-chloropentylphosphonate with NaI, an unusual interaction between the sodium cation and the substrate in acetone solution was discovered. Evidence gleaned from ^1H, ^{13}C and ^{31}P nmr experiments points to the formation of a loose complex between the phosphonate part of the substrate and Na^+. This phenomenon is also observed when other salts such as CaI_2, KSCN and $NaClO_4$ are present in solution.

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CONTENTS

CHAPTER ONE

INTRODUCTION

1.1 Plant growth regulators

Plant growth regulator research[1] is a rapidly expanding field which has the potential for immense benefits to world crop production. Bioregulators are compounds which, when administered to a plant system, are able to influence some reaction in the plant metabolism to produce a required response: increased flowering, accelerated ripening, promotion of abscission (dropping of fruits) at harvest, or stimulation of secretion. Natural control mechanisms in plants are taken over and adapted to suit agricultural needs.

To find a suitable plant growth regulator, the relationship between chemical structure and plant response must be elucidated. Successful results have been achieved in the past using structures analogous to known plant hormones.[2-5] It can be appreciated that the task of finding a viable regulator is a difficult one, since the interactions between regulator and plant metabolism are complex. Often a knowledge of pathways of plant hormone biosynthesis and mechanism for their regulation is required. This is in contrast to herbicide research where a simple lethal effect is required. The environmental response to a proposed plant growth regulator should be taken into

account when testing its activity in the laboratory. Current research is aimed at the discovery of non-toxic bioregulators which improve food quality and crop productivity.[1]

Ethylene is a plant hormone known to play a role in the growth cycles of many species by regulating the activity of a variety of enzymes.[6,7] It is produced naturally in the shoots, leaves and fruits of plants at different stages of their development.[8] The use of ethylene or an ethylene-releasing compound as a plant growth regulator is highly practicable for a number of reasons:

(i) the introduction of ethylene into a plant system leaves no toxic residues.

(ii) ethylene is involved in many naturally regulated plant processes.

(iii) since ethylene seems to play a diverse role in plant physiology, options for regulating that physiology are numerous.[9]

Ethephon (Amchem 66-329), or 2-chloroethylphosphonic acid, is an ethylene-releasing plant growth regulator in commercial use.[1,10] The information available in the scientific literature on the biological activity of Ethephon is vast and increasing. It appears to be active in seeds, plants and fruits - in every stage of a plant's development. Typical biological responses to the administration of Ethephon are:[9]

(i) growth promotion of seedlings (rice)

(ii) inhibition of height growth

(iii) root initiation

(iv) chlorophyll destruction (ripening) in citrus

(v) flower initiation[11]

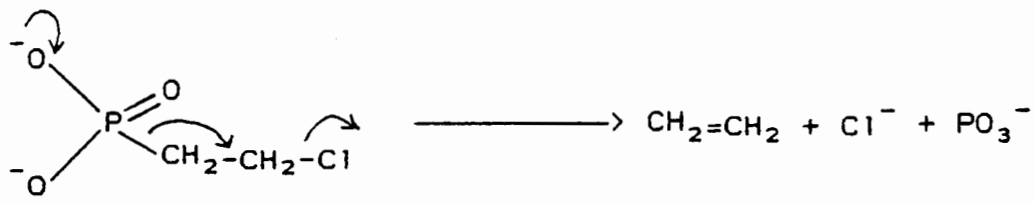
(vi) fruit growth stimulation (figs)

(vii) promotion of secretion (rubber, guayule)[12]

(viii) leaf, fruit and flower abscission by stimulating the activity of cellulases[13]

All of these effects are attributable to the increased concentration of ethylene in the plant system. The quantity of ethylene found in the plant after treatment with Ethephon is greater than that which corresponds to the added phosphonic acid. Ethephon, therefore, not only releases ethylene, but also stimulates ethylene production in plant tissue.[10,14,15]

The release of ethylene from Ethephon occurs via a fragmentation reaction described by Maynard and Swan,[16,17] who reported that 2-halogenoalkylphosphonic acids decompose rapidly and quantitatively in aqueous solution at pH > 5, yielding halide and metaphosphate ions and the corresponding alkene:



This is an unusual observation, since it is known that the bonding of phosphorus to carbon is very strong: the hydrolysis

of alkylphosphonic esters in strong alkali solution is possible without rupture of the carbon-phosphorus linkage.[18] In the case described by Maynard and Swan, fragmentation occurs under comparatively mild conditions. There are few previous reports of facile decomposition of the 2-halogenoalkylphosphonic acids, all of which are provided by J. B. Conant and co-workers.[19-21]

Mechanism of Maynard and Swan fragmentation. M. J. Gregory et al.[22] investigated the fragmentation reaction in aqueous medium by measurement of liberated acid:

$$RCH(Cl)CH_2P(O)(OH)_2 \xrightarrow{H_2O} RCH{=}CH_2 + H_3PO_4 + HX$$

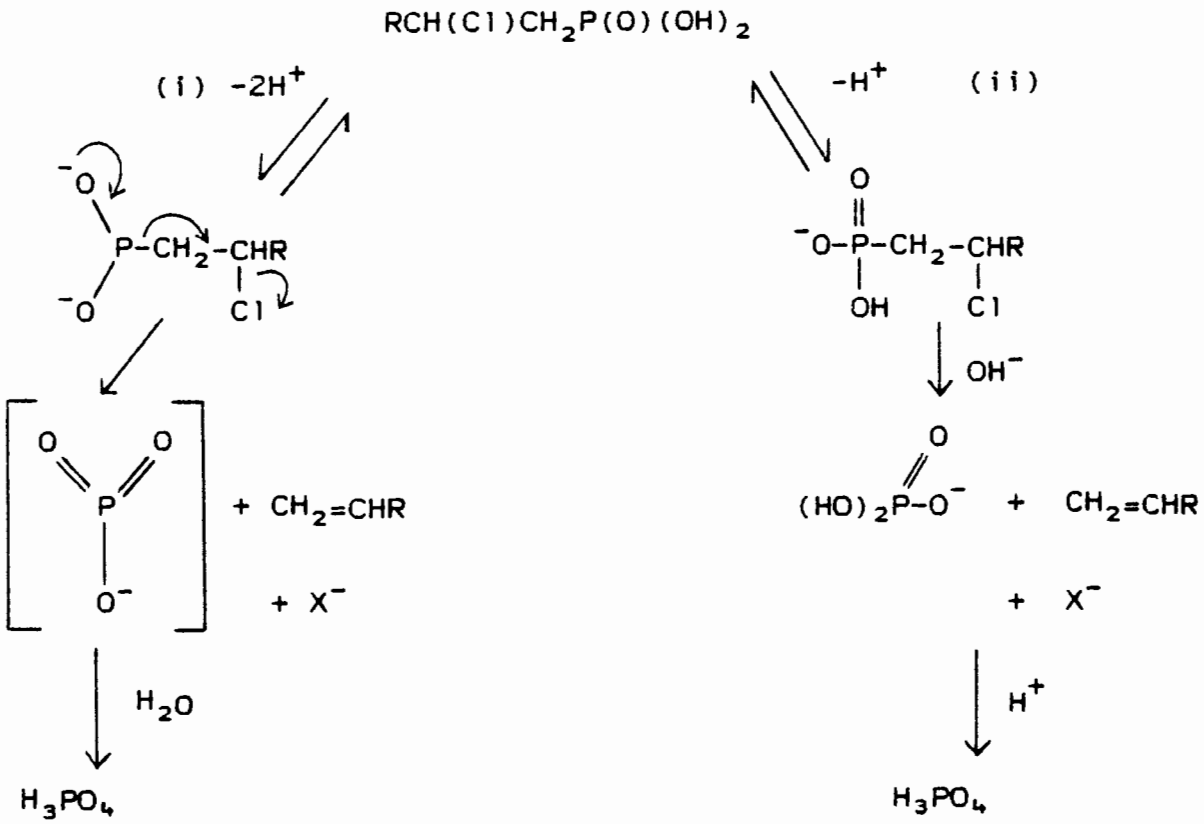
[R=H; Me; n-Bu]

The disappearance of 2-chloroethylphosphonic acid at a given pH follows first-order kinetics to more than four half-lives of reaction. The observed first-order rate constant is directly proportional to the fraction of 2-chloroethylphosphonic acid present in dianionic form. Warner and Leopold [15] reported that ethylene evolution is more rapid with increased pH at a given temperature.

The two possible mechanisms for the decomposition of these 2-chloroalkylphosphonic acids are:

(i) unimolecular fragmentation of the acid dianion

(ii) concerted bimolecular fragmentation



When the fragmentation reactions are carried out in 1M azide or 1M fluoride solutions, reaction rates are not significantly affected. The fluoride and azide nucleophiles appear to have no catalytic effect. Reaction rates are also essentially unaffected by changes in solvent. For reactions performed in methanol-water, as the proportion of methanol in the solution increases, the yield of phosphate decreases, being replaced by methyl dihydrogen phosphate. The fraction of 2-chloroethylphosphonic acid reacting to give the ester is equal to the mole fraction of methanol present. There is therefore no specificity in the competitive phosphorylation of water and methanol.

All the above evidence[22] supports the argument for the unimolecular pathway (i). The driving force for the reaction would be the formation of thermodynamically stable products such as C_2H_4 and Cl^-, as well as the liberation of metaphosphate.

Since the pH of the cytoplasm of plant cells is greater than 5, Ethephon (2-chloroethylphosphonic acid) entering the cell would be degraded to release biologically active ethylene. By monitoring the quantities of Ethephon administered to a species at an appropriate stage of its growth cycle, the desired plant growth regulating effects may be observed.

The mono-ester of 2-chloroethylphosphonic acid is also biologically active, but does not undergo Maynard and Swan-type fragmentation even on heating with excess alkali. Instead, the dominant product is vinylphosphonic acid, formed by base catalysed dehydrohalogenation.[17]

$$Cl\text{-}CH_2CH_2\text{-}P(O)(OR)O^- + OH^- \longrightarrow CH_2{=}CH\text{-}P(O)(OR)O^- + Cl^-$$

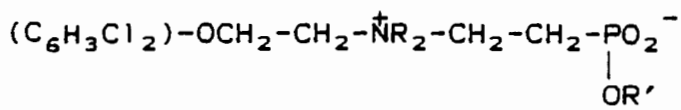
It is postulated that the monoester is hydrolysed by plant hydrolytic enzymes to produce 2-chloroethylphosphonic acid, the species responsible for bioregulating effects.[11]

Another class of plant growth regulators, the substituted (aryloxyethyl)dialkylamines, have been found to stimulate the biosynthesis of rubber in the guayule plant.[23,24] This species is a hardy shrub which, under normal conditions, produces

natural rubber, cis-polyisoprene, in modest amounts. The use of plant growth regulators to increase the production of rubber in the plant is being investigated to determine the feasibility of growing guayule on a commercial scale as an industrial source of natural rubber. The other economically viable source of natural rubber is the rubber tree which requires the tropical conditions of south-east Asia for successful cultivation. By contrast, guayule can be produced in harsh desert conditions. Increased rubber production in the guayule has been achieved by 2-(3,4-dichlorophenoxy)ethyldialkylamine in particular.[25-27]

1.2 Initial aims of the project

The studies described in the following chapters arose from an initial interest in the formulation and synthesis of a plant growth regulator which would combine the bioregulating properties of Ethephon and 2-(3,4-dichlorophenoxy)ethyldialkylamine. The target system was 2-{N,N-dialkyl-N-[2-(3,4-dichlorophenoxy)ethyl]ammonio}ethyl-phosphonate (compound 1):

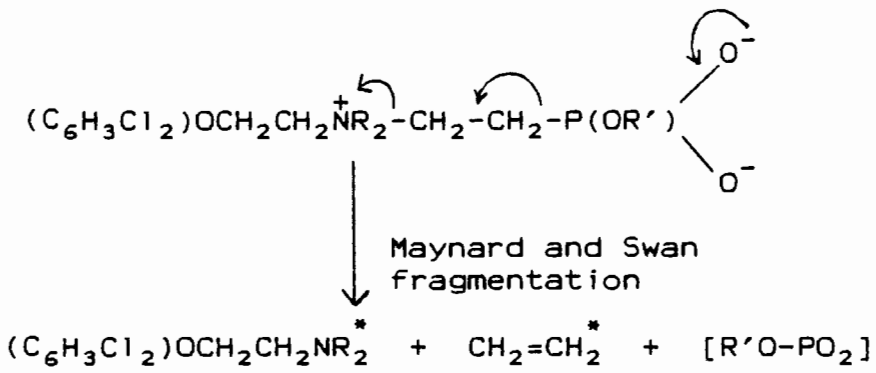


1

R=Me; Et

R′=H or lipophilic group

It was expected that compound 1, as a structural extension of Ethephon, would be capable of Maynard and Swan-type fragmentation to yield two biologically active products: ethylene and 2-(3,4-dichlorophenoxy)ethyldialkylamine:



* biologically active

The lipophilic group on the phosphonate function was introduced to render the molecule membrane-soluble, thus facilitating the absorption of compound 1 into plant tissue.

Possible schemes for the synthesis of compound 1 are set out on the next page:

1. $(R'O)_3P$ —($ArOCH_2CH_2\overset{+}{N}R_2CH_2CH_2X$; Arbuzov reaction[28])→ $ArOCH_2CH_2\overset{+}{N}R_2CH_2CH_2P(O)(OR')_2$ —(hydrolysis)→ Compound 1

2. $(R'O)_2P(O)H$ —(Michaelis-Becker reaction[29]; Na)→ $(R'O)_2P(O)^-Na^+$

either: XCH_2CH_2X → $X\text{-}CH_2CH_2\text{-}P(O)(OR')_2$

or: $ArOCH_2CH_2\overset{+}{N}R_2CH_2CH_2X$[24]

$X\text{-}CH_2CH_2\text{-}P(O)(OR')_2$ + $ArO\text{-}CH_2CH_2NR_2$ → $ArO\text{-}CH_2CH_2\text{-}\overset{+}{N}R_2\text{-}CH_2CH_2\text{-}P(O)(OR')_2$ —(hydrolysis)→ Compound 1

Ar = $3,4\text{-}Cl_2C_6H_3$

X = halogen

The project was to encompass:

(a) the investigation of the most effective synthesis of compound 1

(b) full characterization of compound 1

(c) study of the fragmentation of compound 1 to release plant growth regulating products

(d) investigation of possible reactions in competition with unimolecular fragmentation, eg. the Hofmann degradation[30,31]

(e) monitoring of the effect of pH and temperature on rate of fragmentation

1.3 Overview of studies undertaken

Since the synthesis of compound 1 promised to be a complex and time consuming process, it was considered wise to make a simple model compound which would give an indication of the ability of compound 1 to fragment via the Maynard and Swan reaction pathway. The chosen model, β-trimethylammonioethylphosphonic acid, carried simple methyl groups on the nitrogen atom rather than a substituted aryloxyalkyl function. The ability of a given alkylphosphonate to undergo fragmentation relies on the ability of the substituent at the 2-position to behave as a leaving group.[17] Me_3N^+-, on the 2-position of the model compound, was expected to have a comparable leaving group ability to $(C_6H_3Cl_2)OCH_2CH_2N^+R_2$- on compound 1. The model could therefore provide a realistic simulation of the reactivity of compound 1 towards Maynard and Swan fragmentation.

The model compound, $Me_3N^+CH_2CH_2P(O)(OH)O^-$ was successfully synthesised, then subjected to different alkaline media to measure the rate of its fragmentation to release trimethylamine,

ethylene and metaphosphate. The results obtained indicated that this compound is stable to alkali, even at elevated temperature and high pH. This frustrating result meant that, in order to obtain any measurement of Maynard and Swan fragmentation, modifications of the model compound were required. The indications were that compound 1 would not fragment to any significant extent, either.

Subsequent reactions embarked upon were aimed at the production of a β-trimethylammonioalkylphosphonate which would undergo fragmentation at a measurable rate.

M. J. Gregory et al. reported that the introduction of an alkyl group to the 2-position of 2-chloroethylphosphonic acid enhanced the rate of fragmentation by a factor of $10^{4.22}$ It was hoped that the addition of such an alkyl group to the model compound would result in a rate acceleration of a similar order of magnitude.

The synthesis of a modified model compound, β-trimethylammonio-pentylphosphonic acid was attempted. The synthetic approach employed was by reaction of trimethylamine with the diester, diethyl 2-chloropentylphosphonate (the ester form of the substrate was used in order to prevent fragmentation when the phosphonic acid is reacted with basic trimethylamine). Dehydrohalogenation, or elimination of HCl, was observed rather than substitution of the Cl function by Me_3N.

Experiments which followed were aimed at modification of diethyl 2-chloropentylphosphonic acid to cause the compound to be more susceptible to nucleophilic attack by NMe_3, and less likely to undergo elimination of HX.

It was expected that the replacement of the chlorine in diethyl 2-chloropentylphosphonate by a more effective leaving group such as iodine or bromine would favour nucleophilic substitution by NMe_3.[32] It requires more energy to rupture a carbon-chlorine bond than to break a carbon-iodine or carbon-bromine bond. More stringent reaction conditions, required to cause the Cl to depart from the substrate would favour dehydrohalogenation.[33]

The synthesis of diethyl 2-iodopentylphosphonate and diethyl 2-bromopentylphosphonate was attempted using numerous approaches:

Synthetic approaches employed to convert diethyl 2-chloropentylphosphonate to its 2-iodo and 2-bromo analogues

Synthesis of diethyl 2-iodopentylphosphonate

(a) using the 2-chloropentylphosphonate framework as substrate

1. by reaction of the diethyl ester with excess NaI in acetone solution.
2. by reaction of the unesterified substrate with excess NaI in acetone solution.
3. by reaction of unesterified substrate with HI.

(b) forming a C-P bond ab initio

1. by Michaelis-Becker reaction of $(EtO)_2P(O)^-Na^+$ with 1,2-diiodopentane.

Synthesis of diethyl 2-bromopentylphosphonate

1. by Michaelis-Becker reaction of $(EtO)_2P(O)^-Na^+$ with 1,2-dibromopentane.
2. by Arbuzov reaction of triethyl phosphite with 1,2-dibromopentane.

Where possible, reaction products were characterized and isolated. The required substitution products were not predominant: it appears that these β-substituted long chain alkylphosphonates are unreactive except for a tendency to undergo elimination of HX. A full discussion of synthetic approaches undertaken and results obtained is set out in chapter 2.

One of the attempts to produce diethyl 2-iodopentylphosphonate from diethyl 2-chloropentylphosphonate was by reaction with excess NaI in acetone solution. This method had been used successfully to convert 2-chloroethylphosphonic acid to 2-iodo~~pent~~eth ylphosphonic acid.[22] While no reaction took place per se (starting material was recovered in 100% yield), NaI in an acetone solution of the substrate was found to cause marked changes in the nmr spectrum of the phosphonate. This unusual phenomenon was studied in greater detail and an explanation of the possible interactions between the Na cation and the diethyl

2-chloropentylphosphonate in acetone solution is put forward in chapter 3.

CHAPTER 2

DISCUSSION

2.1 SYNTHESIS AND REACTIVITY OF A SIMPLE CHEMICAL MODEL OF 2-{N,N-DIALKYL-N-[2-(3,4-DICHLOROPHENOXY)ETHYL]AMMONIO}ETHYL PHOSPHONATE

It was decided to investigate the chemistry of β-trimethylammonioethylphosphonic acid, which is a simplified form of 2-{N,N-dialkyl-N-[2-(3,4-dichlorophenoxy)ethyl]ammonio}ethyl phosphonate (compound 1), the target bioregulating system of this project. If this model compound underwent Maynard and Swan[16] type fragmentation, it was hoped that the proposed bioregulator, compound 1,would react in a similar manner, thus performing its appointed function in a plant metabolic system. This would warrant an attempt at synthesis of this complex molecule.

Experimental procedures, therefore, began with the synthesis of the simplified chemical model.

2.1.1 Synthesis of β-trimethylammonioethylphosphonic acid[34]

The production of $Me_3N^+CH_2CH_2P(O)(OH)O^-$ was by way of four steps:

(i) Arbuzov reaction of triethylphosphite with 1,2-dibromo-ethane:[35]

$$(EtO)_3P + BrCH_2CH_2Br \xrightarrow[3h]{145^{\circ}C} BrCH_2CH_2P(O)(OEt)_2 + EtBr$$

77% yield

(ii) reaction of diethyl β-bromoethylphosphonate with dimethylamine:

$$BrCH_2CH_2P(O)(OEt)_2 + \text{excess } Me_2NH \xrightarrow[48h]{r.t.} Me_2NCH_2CH_2P(O)(OEt)_2$$

83% yield

$$+ Me_2\overset{+}{N}HBr^-$$

(iii) quaternisation with methyl iodide:

$$Me_2NCH_2CH_2P(O)(OEt)_2 + MeI \xrightarrow{r.t.} I^-Me_3\overset{+}{N}CH_2CH_2P(O)(OEt)_2$$

60% yield

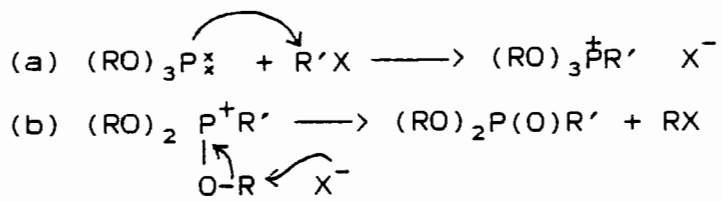
(iv) hydrolysis of ester to yield the required zwitterion:

$$Me_3\overset{+}{N}CH_2CH_2P(O)(OEt)_2 + 2H^+ \longrightarrow Me_3\overset{+}{N}CH_2CH_2P(O)(OH)O^- + 2\ EtOH$$

76% yield

<u>(i) the Arbuzov reaction</u>[36]

Trialkyl phosphites react with alkyl halides to produce phosphonate esters in a two stage process: (a) internal quaternisation of the phosphite by nucleophilic attack of phosphorus on the halide and (b), dealkylation of the alkoxyphosphonium cation by the displaced halide.



In most cases, it is not possible to isolate stable phosphonium salts of alkyl phosphites. With primary alkyl halides like 1,2-dibromoethane used in this synthesis, the reaction is bimolecular. If RX is more reactive than R'X, then a mixture of $(RO)_2P(O)R$ and $(RO)_2P(O)R'$ will result.

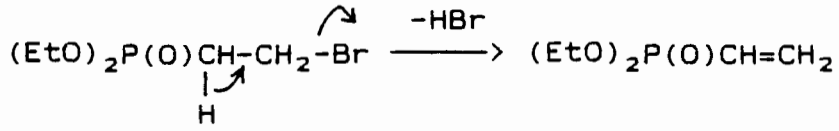
In the first step of the synthesis of the model compound, 1,2-dibromoethane and triethyl phosphite were heated to 145°C for three hours. In one pilot experiment, reagents were heated in a flask which had an air cooled condenser fitted above it, which in turn was connected to a cold trap for collecting escaped EtBr. The amount of EtBr collected was to be an indication of the progress of the reaction. Throughout three hours, no EtBr was collected, although ^1H nmr analysis of the reaction mixture indicated that some product had formed. EtBr (b.p 37-40°C) was clearly refluxing along with the higher boiling reagents and was therefore not escaping through the air-cooled condenser. The possibility of the isomerisation reaction

$$(EtO)_3P + EtBr \longrightarrow (EtO)_2P(O)\text{-}Et + EtBr$$

is increased when EtBr remains in the reaction solution. An experimental design was required which would aid the departure

of EtBr and at the same time prevent the evaporation of higher boiling components from the reaction mixture. The answer was to pump water heated to 50°C through the condenser above the reaction flask. At 50°C, EtBr would escape but 1,2-dibromoethane and triethyl phosphite would condense back into the reaction flask.

After three hours, unreacted 1,2-dibromoethane and triethylphosphite were removed from the mixture under reduced pressure leaving the required product, diethyl β-bromoethylphosphonate, in 77% yield. This was purified by high vacuum distillation (b.p. 99-106°C at 1mmHg). Some of the diethyl β-bromoethylphosphonate underwent β-elimination of HBr at the temperature required for distillation, to produce diethyl vinylphosphonate:



This process could be minimised by careful distillation under a high vacuum (high temperatures increase the probability of such eliminations).

^{1}H nmr and elemental analysis confirmed the production of the required Arbuzov product.

(ii) Preparation of diethyl β-dimethylaminoethylphosphonate

Dimethylamine (a freshly prepared 4.36 M solution in absolute ethanol) was reacted with the compound made in step(i). (Aqueous dimethylamine could not be used because of the possible hydrolysis of the ester function of the phosphonate in basic aqueous medium). The reaction mixture was stirred at room temperature: at the onset, evolution of heat was noted. After two days, removal of solvent yielded a viscous liquid and solid, identified spectroscopically as $Me_2NCH_2CH_2P(O)(OEt)_2$ and $Br^-HN^+(Me)_2CH_2CH_2P(O)(OEt)_2$, respectively. To deprotonate the solid product, Na_2CO_3 was added to the reaction residue which had been taken up in diethyl ether. The amount of Na_2CO_3 added was based on the assumption that phosphonate bromide salt was present in 100% yield, to maximize the extent of the deprotonation:

$$HN^+(Me)_2CH_2CH_2P(O)(OEt)_2Br^- + Na_2CO_3 \longrightarrow (Me)_2NCH_2CH_2P(O)(OEt)_2 + NaHCO_3 + NaBr$$

(required)

Subsequent vacuum filtration to remove solid material, followed by evaporation of solvent, left a clear liquid, identified as the desired product, diethyl β-dimethylaminoethylphosphonate, in 83% yield. Purification was delayed until the end of step(iii) in which a crystalline, and hence easier to purify, product was expected to be obtained.

(iii)Quaternisation with methyl iodide

The crude product from step(ii) was placed in CCl_4 and stirred with cooling with one equivalent of methyl iodide. The addition of this reagent was accompanied by prodigious evolution of heat. Within minutes the quaternised β-trimethylammonioethylphosphonate iodide precipitated. Recrystallization of the product from ethyl acetate and methanol was highly effective, yielding a crystalline solid (m.p. 156-159°C).

(iv)Hydrolysis of the ester function

To produce the required zwitterionic phosphonic acid, the phosphonate ester groups were hydrolysed by refluxing the quaternary salt prepared in step(iii) in 10 M HCl for 22 hours. The HCl was then removed by thorough evacuation at reduced pressure. Any remaining HCl was removed by the addition of aqueous silver oxide, which precipitated AgCl. This precipitate was extremely fine and its effective filtration from the reaction solution could not be achieved without the use of a filter aid (CELITE). The filter aid induces co-precipitation of finely suspended solids. H_2S gas was bubbled through the filtrate to produce further precipitation, consisting this time of Ag_2S which was also removed by filtration. Concentration of the remaining solution produced the zwitterion monohydrate, $Me_3N^+CH_2CH_2P(O)(OH)O^-.H_2O$, which was recrystallized as a white

solid from ethanol/methanol. The zwitterion, when protected from moisture, is stable for several months.

Having successfully completed the synthesis of the chemical model of our target bioregulator (see experimental section 5.1), we were now in a position to investigate its susceptibility to fragmentation in basic solution by way of the Maynard and Swan pathway.

2.1.2 Reaction of β-trimethylammonioethylphosphonic acid in two different basic media

(i) reaction in D_2O with NaOD as base

One hundred milligrams of zwitterionic β-trimethylammonioethylphosphonic acid monohydrate was dissolved in half a millilitre of D_2O containing 50µl of a 25% solution of $(Me)_4N^+OH$, and the ^1H nmr spectrum of the solution was recorded.

The Me_3N^+- function on the substrate gave a singlet at δ3.12 ppm, and the methyl protons of Me_4NOH gave another singlet at δ3.16 ppm. When, in a separate experiment, the solution in the nmr tube was spiked with a small quantity of Me_4NOH, the peak at δ3.16 ppm increased in height, confirming the assignment of the respective singlets in the nmr spectrum.

So little tetramethylammonium hydroxide was present in the D_2O solution, that the pH of the reaction mixture was neutral at this stage. The Me_4NOH served as an internal standard. A ratio

$$R = \frac{\text{peak height } Me_4N^+}{\text{peak height } Me_3N^+-}$$

could be measured to give an indication of the progress of the reaction once the pH of the solution was increased to alkaline. Under basic conditions, the substrate would be in the dianionic form:

$$Me_3\overset{+}{N}CH_2CH_2P(O)(OH)O^- \xrightarrow{\text{pH basic}} Me_3\overset{+}{N}\text{-}CH_2\text{-}CH_2\text{-}P(O)(\text{-}O^-)_2 + H^+$$

$$\xrightarrow[\text{Swan fragmentation}]{\text{Maynard and}} Me_3N + CH_2{=}CH_2 + PO_3^-$$

If fragmentation were to take place, the Me_3N^+- resonance at δ3.12 ppm would be expected to decrease in height as the volatile trimethylamine (b.p. 38°C) evaporated. R would increase, therefore, since the peak height of Me_4NOH at δ3.16 ppm would remain constant.

The reaction solution was made basic by the addition of 100µl of NaOD (a 40% solution) and the R values were measured over an extended period, as shown in the table below. After 24 hours, the nmr tube was incubated at 60°C.

Time	Temp (^{o}C)	R
0 hours	Room	0.619
24 hours	Room	0.589
29 "	60^{o}C	0.602
5 days	"	0.554
14 "	"	0.579
28 "	"	0.604
51 "	"	0.560
69 "	"	0.560
96 "	"	0.526
124 "	"	0.524
8 months	"	0.510

Table 2.1 Reaction of $Me_3\overset{+}{N}CH_2CH_2P(O)(O)_2^-$ with NaOD

Throughout the course of eight months the observed decrease in the R value was very small (ca. 18%), indicating very low conversion (see table 2.1). Clearly, this compound is reluctant to fragment under these conditions.

(ii) reaction in DMSO with NaH as base

It was hoped that improved results would be obtained in a different basic medium. It would be expected that the fragmentation reaction in dimethylsulphoxide solution using NaH as base would be of the order of 10^4 times faster than in D_2O with NaOD as base.[37] Perhaps the D_2O system did not yield fragmentation products because of solvation of the substrate, which might form a protective sheath around the substrate, thus impeding the attack of the base. In DMSO medium,no such solvation would occur.

$$Me_3\overset{+}{N}CH_2CH_2P(O)(OH)(O^-) \xrightarrow{CH_3S(O)CH_3/NaH \rightarrow Na^+CH_3S(O)CH_2^- + H_2} Me_3\overset{+}{N}CH_2CH_2P(O)(O^-)_2Na^+ \xrightarrow{CH_3S(O)CH_2^-} \text{fragmentation}$$

A ratio of 2.2 : 1 (sodium hydride : acid) is required in this reaction. One equivalent of NaH reacts with the OH function on the zwitterionic substrate to produce the dianionic form. Another equivalent of NaH reacts with the monohydrate associated with the phosphonic acid. An excess of 0.2 equivalents should provide rate enhancement of the reaction.

β-trimethylammonioethylphosphonic acid monohydrate was added to a solution of NaH in freshly distilled DMSO. Additions were done slowly, with cooling, under a flow of nitrogen gas, dried by conc. H_2SO_4 and P_2O_5.

The substrate was reluctant to dissolve in DMSO, but did form a fine suspension. The N_2 gas flow was stopped after the suspension had formed and a tube connecting the reaction vessel to a water-filled inverted flask in a water bath was attached in such a way as to collect any ethylene/trimethylamine gas which may evolve. Over a period of 5 days, no reaction took place. Experiments done at room temperature and 100°C yielded the same results. No gas evolved and the pH of the water bath remained neutral.

It was concluded from these experiments that β-trimethylammonioethylphosphonic acid is reluctant to fragment even under harsh pH and temperature conditions.

Modifications which would render the substrate more susceptible to fragmentation via the Maynard and Swan pathway were required.

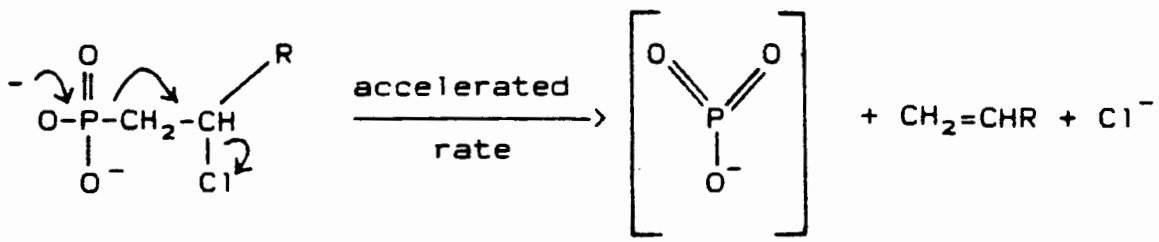
2.2 MODIFICATIONS OF THE MODEL COMPOUND

M. J. Gregory et al.[22] reported that the higher 2-chloroalkylphosphonic acids fragment in a Maynard and Swan type reaction at a rate about 10^4 times faster than that for 2-chloroethylphosphonic acid, as shown in table 2.2.

Table 2.2 First order rate constants for the fragmentation of $RCH(Cl)CH_2PO_3^{2-}$ at 26.5°C in 1 M KCl solution[22]

R	$10^2 k_{obs}/min^{-1}$
H	0.13
Bu^n	920
Me	1460

Given the evidence cited in chapter 1, it appears that the fragmentation described by Maynard and Swan is unimolecular. (The rate of the reaction is not so much affected by catalysis of nucleophiles or solvent effects, but dramatic changes in the rate are observed when the β-carbon atom of the phosphonate dianion carries an alkyl group).



The acceleration of the reaction rate on β-alkyl substitution could be due to relief of steric interactions in the transition state: bond lengthening as the concerted reaction proceeds may reduce atomic congestion in the substrate. In other words, loss of non-bonding energy of compression may lead to a reduction of the activation energy, producing "steric acceleration".[38]

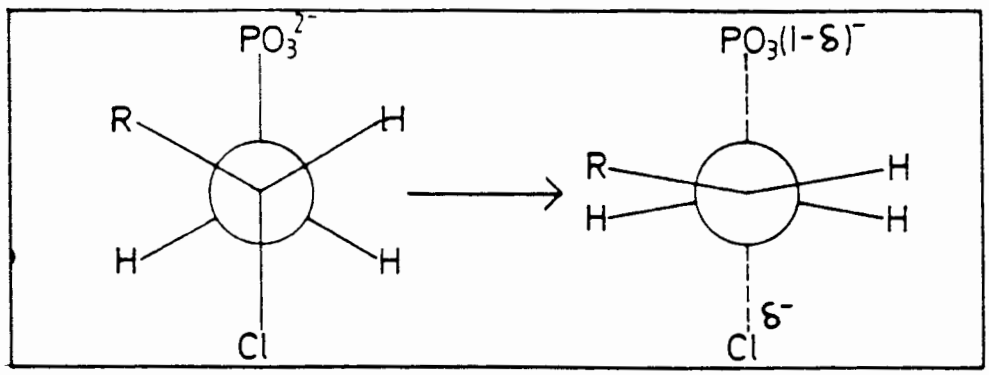


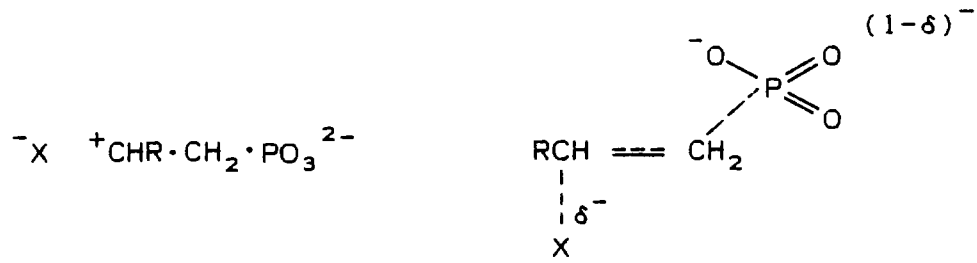
Fig. 2.1 Relief of steric hindrance between R and phosphonate by bond lengthening in the transition state.

Steric repulsions cannot be responsible entirely for rate acceleration, however, since the rate of reaction differs little when R = Bu^n and R = Me.

It is postulated[22] that the fragmentation of the phosphonate dianions proceed via a transition state in which the β-carbon atom carries a substantial positive charge. That is, C-X bond breaking is more advanced in the transition state than is π-bond formation. One extreme of this would be the carbonium ion, $X^-C^+HR-CH_2PO_3^{2-}$. π-bond formation in the transition state is thought to be small because any flow of electrons into the π-bond from the C-P bond fission would decrease the positive charge on the β-carbon which in turn should lower the sensitivity of the rate to β-substitution.

The kinetic polar effect of alkyl branching (on the β-carbon atom) on the reaction rate is comparable to that for alkyl branches on the α-carbon atom of a primary carbonium ion in SN1 reactions.[22] It is plausible that the β-carbon atom bears a positive charge which approximates to that on a primary carbonium ion.

It seems, therefore, that the transition state of the fragmentation reaction is a dipolar ion species rather than a charge-dispersed species.



DIPOLAR ION CHARGE DISPERSED

Carboxylic acid analogues of these phosphonates have also been studied, and similar transition states have been proposed for their fragmentation reactions.[39]

The above arguments attempt to rationalize the rate acceleration observed when alkyl substituents are included at the β-carbon atom of these 2-halogenoalkylphosphonates. Considering that fragmentation did not occur to any significant extent for the β-trimethylammonioethylphosphonic acid dianion, it was hoped that substitution of a methyl at the β-carbon group would accelerate the reaction rate to an extent which allowed it to be measured. The substrate which was required was β-trimethylammonioproylphosphonic acid, to be obtained in three synthetic steps:

(i) synthesis of 2-chloropropylphosphonic acid
(ii) esterification of the acid to produce diethyl 2-chloropropylphosphonate
(iii) reaction of the trimethylamine with the ester (the esterification step is neccessary to prevent the phosphonic acid

from fragmenting in the presence of the basic amine reagent in step(iii) before substitution of the chlorine by the trimethylamino group on the β-carbon atom can occur).

2.2.1 Preparation of 2-chloropropylphosphonic acid

Attempts to reproduce the method used in the literature[22] to prepare 2-chloropropylphosphonic acid were unsuccessful (see experimental section 5.4). Propene gas is expected to react with phosphorus pentachloride and phosphorus pentoxide in benzene solution yielding 2-chloro-propylphosphonic dichloride which is isolated by distillation and reacted with water to give the product (lit. m.p. 85-87°C).

The only modification of the literature method which was employed was that no commercial source of propene gas was used. Propene gas was generated from the reaction of concentrated sulphuric acid with isopropanol.[40] Isopropyl alcohol is more successful in the production of propene than n-propanol because the reaction with sulphuric acid involves a carbonium ion intermediate and a secondary carbonium ion (such as that produced from isopropyl alcohol:CH_3-C^+H-CH_3) is more stable than its primary analogue.

Although quantities of reagents to produce twenty times the required amount of propene gas were used and a steady flow of propene into the PCl_5/benzene solution was observed, there was

no evidence that any addition product formed. Distillation of the reaction mixture after eight hours yielded solvent and $POCl_3$. The reaction was repeated several times, taking care to reproduce the reaction conditions described, but results were consistent with those of the first attempt. It was concluded that, contrary to the literature report, propene gas takes longer to be absorbed into the reaction suspension than anticipated.

Rate enhancement of the fragmentation reaction of 2-chloroethylphosphonic acid by substitution of a methyl group at the β-carbon atom and that for an n-butyl group is of the same order of magnitude. It was therefore decided to use another higher analogue of 2-chloroethylphosphonic acid to produce a β-trimethylammonioalkylphosphonate dianion which would fragment at a measurable rate. 2-chloropentylphosphonic acid was decided upon because it can be prepared from 1-pentene, which is a liquid, so practical problems associated with the handling of gaseous reagents would be circumvented.

2.2.2 Preparation of 2-chloropentylphosphonic acid

No account of the synthesis of the pentylphosphonic acid was available in the literature. The method employed was as for the higher analogue 2-chlorohexylphosphonic acid.[22] The synthesis described in the literature works very well but has the drawback that the phosphonic acid is produced in low yields

(13%)-large quantities of starting material are needed to obtain sufficient product.

The 2-chloropentyl derivative was prepared from 1-pentene and PCl_5 which were stirred overnight in benzene. The acid dichloride was not isolated, instead the reaction was quenched by pouring the mixture onto ice. This step of the reaction was highly exothermic and there was rapid evolution of acrid gaseous byproducts:

$$C_3H_7CH(Cl)CH_2\text{-}P(O)Cl_2 + 2H_2O \xrightarrow{0^\circ C} C_3H_7CH(Cl)CH_2P(O)(OH)_2 + 2HCl$$

Aqueous and benzene layers separated out and the product was isolated from the latter as a brown oil. This residue was converted into solid by addition of cold petroleum ether (b.p. 60-80°C). It was extremely difficult to obtain pure recrystallized product, since these long chain 2-halogenoalkyl-phosphonic acids are low melting solids. In a variety of solvents they come out of solution as sticky oils rather than crystalline precipitates. Often the preparation of the dicyclohexylamine salts of low melting organic acids is a useful technique to isolate pure products, since these salts are sometimes highly crystalline. This was not the case for 2-chloropentylphosphonic acid. After many attempts at recrystallization, it was found that the best results were obtained by dissolving the crude residue of the phosphonic acid in boiling chloroform and then dousing the hot solution in

chilled petroleum ether (b.p. 30-40°C). This produced a white solid precipitate (m.p. 87-89°C).

To synthesize β-trimethylammoniopentylphosphonic acid from 2-chloropentylphosphonic acid, it is necessary that the latter is in an esterified form for reaction with trimethylamine.

2.2.3 Esterification of 2-chloropentylphosphonic acid

(i) Esterification was attempted first by reaction with thionyl chloride to form the 2-chloropentylphosphonic dichloride, which was then to be reacted with dry ethanol and dry triethylamine in benzene to yield the required product. This particular approach had the advantage that by-products of the first step of the reaction are gases and are therefore easily removed from the reaction solution. The esterification step was expected to go to completion and to be irreversible, resulting in good product yields.[41]

$$C_3H_7CH(Cl)CH_2P(O)(OH)_2 \xrightarrow[SOCl_2]{\text{reflux in}} C_3H_7CH(Cl)CH_2P(O)Cl_2 + SO_2 + HCl$$

$$C_3H_7CH(Cl)CH_2P(O)Cl_2 + 2EtOH(dry) + 2Et_3N(dry) \xrightarrow[2h]{60^\circ C}$$

$$C_3H_7CH(Cl)\text{-}CH_2P(O)(OEt)_2 + Et_3\overset{+}{N}HCl^{-}(ppt)$$

The dichloride intermediate was not purified before the second step of the reaction, but unreacted thionyl chloride was removed leaving an oily residue which was used for further reaction.

Isolation of the product proved to be difficult-although a precipitate, presumably $Et_3N^+HCl^-$, formed, the ester gave a poorly resolved ^1H nmr spectrum and charred even on careful distillation. Characterization of the reaction products was therefore not possible.

(ii) Another more convenient method to convert the phosphonic acid to the ester form was by reaction with triethyl orthoformate. This reagent had been used successfully to esterify sulphonic acids,[42] so it was expected that similar results for analogous phosphonic acids would be observed.

$$C_3H_7CH(Cl)CH_2P(O)(OH)_2 + 2HC(OEt)_3 \xrightarrow[2h]{105^oC} 2EtOH + 2HCO_2Et + C_3H_7CH(Cl)CH_2P(O)(OEt)_2$$

The substrate was dissolved in triethyl orthoformate and heated to 105°C. The progress of the reaction was monitored by ^1H nmr analysis of volatile byproducts, ethanol and ethyl formate, which were allowed to escape from the reaction flask, then were collected in a cold trap. The ^1H nmr spectra recorded indicated that the reaction was indeed progressing as anticipated. The rate of collection of volatiles in the trap diminished after a couple of hours, indicating that the process was approaching completion. The crude reaction residue, on removal of remaining triethyl orthoformate and volatile byproducts, gave 75% yield by mass. This synthetic approach proved to be as successful as for the reported sulphonic acid

systems. Purification of the ester was not without some difficulties, since distillation of such a high boiling liquid meant that a large proportion of the crude product was lost in polymerisation reactions and charring even though precautions were taken to prevent superheating of the distillation flask. In fact, although a pure fraction was isolated (b.p. 99-102^{o}C at 1mmHg), the product yield dropped to 31% in the high vacuum distillation step alone.

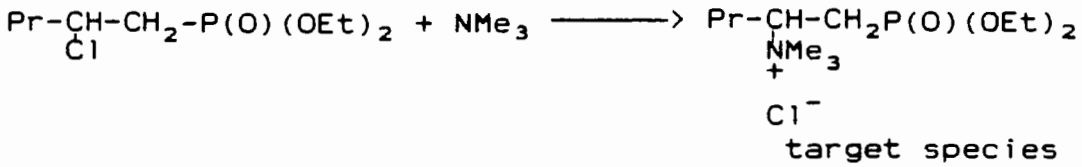
A milder purification procedure, such as silica gel column chromatography, was clearly neccessary. Little of the applied sample was lost on the column and pure product identified by elemental analysis and ^{1}H, ^{31}P,and ^{13}C nmr spectroscopy, was isolated as a viscous, colourless liquid. An eluting solvent consisting of 80% chloroform, 15% acetone and 5% toluene was employed, since in this system the target ester had an R_f of 0.7 in thin layer chromatography tests which were used as a column monitoring technique. Other spots on the t.l.c plates of the unpurified ester were at R_f values of ~0.6 and near the origin (R_f = 0-0.2), presumably due to diethyl 1-pentenylphosphonate, obtained from elimination of HCl from the product, and polymerisation species, respectively. It is likely that both of these side products would form to some extent during heating of the reaction mixture.

Having successfully prepared the diethyl 2-chloropentyl-phosphonate ester, the substrate was now protected against fragmentation in base.

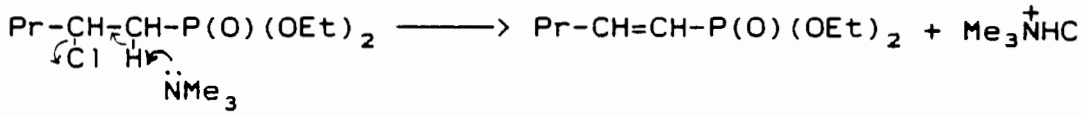
2.2.4 Reaction of trimethylamine with diethyl 2-chloropentyl-phosphonate.

The next step was to react the ester with trimethylamine to replace the chlorine function on the β-carbon atom by a $-N^{+}Me_3$ group. Several possibilities exist for reaction of the amine with the phosphonate, however:

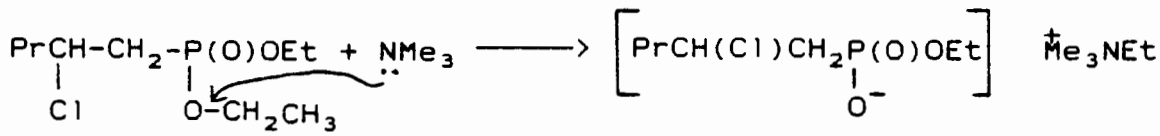
(a) product resulting from SN2 at the β-carbon atom:



(b) elimination of HCl (E2)



(c) SN2 at the substrate ester function:



Pathway (a) would yield the required product which could then be hydrolysed in a similar manner to the hydrolysis of diethyl β-trimethylammonioethylphosphonate iodide to produce β-trimethylammoniopentylphosphonic acid.

Diethyl 2-chloropentylphosphonate was reacted with trimethylamine in dry acetonitrile solution in an ampoule which was incubated in a 60°C water bath for one day. After this period, $Me_3N^+HCl^-$ precipitated out of solution as white needle-like crystals, which were identified by ^1H nmr analysis and by comparison with a standard sample of Me_3NHCl.

After removal of the acetonitrile, the reaction residue was partitioned ~~separated~~ between D_2O and $CDCl_3$. Subsequent ^1H nmr studies indicated that pathway (b) was the dominant reaction. The D_2O layer contained traces of the substitution product of pathway (a), ie. $C_3H_7CH(N^+Me_3)CH_2P(O)(OEt)_2Cl^-$, and additional Me_3NHCl. The $CDCl_3$ layer contained diethyl 1-pentenylphosphonate in 60% yield.

The appearance of two multiplets integrating for one proton each at δ5.60 ppm and δ6.70 ppm and the disappearance of the signals for the protons on the α and β carbon atoms of the phosphonate in the ^1H nmr spectrum of the $CDCl_3$ layer indicated that the product contained vinylic hydrogens, confirming that reaction had occurred via pathway (b).

The ^{1}H nmr spectrum of the D_2O layer contained signals for the protons of the substrate (integrating for trace amounts) with two extra singlets at δ2.90 and δ3.08 ppm due to Me_3NHCl and Me_3N^{+}- respectively.

No evidence of nucleophilic substitution at the ester function of the phosphonate (pathway(c)) was evident. The loss of HCl from the substrate carbon skeleton was the predominant reaction.

Competition between elimination and nucleophilic substitution was encountered in this system, therefore. Reaction conditions were required to be adjusted in such a way that would favour substitution over elimination at the β-carbon. The latter tends to prevail over SN2 mechanisms where reaction conditions are harsher, i.e. the higher temperature at which a reaction takes place, the more likely that elimination will occur.[33]

A reason for this is perhaps that the equation for free energy of activation $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$ ($\Delta H^{\ddagger}$ = enthalpy of activation; $\Delta S^{\ddagger}$ = entropy of activation; T = temperature)has a more favourable entropy term, $T\Delta S^{\ddagger}$, in the case of elimination, since more particles are produced during the course of the reaction. The number of particles produced during a substitution reaction does not increase. As the temperature rises, the $T\Delta S^{\ddagger}$ term for the elimination reaction will increasingly outweigh a less favourable $\Delta H^{\ddagger}$, resulting in a reduction in the free energy of activation, $\Delta G^{\ddagger}$.[33]

The trimethylamine reaction was repeated at room temperature, but elimination occurred to the same extent as for reaction at 60°C.

A change in the leaving group of the substrate to a softer, more polarisable group such as iodine should make the substrate more susceptible to the SN2 mechanism. Iodine is a better leaving group than chlorine,[32] requiring milder conditions for rupture of a C-X bond in many systems (X = halogen). It was expected that, if chlorine was substituted by iodine at the β-carbon atom of the substrate, reaction with trimethylamine would increase yield of substitution product and diminish the extent to which HX is eliminated from the pentyl chain on the phosphonate.

2.2.5 Conversion of diethyl 2-chloropentylphosphonate to its 2-iodo analogue.

The conversion of 2-chloroethylphosphonic acid to 2-iodoethylphosphonic acid is easily achieved by refluxing the former in acetone with a three-fold excess of NaI for 24 hours.[22]

(i) The analogous system with diethyl 2-chloropentylphosphonate as substrate gave no reaction whatsoever, even though excess of NaI in the solution was increased until saturation point and the reaction mixture was allowed to reflux for several days (see experimental section 5.9).

At first it was thought that a reaction had indeed taken place since the ^{1}H nmr spectra of aliquots from the reaction flask showed significant changes, particularly in the region of the CH_2-P signal. The effects observed proved to be due to the presence of NaI in the samples. Once the salt had been removed, only starting material remained. This surprising result inspired further investigation of the phenomenon by detailed nmr studies. The associations of NaI and diethyl 2-chloropentylphosphonate in acetone solution are discussed in chapter 3.

(ii) Note that the publication which described the easy conversion of a chlorine substituent to an iodine group used 2-chloroethylphosphonic acid, not an ester, as the substrate for the reaction. In order to reproduce as similar a set of reaction conditions as possible, the substrate for reaction with NaI was changed to the unesterified 2-chloropentylphosphonic acid which had been made previously (see experimental section 5.5). Although the reaction mixture was heated to reflux temperature of acetone for 24 hours, as prescribed, ^{1}H nmr analysis revealed no changes and elemental analysis indicated that starting material had not converted to 2-iodopentylphosphonic acid.

(iii) G. K. Fedorova et al[43]. reported the synthesis of 2-iodo-alkylphosphonic acids by reaction with hydriodic acid:

$$RCH(Cl)CH_2P(O)OH_2 \xrightarrow[\text{reflux for 5h}]{57\%\ HI} RCH(I)CH_2P(O)(OH)_2$$

The products were described as crystalline solids, stable to elimination of HI on addition of alkali. Following the procedure in this publication, another attempt to produce 2-iodopentylphosphonic acid was made. 2-chloropentylphosphonic acid was allowed to reflux in 57% HI for 17 hours. The volatile products were removed using a high vacuum pump, leaving a dark residue. This was dissolved in diethyl ether and decolourised with aqueous sodium thiosulphate by removal of iodine.

$$2S_2O_3^{=} + I_2 \longrightarrow 2I^- + S_4O_6^{=}$$

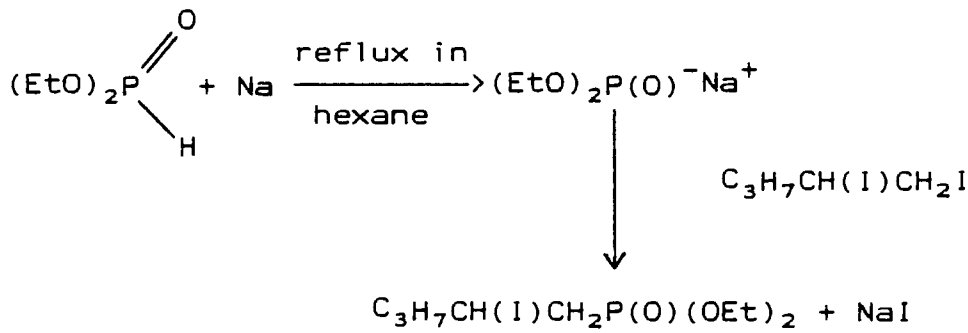
The ethereal layer was dried and stripped of solvent, leaving a sticky residue. The literature recommended the use of diethyl ether/petroleum ether or benzene/decane as solvent systems for recrystallization, but all attempts to obtain pure product were unsatisfactory: the residue was taken up in a variety of solvents and recrystallized, but the solid precipitates were not crystalline. Attempts to make the monoaniline salt and the dicyclohexylamine salts of the phosphonic acid were also

unsuccessful, giving elemental analysis which indicated the presence of impurities in the samples. Reference to the experimental chapter (section 5.12) will reveal that the crude phosphonic acid gave elemental analysis which was close to the theoretically expected values. Although ^{1}H nmr spectra were poorly resolved, it seemed that all required signals were apparent. It was difficult to assess by ^{1}H nmr whether a reaction had taken place - ^{1}H nmr spectra of 2-iodoalkyl-phosphonates are very similar to those of their 2-chloroalkyl analogues.[43] Considering the difficulties experienced in isolating an unequivocally pure diethyl 2-iodopentylphosphonic acid , it was decided to continue to the next reaction step (esterification of the phosphonic acid to obtain diethyl 2-iodopentylphosphonate) in the hopes that this product would be isolated and characterized more easily.

(iv) "Crude 2-iodopentylphosphonic acid" was esterified by reaction with triethyl orthoformate, as described above for 2-chloropentylphosphonic acid (see experimental section 5.13). The resulting product was purified by silica gel column chromatography using chloroform : acetone (4:1) as eluting solvent. The major product proved to be pure diethyl 2-chloropentylphosphonate, with trace amounts of diethyl 1-pentenylphosphonate. Although the esterification process had been as successful as before, substitution of chlorine by iodine in the substrate had never taken place.

Clearly, practical impediments of this substitution reaction were more serious than indicated in the publications used. Other approaches to the synthesis of these iodine substituted compounds were required.

(v) One possibility was via the sodium salt of diethyl phosphite which is reacted with appropriate dihaloalkane to produce 2-iodopentylphosphonate directly (Michaelis-Becker reaction):[29,44]



This reaction first required preparation of 1,2-diiodopentane (see experimental section 5.14).

Preparation of 1,2-diiodopentane[45] Iodine reacts with a two-fold excess of 1-pentene in the liquid phase to give 1,2-diiodo-pentane by an addition reaction across the double bond of the alkene.

$$I_2 + 2C_3H_7CH{=}CH_2 \rightleftharpoons C_3H_7CH(I)CH_2(I) + C_5H_{10}$$

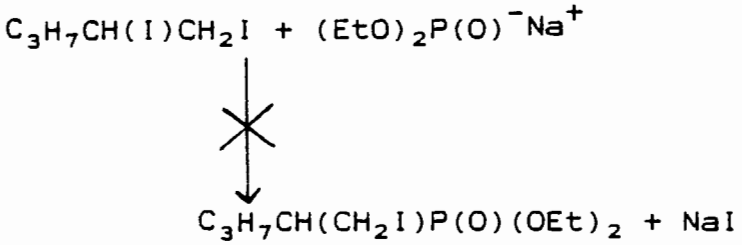
(100% yield, based on I_2)

The reaction was slightly exothermic at first, so during the addition of crystals of iodine to 1-pentene the reaction solution was cooled in an ice-salt bath. I_2 was allowed to dissolve in small quantities at a time, so that the solution remained colourless and little heat was generated. Once all the iodine had been absorbed into the solution, the mixture was stirred for an hour at room temperature.

The ^1H nmr spectrum of 1-pentene has a series of multiplets from δ4.70 to δ6.12 ppm which are the resonances of the three vinyl hydrogens of the olefin functional group. The spectrum of the reaction mixture had an additional series of multiplets from δ3.40 - δ4.63 ppm which may be ascribed to the three protons of the $-CH(I)-CH_2(I)$ group of the product. The heights of the integration curves for these two sets of multiplets were equal, indicating that the reaction solution consisted of 50% 1,2-diiodopentane and 50% unreacted 1-pentene. The twofold excess of 1-pentene is neccessary in order to dissolve all the iodine: any smaller excess leaves some of the iodine unreacted. This is detectable by a yellow tinge to what should be a clear, colourless solution. The reaction temperature cannot be elevated because the equilibrium (above) shifts back to increase the proportion of product which decomposes to 1-pentene and iodine once more. This decomposition occurs even at room temperature at a slow rate, so freshly prepared solutions should be used in further experiments. The presence of 1-pentene in the reaction mixture should not interfere with the Michaelis-

Becker reaction of 1,2-diiodopentane with the sodium salt of diethyl phosphite, so it was not deemed neccessary to isolate the substituted alkane from the reaction mixture.

The possibility that the dihaloalkane would react via the iodine on the C[2] atom rather than that on the C[1] atom to form an isomer of the required product was not ruled out as a reaction option, but results obtained indicated that this did not take place.



The C[2] iodine atom would be expected to be more sterically hindered than its C[1] counterpart and therefore less accessible for reaction.

The procedure for the Michaelis-Becker reaction was as follows:

Na metal was added in small, freshly sliced sections to a solution consisting of diethyl phosphite in dry hexane under an inert atmosphere of dry nitrogen. The last few pieces of sodium were reluctant to dissolve (the rate of absorption of Na decreases as the reaction approaches completion), so the reaction mixture was warmed to hasten the disappearance of

dissolving Na towards the end. The dihaloalkane mixture (50% 1,2-diiodopentane and 50% 1-pentene) was added dropwise to the solution at room temperature. After three hours of refluxing, the solution was left to stand overnight. The mixture was then washed with water to remove any salt product. The hexane layer produced a small amount of residue (2% by weight of expected yield) which appeared to consist of 74% unreacted diethyl phosphite and 26% of the required species. At such low yields, the ^{1}H nmr spectrum was poorly resolved, but all required signals were apparent to some extent. Assignment of peaks for the iodo-substituted product was tentative and detailed characterization was not attempted (see experimental section 5.15).

After attempting many times to synthesize the iodo-substituted phosphonate by five different reaction pathways (i-v), it was decided to abandon further attempts and spend time on the preparation of 2-bromopentylphosphonic acid (or its diethyl ester):

• Bromine, like iodine, is a better leaving group than chlorine, so the argument set out above that SN2 reactions would be favoured over E2 reactions with a modified substrate still applies here. (That is, it was hoped that reaction of the bromine-substituted phosphonate with trimethylamine would yield diethyl β-trimethylammoniopentylphosphonate rather than diethyl 1-pentenylphosphonate).

• In terms of chapter 3, it would be interesting to compare the effect of NaI on the ^1H nmr spectrum of diethyl 2-chloropentylphosphonate with the effect on its 2-bromo analogue.

• reactions described above which yield unsatisfactory results might produce better results with bromine reagents.

2.2.6 Preparation of diethyl 2-bromopentylphosphonate

(i) The Michaelis-Becker reaction of 1,2-dibromopentane with the sodium salt of diethylphosphite was performed by an analogous reaction to that done with 1,2-diiodopentane.

$$(EtO)_2P(O)H + Na \xrightarrow[\text{reflux temp.}]{\text{hexane}} (EtO)_2P(O)^-Na^+$$

$$(EtO)_2P(O)^-Na^+ \xrightarrow{C_3H_7CH(Br)CH_2Br} C_3H_7CH(Br)CH_2P(O)(OEt)_2 + NaBr$$

Preparation of 1,2-dibromopentane The preparation of 1,2-dibromopentane was by the same procedure as for 1,2-diiodopentane (see experimental section 5.16). Br_2 liquid was added to 1-pentene in a 1:1 molar ratio to yield 100% disubstituted haloalkane. This result was in contrast to the preparation of the iodoalkane which yielded only 50% of product at the most, leaving 50% of the alkene unreacted. A possible reason for this is that iodine crystals are less soluble in 1-pentene than bromine liquid is.

The addition of Br_2 liquid to 1-pentene is highly exothermic (may even be termed explosive) and should be be done with extreme caution and effective cooling. The product is easily identified by ^1H nmr analysis. The protons of C[1] and C[2] atoms give rise to a multiplet at $\delta 3.33$ - $\delta 4.70$ ppm.

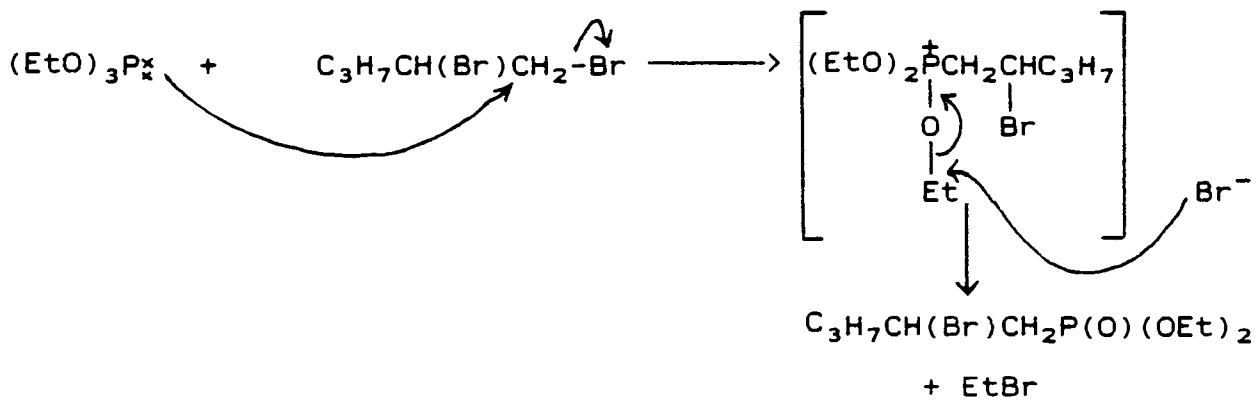
Na was added to diethylphosphite in hexane as for the Michaelis-Becker reaction described previously. The mixture was reacted with 1,2-dibromopentane (added dropwise with stirring). After three hours of refluxing, the flask was left to stand overnight, during which time a small amount of white precipitate formed, presumed to be NaBr. After washing the reaction mixture with a small volume of water, the organic layer was dried and stripped of solvent. This layer appeared to consist mainly of unreacted 1,2-dibromopentane, with a trace of some uncharacterized species which gave a broad multiplet from $\delta 2.46$ - $\delta 3.03$ ppm in the ^1H nmr of the reaction residue. Elemental analysis was consistent with these results:

	%C	%H
Required for 1,2 dibromopentane	26.12	4.38
Required for diethyl 2-bromopentylphosphonate	37.65	7.02
Found	29.40	5.10

If the uncharacterized species is diethyl 2-bromopentylphosphonate, it is present in only ~12% yield. Clearly, a more efficient synthetic approach was required.

(ii) trialkyl phosphites react with alkyl halides to produce phosphonate esters via the Arbuzov reaction, as was seen at the beginning of chapter 2 (refer to the synthesis of the diethyl β-bromoethylphosphonate).

Synthesis of diethyl 2-bromopentylphosphonate was embarked upon using the Arbuzov reaction as an alternative pathway to the Michaelis-Becker reaction. The proposed reaction is shown below:

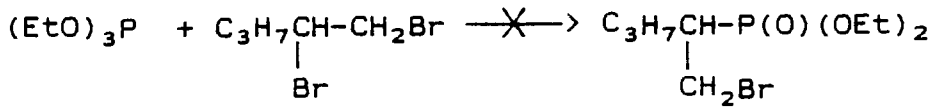


Relative reactivity of alkyl halides (RX) in the Arbuzov reaction is quoted as

$$MeX > 1^{o} > 2^{o}$$ [46]

i.e. primary alkyl halides are observed to be more reactive than secondary alkyl halides. It would be expected, therefore, that

the above reaction would take place rather than the production of the isomer below:



The method employed for the Arbuzov synthesis was the same as that for diethyl 2-bromoethylphosphonate.

1,2-dibromopentane and triethyl phosphite were stirred together for one day in an oil bath heated to 200° C. By attaching a condenser above the reaction flask through which water heated to 50°C was pumped, EtBr, a side product, was allowed to escape from the reaction vessel. It was trapped by condensation in a water-cooled condenser which had a dry ice/acetone trap fitted to it. By measuring the yield of EtBr accumulated, the progress of the reaction could be monitored. Removal of EtBr from the reaction solution minimizes the possibility of its reaction with remaining triethyl phosphite. 62% of the expected yield of EtBr was collected in the cold trap, indicating that the reaction had gone to that extent at least. The identity of EtBr was confirmed by ^{1}H nmr analysis.

On removal of volatiles from the reaction mixture, a yellow liquid remained as residue, which proved to consist of some mixture of products and unreacted alkyl halide. This residue

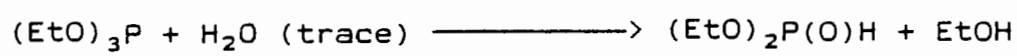
was applied to a silica gel column, and, using chloroform as eluting solvent, was separated into a set of fractions containing 1,2-dibromopentane and another set containing what appeared to be 52% diethyl 1-pentenylphosphonate and 48% diethyl 2-bromopentylphosphonate (according to ^{1}H nmr analysis). 73% of the sample was recovered from the column.

While column chromatography assisted in the separation of unreacted 1,2 dibromopentane from reaction products, it hampered isolation of the required 2-bromo-substituted phosphonate since some of the sample seemed to decompose on the column. This was most clearly illustrated by ^{31}P nmr analysis: the spectrum of the pre-column crude sample had fewer peaks than the spectrum obtained after the sample had eluted from the column. Phosphorus-containing species which gave rise to new resonances in the ^{31}P nmr spectrum were being formed on the column.

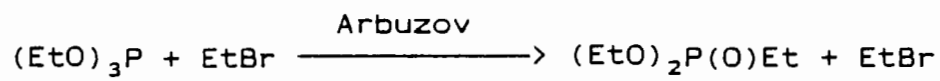
The reaction mixture is clearly more complex than anticipated and could consist of a variety of components many of which would give similar ^{1}H nmr resonances. In other words, the ^{1}H nmr spectrum of, for example, fraction no. 16 from the column (see experimental section 5.18) may be due to a mixture of compounds whose signals are superimposed on each other, making analysis of reaction products more difficult.

Reactions which could have taken place, either in the reaction flask or on the column, in competition with the required reaction are the following:

(1) hydrolysis of triethyl phosphite to yield diethyl phosphite

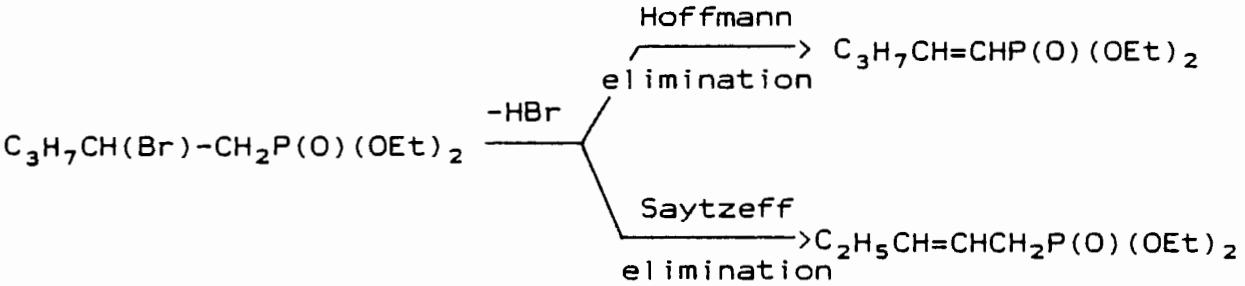


(2) isomerisation of triethyl phosphite

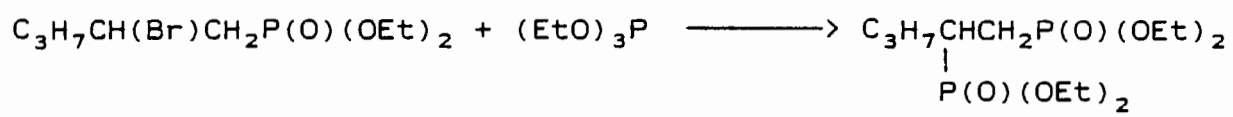


(3) Arbuzov reaction at the C[2] position

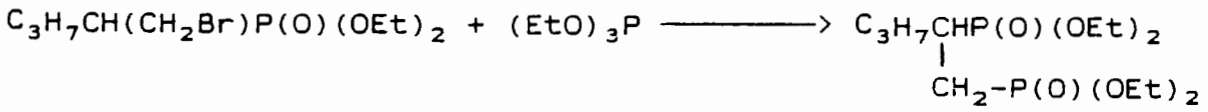
(4)elimination of HBr from diethyl 2-bromopentylphosphonate[30,31]



(5) Further reaction of triethyl phosphite with Arbuzov products to yield diphosphonate products



OR



With such a wide variety of possible products it was difficult to assess the exact composition of the reaction mixture. ^{31}P nmr gave an indication of the number of phosphorus-containing compounds present in the sample. The task of assigning peaks was made easier by the recording of ^{31}P nmr spectra of known compounds. Some of these standards could be prepared in separate experiments, and some were commercially available.

Reaction no.	Name of standard	Source
1	diethyl phosphite	commercially available
2	diethyl ethylphosphonate	$(EtO)_3P + EtI$ [a]
3	———	———
4	1-pentenylphosphonate	$C_3H_7CH(Cl)CH_2P(O)(OEt)_2 + NMe_3$ [b]
5	———	———

Table 2.3 Standards prepared for ^{31}P nmr analysis
Notes: (a) for procedure see experimental section 5.19
(b) see experimental section 5.8

With the aid of these standards, some of the peaks in the spectrum of the crude Arbuzov reaction mixture were assigned (See table 2.4 below).

δ (ppm) relative to 89% H_3PO_4	Reaction number	Assignment
34.26	2	diethyl ethylphosphonate
28.65	–	unassigned
26.28	Arbuzov	diethyl 2-bromopentylphosphonate[b]
19.41	4	1-pentenylphosphonate[c]
7.78	–	unreacted triethylphosphite
0.41	–	unassigned
-0.61[a]	4	2-pentenylphosphonate[c]

Table 2.4 ^{31}P nmr spectrum of product mixture of the Arbuzov reaction $(EtO)_3P + C_3H_7CH(Br)CH_2Br \longrightarrow ?$

Notes: (a) negative ppm: upfield of H_3PO_4

(b) tentative assignment based on the ^{31}P chemical shift of diethyl 2-chloropentylphosphonate.

(c) tentative assignment based on standard (see table 2.3). 2-pentenylphosphonate, if present in the ^{31}P nmr spectrum of the standard, is a minor component of the mixture.

The unassigned peaks are probably due to the other reactions mentioned (1, 3 and 5) but unambiguous conclusions cannot be drawn from the data available, since standards are not available for these reactions. Note that reaction no. 5 would yield two ^{31}P nmr peaks for one species.

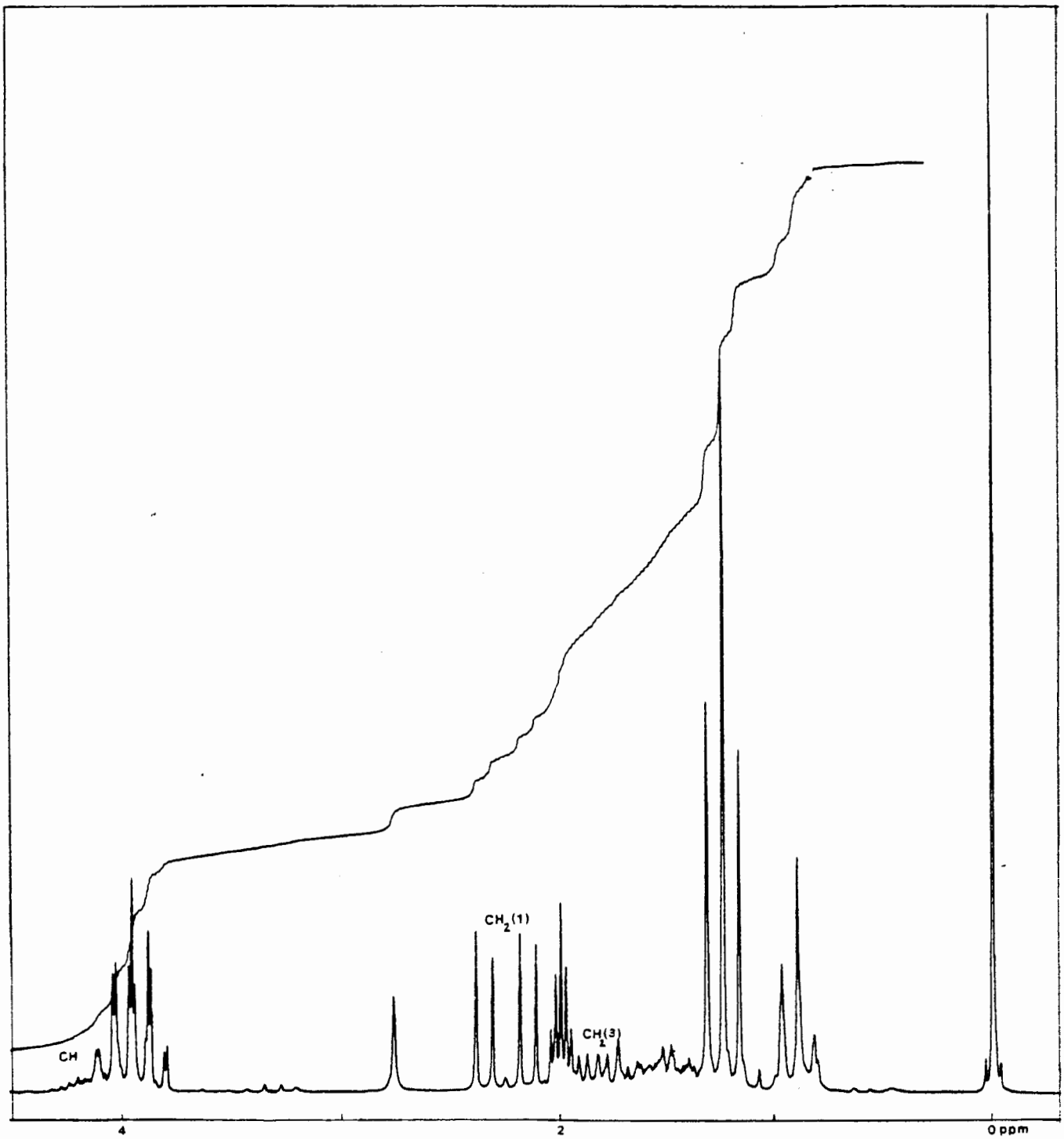
It would appear that the required product, diethyl 2-bromo-pentylphosphonate can be made, but its isolation and purification from the reaction mixture would be a time-consuming task with little reward in terms of product yield.

CHAPTER 3

NMR STUDY OF DIETHYL 2-CHLOROPENTYLPHOSPHONATE

3.1 Observations (using a 90 MHz BRUCKER Spectrometer)

2-chloroethylphosphonic acid is easily converted to 2-iodoethylphosphonic acid when refluxed with 2 moles of sodium iodide in acetone for 24 hours.[22] On the basis of this reaction, conversion of diethyl 2-chloropentylphosphonate to diethyl 2-iodopentylphosphonate was attempted using the same method. To ensure maximum formation of the iodo-substituted phosphonate, a five-fold excess of sodium iodide was used and the reaction was allowed to continue at reflux temperature for longer than a day. The ^{1}H nmr spectrum of the required product would be expected to be very similar to that of the starting material, with perhaps the most marked difference observed for the CH[2], and, possibly for the CH_2[3] and the CH_2[1] protons. Since the first signal is masked by the signals of the ester methylene groups (see spectrum 3.1) and the second forms a part of the multiplet of the ethylene group at the propyl substituent, we focused our attention on the possible changes observed for the signal of the CH_2-P group. Indeed, this signal was different in the nmr spectrum of the reaction mixture (diethyl 2-chloropentylphosphonate and five-fold excess of NaI in acetone-d_6) which led us to the conclusion that the reaction had gone to completion. However, when the supposed product was extracted into chloroform and isolated, it was discovered that starting material had been



Spectrum 3.1 90 MHz ^{1}H nmr spectrum of diethyl 2-chloropentylphosphonate in acetone-d_6

recovered and no reaction had taken place at all. These results are shown in the following table:

(b) ^{1}H nmr signal	CH_3[5]	CH_3[3′]	CH_2-CH_2	CH_2[1]	CH_2[2′]; CH[2]	(a)
δ(ppm)	0.92	1.27	1.40-1.98	2.29	4.05	A
	0.92	1.30	1.42-2.03	2.44	4.15	B
	0.92	1.27	1.41-1.98	2.31	4.06	C
no. of peaks	3	3	multiplet	4	multiplet	A
	3	3	multiplet	8	multiplet	B
	3	3	multiplet	4	multiplet	C
J_{H-H}/Hz	8	8		8	8	A
	8	8		8 ; 4	8	B
	8	8		8	8	C
J_{H-P}/Hz				21		A
				21		B
				21		C
down-field shift (B-A) Δδppm	0	0.02	0.02-0.05	0.15	0.10	

Table 3.1 ^{1}H nmr signals for the reaction of diethyl 2-chloro-pentylphosphonate with 5 moles NaI in acetone-d_6

Notes: (a) A. $C_3H_7CH(Cl)P(O)(OCH_2CH_3)_2$ in acetone-d_6
B. A + 5NaI after 3 days at 36°C
C. B after NaI has been removed
(b) Numbering of C atoms: 1-5 away from P down the pentyl chain; C[2′] = $-OCH_2$; C[3′] = CH_3 of ester groups.
(c) Spectra were recorded on a 90 MHz BRUCKER spectrometer

It is apparent from table 3.1 that the ^{1}H nmr spectrum of the β-substituted phosphonate before "reaction" with NaI and after "reaction" with NaI are the same (cases A and C). In the

presence of NaI in acetone-d_6 (case B), all peaks (excluding the CH_3[5] resonance) shift downfield, some to a greater extent than others. The CH_2[1] signal is most affected, followed by the multiplet due to CH_2[2'] and CH[2]. The most dramatic change in the nmr spectrum when comparing case A and case B is the additional splitting of the CH[1] signal in the presence of NaI. The number of peaks in the CH_2[1] signal increases from 4 to 8: the doublet of doublets splits into a further doublet.

The effect of sodium iodide on the spectrum of diethyl 2-chloropentylphosphonate is clearly demonstrated when the mole ratio of the ester to NaI is varied. Samples were made up in acetone-d_6 with phosphonate: NaI ratios ranging from 1:0 to 1:3 and their nmr spectra were recorded on a 90 MHz BRUCKER spectrometer . The results are listed in table 3.2.

Addition of one mole of NaI to the ester had the most marked effect on the nmr spectrum. The effect lessens with further additions of NaI, but the trends are still clearly observable. There is a downfield shift of all peaks (excluding the pentyl methyl signal). Table 3.2 shows only the signals where effects are most noticeable. The CH_2[1] peaks show a progressive increase in the $J_{H(1A) - H(1B)}$ coupling constant, indicating that the protons on C[1] which were equivalent, become non-equivalent in NaI solution.

^{1}H nmr signal in acetone-d_6		$CH_2[2']^a$	$CH_2[1]$				
		δ (ppm)	δ (ppm)	$J_{H(2)-H(1)}$	$J_{H(1A)-H(1B)}$ [b]	J_{H-P} (Hz)	Appearance[c]
A	ester alone	4.05	2.29	8	-	21	
B	A + 1NaI	4.11	2.36	8	0 - 1	21	
C	A + 2NaI	4.14	2.42	8	3	21	
D	A + 3NaI	4.16	2.44	8	4	21	

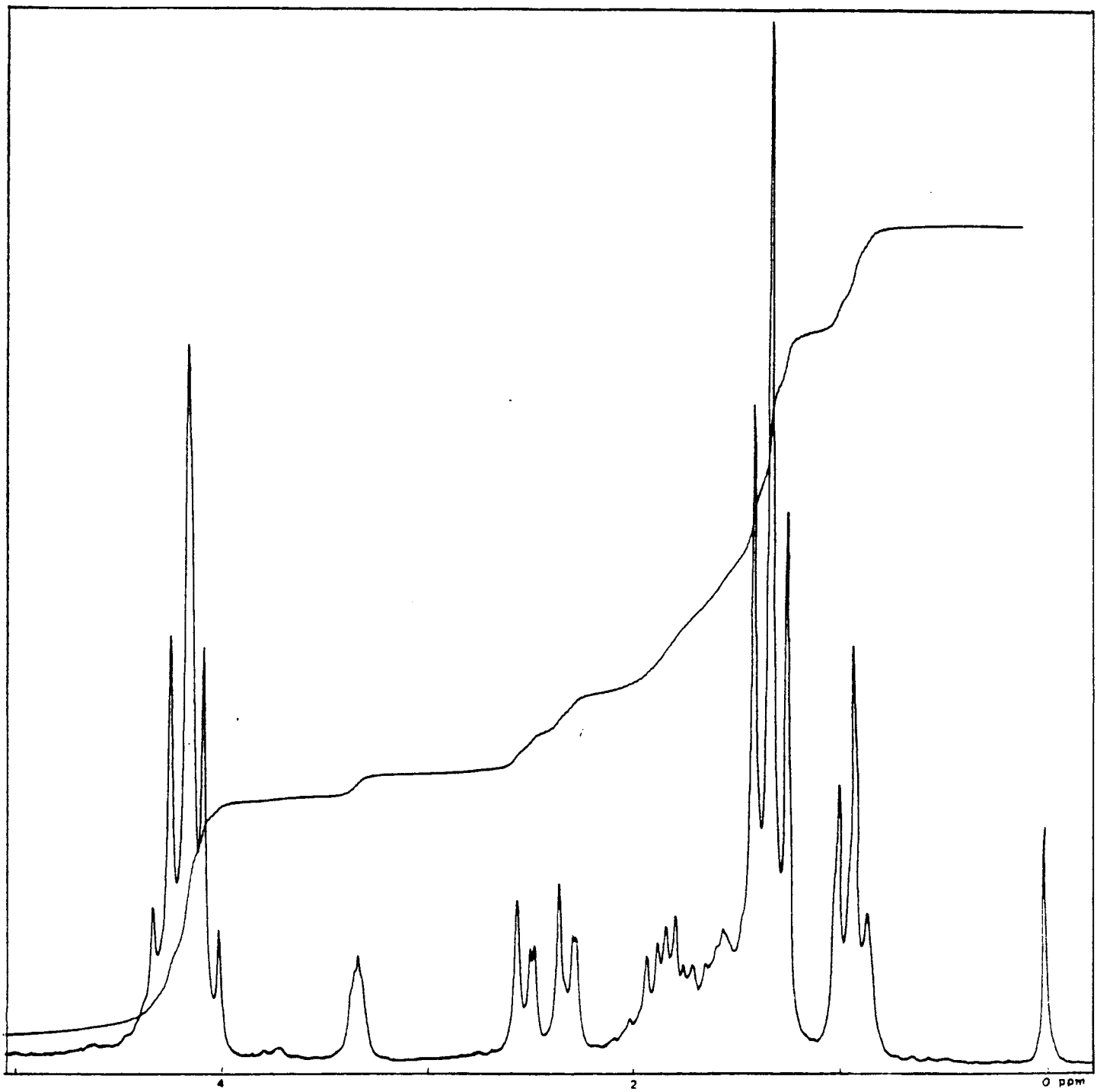
Table 3.2 Effect of varying the mole ratio of NaI on the nmr spectrum of diethyl 2-chloropentylphosphonate in acetone-d_6

Notes: (a) At this chemical shift, the $CH_2[2']$ and CH[2] resonances are superimposed. δ values quoted are the midpoints of the near symmetrical multiplet.
(b) Protons on C[1] coupling with each other.
(c) Scale: 1mm = 2 Hz.

Addition of NaI to the substrate in acetone-d_6 solution appears to have an immediate effect on the nmr spectrum. Spectra recorded after NaI had been dissolved in the sample solution for five minutes were identical to those recorded for the same sample after three days.

The above observations are repeated when the solvent used in the nmr samples is deuterated methanol (see spectrum 3.2). Changes in the spectrum recorded upon addition of 3 moles of NaI to substrate are smaller, however. In acetone, the $CH_2[1]$ peak shifts downfield by 0.15 ppm whereas in methanol the same signal shifts downfield by only 0.06 ppm. The $CH_2[2']$ signal shifts downfield by 0.11 ppm in acetone and by ~0.03 ppm in methanol. Coupling constants of the signals are generally the same in acetone and methanol solution. The addition of 3 moles of NaI to the sample causes the $CH_2[1]$ peak to broaden and, depending on the resolution, to be split further ($J_{H(1A) - H(1B)}$ ~ 0-2 Hz). The low solubility of NaI in other organic solvents prevented further investigations using these solvents.

A sample containing salt: ester (3: 1) in acetone-d_6 was heated to 318 K, 20 K above ambient spectrometer probe temperature, to observe any spectral changes. The sample was also cooled to 20 K below (278 K) ambient temperature. There were no marked differences in chemical shifts and the $CH_2[1]$ signal had nearly the same pattern of 8 peaks as for ambient temperature conditions, but the additional coupling, $J_{H(1A) - H(1B)}$ was



Spectrum 3.2 ^{1}H nmr spectrum of diethyl 2-chloropentylphosphonate and 3NaI in methanol-d_4

~ 3 Hz at 318 K and increased to 4-5 Hz at 278 K. At normal probe temperature (298 K), $J_{H(1A) - H(1B)}$ = 4 Hz. Cooling the sample solution restricts rotation around single bonds in the substrate, so that the non-equivalence of the $CH_2[1]$ protons would be expected to to be more obvious (i.e. a larger $J_{H(1A) - H(1B)}$). The converse argument is true for heating the sample.

An investigation of the effects of other salts on the nmr spectrum of diethyl 2-chloropentylphosphonate was embarked upon. Sodium perchlorate yielded similar results to sodium iodide (discussed in more detail further on in this chapter), indicating that it is the presence of the cation, rather than the anion in the sample spectra which brings about these spectral changes. It would have been interesting to record nmr spectra in the absence of the sodium cation using salts like tetramethylammonium iodide or phenyltrimethylammonium iodide, but solubility problems hampered these investigations. The spectra of the ester in the presence of 3 moles of calcium iodide or potassium thiocyanate were studied, however, and the results are summarized in table 3.3.

The effect of KNCS on the chemical shifts is of similar magnitude to that of NaI. The change in $J_{H(1A) - H(1B)}$ coupling constants are less dramatic, but comparable to the effect brought about by one mole of NaI in the sample solution. Calcium iodide brings about large downfield shifts in the $CH_2[2']$ and $CH_2[1]$ resonances. The entire pattern of the $CH_2[1]$

signal changes from 4 lines (doublet of doublets) to fourteen when three moles of CaI_2 are present in the solution.

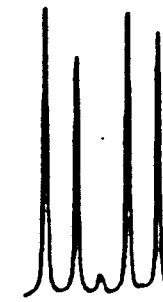
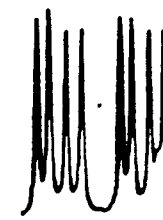
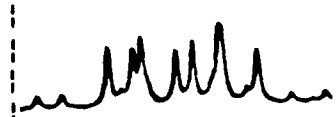
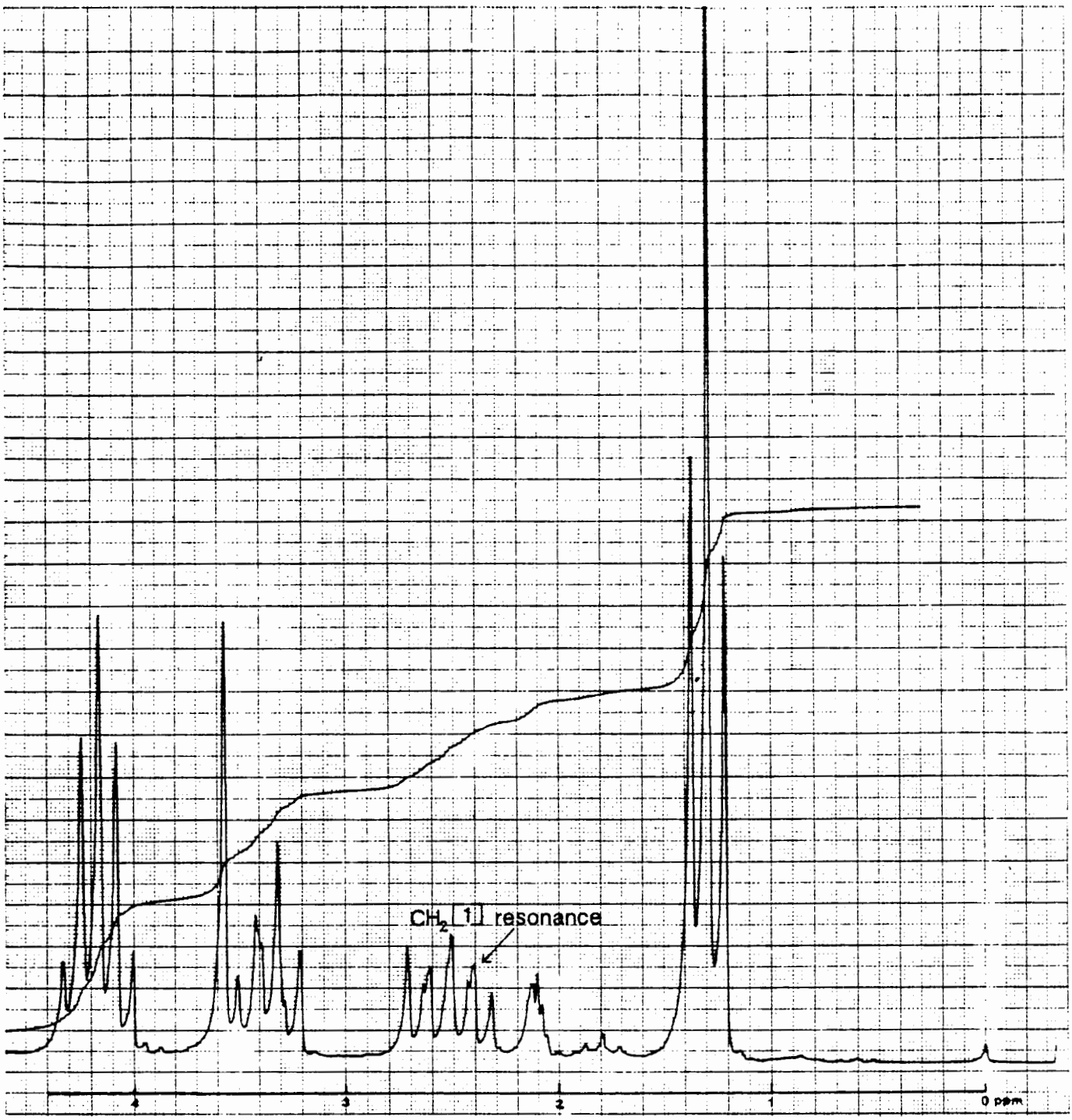
^{1}H nmr signal in acetone-d_6		CH_2[2']	CH_2[1]				
		δ (ppm)	δ (ppm)	$J_{H(2)-H(1)}$	$J_{H(1A)-H(1B)}$	J_{H-P} (Hz)	Appearance
A	ester alone	4.05	2.29	8	-	21	
B	A + 3KNCS	4.13	2.42	8	1 - 2	21	
C	A + 3NaI	4.16	2.44	8	4	21	
D	A + 3CaI_2	4.28	2.64	complex			

Table 3.3 Effect of different salts on the ^{1}H nmr spectrum of diethyl 2-chloropentylphosphonate

(the same notes apply here as for table 3.2)

Replacing diethyl 2-chloropentylphosphonate by diethyl 2-bromo~~ethyl~~pentylphosphonate yielded a further variation of the "NaI effect" (see spectrum 3.3). While no changes in the splitting pattern of the spectrum of $CH_3CH_2CH_2CH(Br)CH_2P(O)(OCH_2CH_3)_2$ are evident on addition of 3 moles of NaI to the sample in acetone-d_6, significant changes in chemical shifts of the signals are observed: the CH_2-P multiplet shifts downfield from δ2.16-δ2.58 ppm to δ2.30-δ2.76 ppm, the CH_2-Br multiplet shifts upfield from δ3.34-δ3.70 ppm to δ3.15-δ3.52 ppm, the OCH_2 signal shifts downfield from δ4.04 (midpoint of multiplet) to δ4.14. The ester-CH_3 signal remains effectively unchanged by the presence of NaI in the sample.

NaI has no effect on the ^1H nmr spectrum when using 2-chloropentylphosphonic acid as the substrate instead of the diethyl ester. It appears that the ester group is needed for any spectral changes to be observed. Spectra from which all the above results were derived, were recorded on a 90 MHz BRUCKER nmr spectrometer. A more detailed study of the NaI effect on the spectrum of diethyl 2-chloropentylphosphonate was made using a 250 MHz BRUCKER spectrometer, a 200 MHz VARIAN spectrometer and a 400 MHz VARIAN spectrometer.



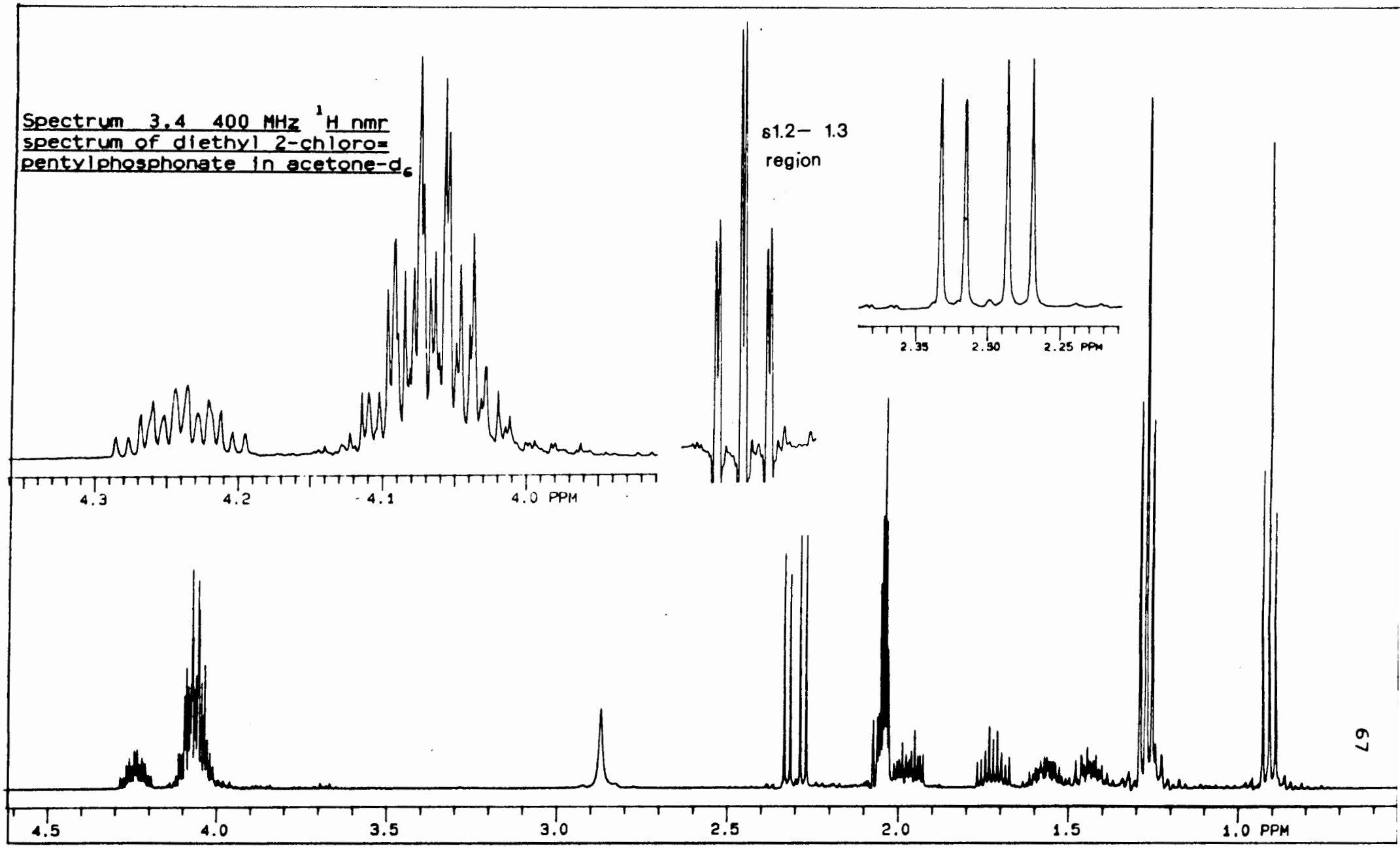
Spectrum 3.3 ^{1}H nmr spectrum of diethyl 2-bromoethylphosphonate + 3NaI in acetone-d_6

3.2 400 MHz ^{1}H nmr spectrum of diethyl 2-chloropentylphosphonate in acetone-d_6.

All signals are well spread out and distinct using this high frequency spectrometer (see spectrum 3.4). Characteristics of the substrate spectrum which had not been apparent on the 90 MHz ^{1}H nmr spectrum are now clearly seen. Some of the signals become simplified since they are separated from adjacent resonances. Other signals become more complex since long-range coupling can now be seen.

^{1}H nmr signal	Multiplicity	δ(ppm)	J_{H-H} (Hz)	J_{H-P} (Hz)
CH_3[5]	triplet	0.91	7	
CH_3[3′]	triplet with additional splitting	1.27	7	long range 1.5
CH_2[4]	two distinct multiplets	1.37-1.50 1.51-1.63		
CH_2[3]	two distinct multiplets	1.67-1.77 1.92-2.02	4.2	
CH_2[1]	doublet of doublets	2.30	7	18.45
CH_2[2′]	29 line complex multiplet	4.00-4.12		long range 2.4-2.6
CH[2]	12 line symmetrical multiplet	4.19-4.29	3.5	

Table 3.4 400 MHz ^{1}H nmr spectrum of diethyl 2-chloropentyl phosphonate in acetone-d_6


Spectrum 3.4 400 MHz ^{1}H nmr spectrum of diethyl 2-chloro-pentylphosphonate in acetone-d_6
δ1.2– 1.3 region
4.3
4.2
4.1
4.0 PPM
2.35
2.30
2.25 PPM
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0 PPM

Various properties of the 400 MHz spectrum are highlighted below:

(1) the CH_3[3'] resonance

With this degree of resolution, the H(3') protons show residual $^4J_{P-H}$ long-range coupling (ca. 1.5 Hz).

(2) the CH_2[2'] resonance

This is a complex signal, indicating that the two ester methylene groups are not equivalent, perhaps because the ester is a chiral molecule, with either R or S enantiomers having some conformational difference, rendering the ester-methylene signal non-equivalent. (This is confirmed by ^{13}C nmr, discussed further on in this chapter). It is difficult to measure the $^3J_{P-H}$ coupling of the signal, but an approximation for this value is $^3J_{P-H}$ ~ 2.4-2.6 Hz.

(3) the CH_2[1] doublet of doublets

This signal is of particular interest since it is the one that changes most noticeably when NaI is added to the nmr sample. It is also a "deceptively simple" signal, in that it shows fewer lines than expected from classical analysis. In theory, the signal should contain sixteen lines - an AB quartet from the methylene protons coupling with each other, then each line split by the methine proton on C[2] and phosphorus. Instead an A_2BX system is observed with $^2J_{P-H}$ = 18.45 Hz. Even with resolution enhancement, using a high frequency instrument, no further

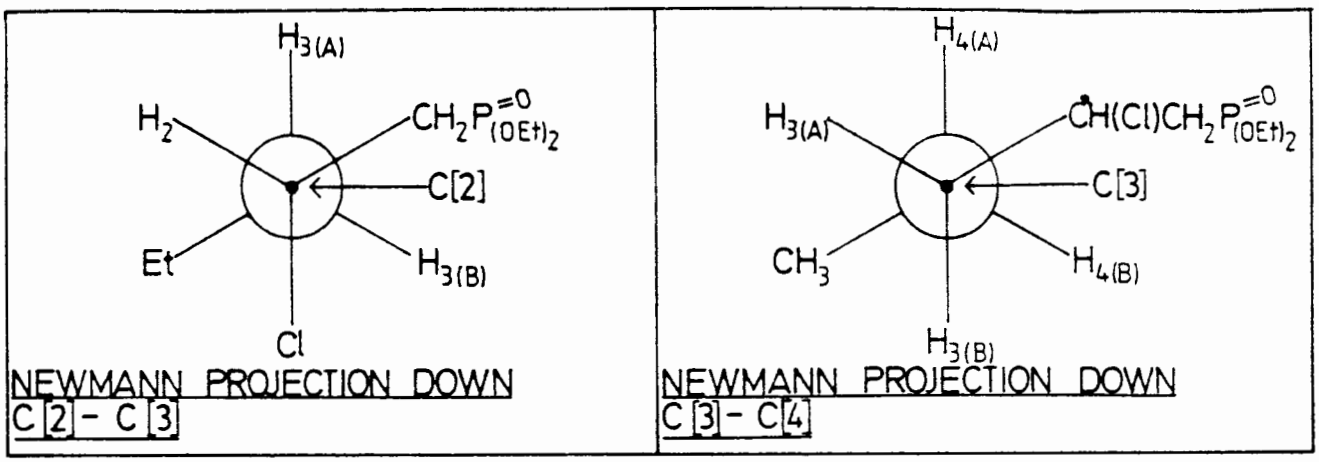
splitting is observed. The two protons on C[1] can never be in exactly the same chemical environment because of the C[2] chiral centre, but coincidentally have the same chemical shifts. They are not magnetically equivalent, but are termed "isochronous". No rotation around single bonds will render them equivalent. Deceptively simple signals can sometimes be resolved by changing the solvent system of the sample,[47] but this is not the case for this ester - no further splitting of the signal has been observed in other solvents.

(4) the CH[2] signal

This signal was never observed until the spectrum was recorded on a 400 MHz spectrometer, since it was always masked by the CH_2[2'] multiplet. At high resolution, it appears as a symmetrical 12-line multiplet, with J_{H-H} = 3.5 Hz.

(5) the CH_2[3] and CH_2[4] multiplets

There appear to be four different multiplets, each integrating for a single proton. This would indicate that none of the protons on C[3] or C[4] are magnetically equivalent. If, for some reason (such as steric bulk), there is restricted rotation around C-C single bonds [2] to [3] and [3] to [4], then non-equivalence of the protons can be explained as illustrated by the following Newmann projections:



(Assuming restricted rotation H[3A]≠H[3B]. Similar argument for the enantiomer)

(if restricted rotation i.e. a preferred conformer exists, H[3A]≠H[3B], ∴H4[A]≠H4[B]. Similar argument for the enantiomer

Figure 3.1

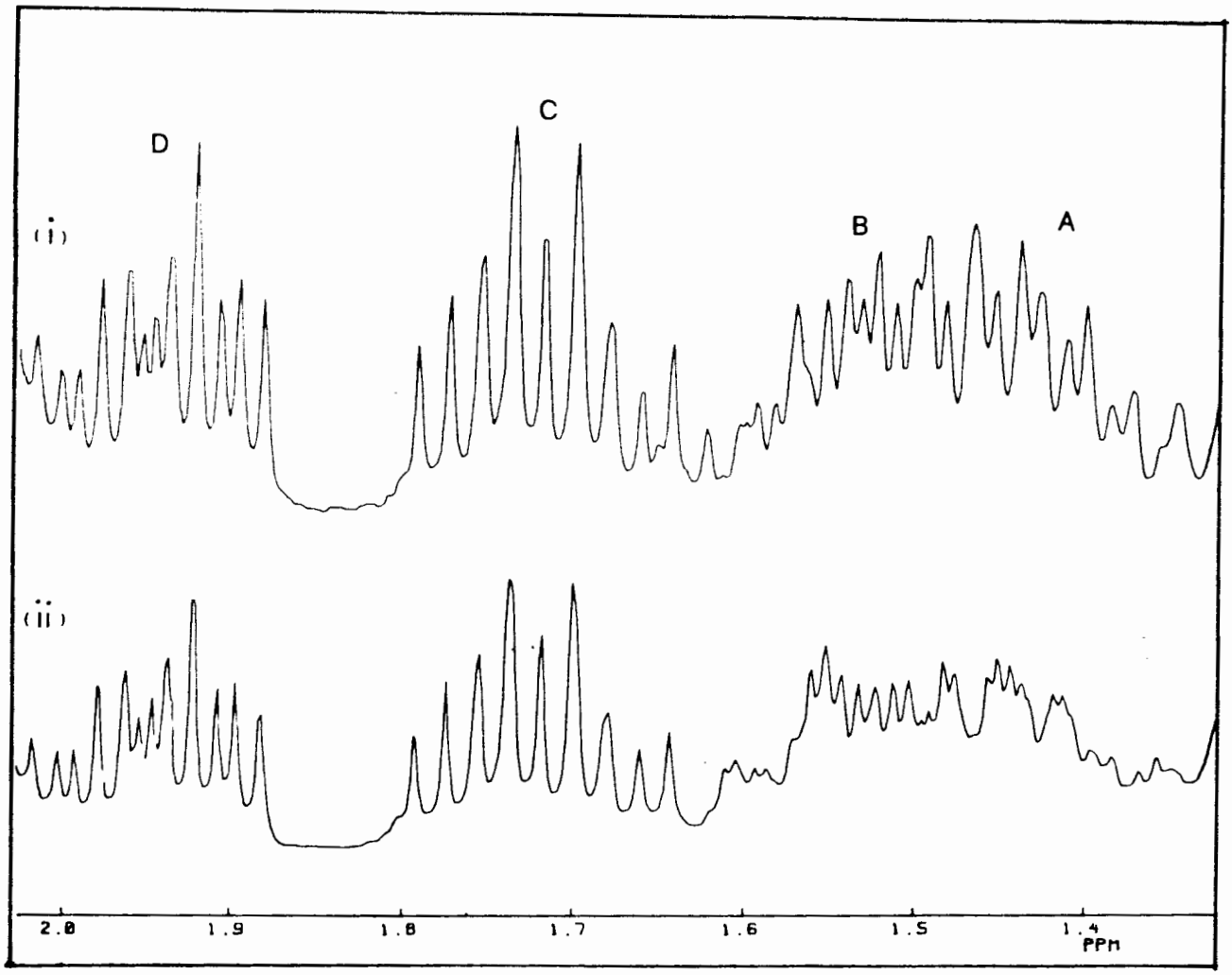
As in table 3.4, the CH_2[4] protons are assigned to multiplets at δ1.37 - 1.50 ppm and δ1.51 - 1.63 ppm. The CH_2[3] protons are assigned to multiplets further downfield at δ1.67 - 1.77 and δ1.92-2.02 ppm. These assignments were confirmed by selective decoupling experiments, performed on a 250 MHz BRUCKER spectrometer and a 200 MHz VARIAN spectrometer.

3.3 Selective Decoupling Experiments

Selective spin decoupling experiments were performed using a 250 MHz BRUCKER spectrometer to assign unambiguously some of the resonances in the ^1H nmr spectrum of diethyl 2-chloropentyl-phosphonate.

(i) Irradiation at δ0.92 ppm (pentyl-CH_3 group) (Spectrum 3.5)

The peaks in the two multiplets from ~δ1.35-δ1.65 ppm become less distinct when the pentyl-CH_3 group is decoupled. The multiplets further downfield at ca. δ1.65-δ2.00 ppm remain unaffected by the decoupling. It can therefore be concluded that the higher field multiplets result from the CH_2[4] protons which are directly coupled to the CH_3[5] protons. The other two multiplets, at least three bonds from the CH_3 C[5] protons would not be affected to any noticeable extent. It is not possible, however, to decide which of the two upfield multiplets result from which of the CH_2[4] protons and, similarly, which of the two lower field multiplets result from which of the CH_2[3] protons. Even in decoupling experiments H[3A] ≠ H[3B] and H[4A] ≠ H[4B]. This would suggest that the ~~conformations~~ rotations about the C[2] - C[3] and C[3] - C[4] bonds are restricted to some degree.



Spectrum 3.5 (i) ^{1}H nmr spectrum of the CH_2[3] and CH_2[4] protons of diethyl 2-chloro-pentylphosphonate in acetone-d_6 (Multiplets A and B represent the CH_2[4] protons and multiplets C and D represent the CH_2[3] protons)

(ii) ^{1}H nmr spectrum as for (i) above with irradiation at δ0.93 ppm. Note the change in the A and B multiplets.

(ii) Irradiation at δ4.25 ppm (CH(Cl) methine group)

Decoupling experiments at δ4.25 ppm confirm that the CH_2[1] doublet of doublets is indeed coupled only to the CH[2] proton and ^{31}P, with no residual coupling apparent, even in a 400 MHz ^{1}H nmr spectrum with resolution enhancement. The CH_2-P group appears to be isolated from the rest of the molecule in terms of spin coupling, except of course for the ^{31}P atom and the CH[2] proton. Irradiation at the frequency of the signals of any other protons in the spectrum have no effect on the doublet of doublets. Only irradiation at δ4.25 ppm produces a simple ^{31}P coupled doublet.

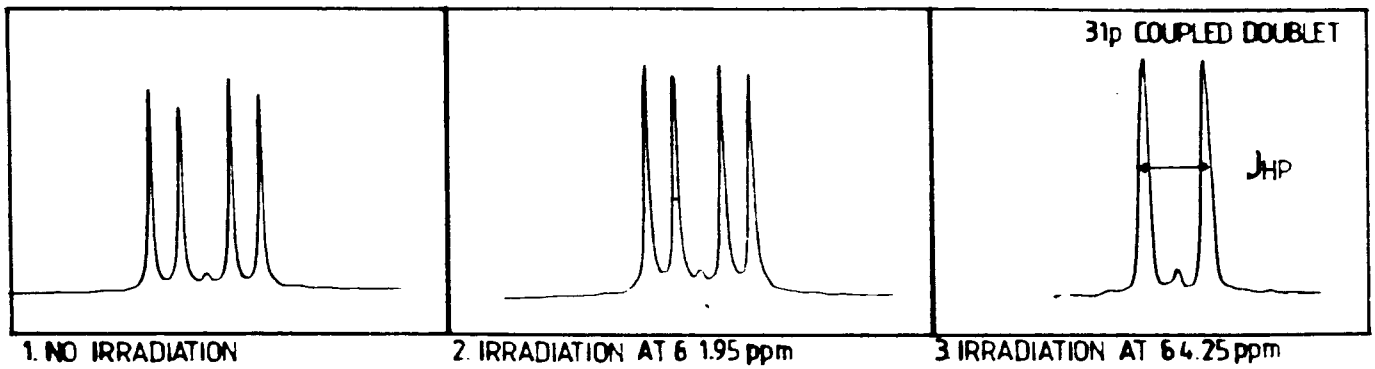
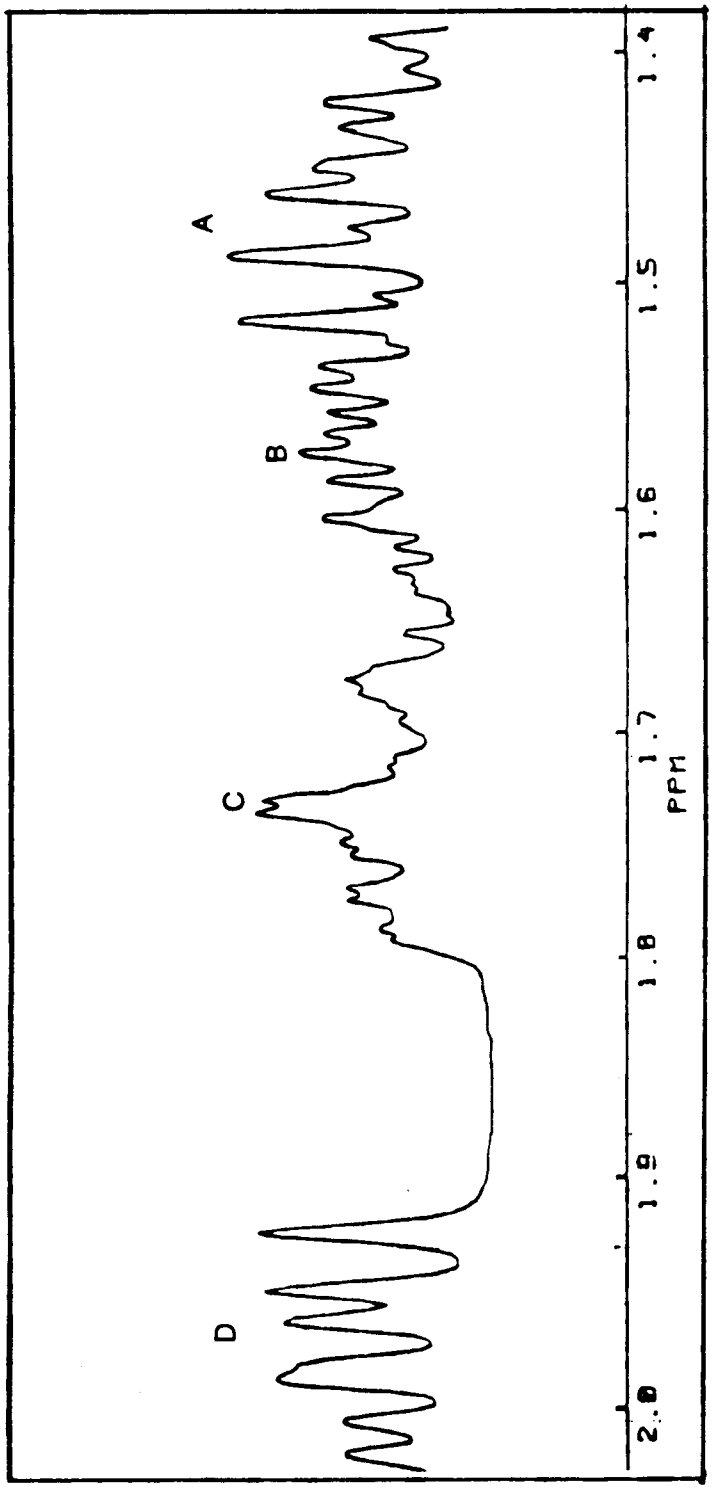


Figure 3.2 Decoupling of the CH_2[1] resonance

CH[2] is also coupled to the CH_2[3] protons, as one would expect. This is apparent from the change in the multiplets from δ1.65 - δ2.00 ppm when the δ4.25 ppm signal is irradiated (see spectrum 3.6). This confirms once more the assignment of the CH_2[3] and CH_2[4] multiplets.



Spectrum 3.6 ^{1}H nmr spectrum of the CH_2[3] and CH_2[4] protons of diethyl 2-chloropentylphosphonate in acetone-d_6 when irradiated at δ4.25 ppm (Compare with (1) of spectrum 3.5)

3.4 Effect of NaI on the ^{1}H nmr spectrum of the ester

At high frequency (400 MHz), the effect of NaI on the spectrum of the diethyl 2-chloropentylphosphonate is quite clear. Even with the addition of a small amount of sodium iodide, all peaks (excluding the CH_3[5] peak) shift downfield, as was seen previously. The splitting pattern of the spectrum remains essentially unchanged, except for the CH_2[1] signal which has marked additional splitting (the multiplet increases from 4 to 13 lines now), and the CH_3[3'] signal, already split by $^4J_{P-H}$ coupling as mentioned above, is now further split by the addition of NaI to the sample. Clearly, the ester group plays a major part in the interaction of the substrate with NaI. The opposite end of the molecule (pentyl-CH_3) is unaffected by both small and large additions of NaI: the triplet at δ0.92 remains unchanged, indicating that this end of the molecule has little interaction with the salt in solution. (see spectrum 3.7)

When the mole ratio of NaI: ester = 3:1, the CH_2[1] doublet of doublets becomes a complex symmetrical multiplet (see figure 3.3). At 200 MHz, the signal consists of 16 lines (the middle line of the multiplet is assumed to be two lines collapsed into one) which corresponds to the theoretically expected pattern.

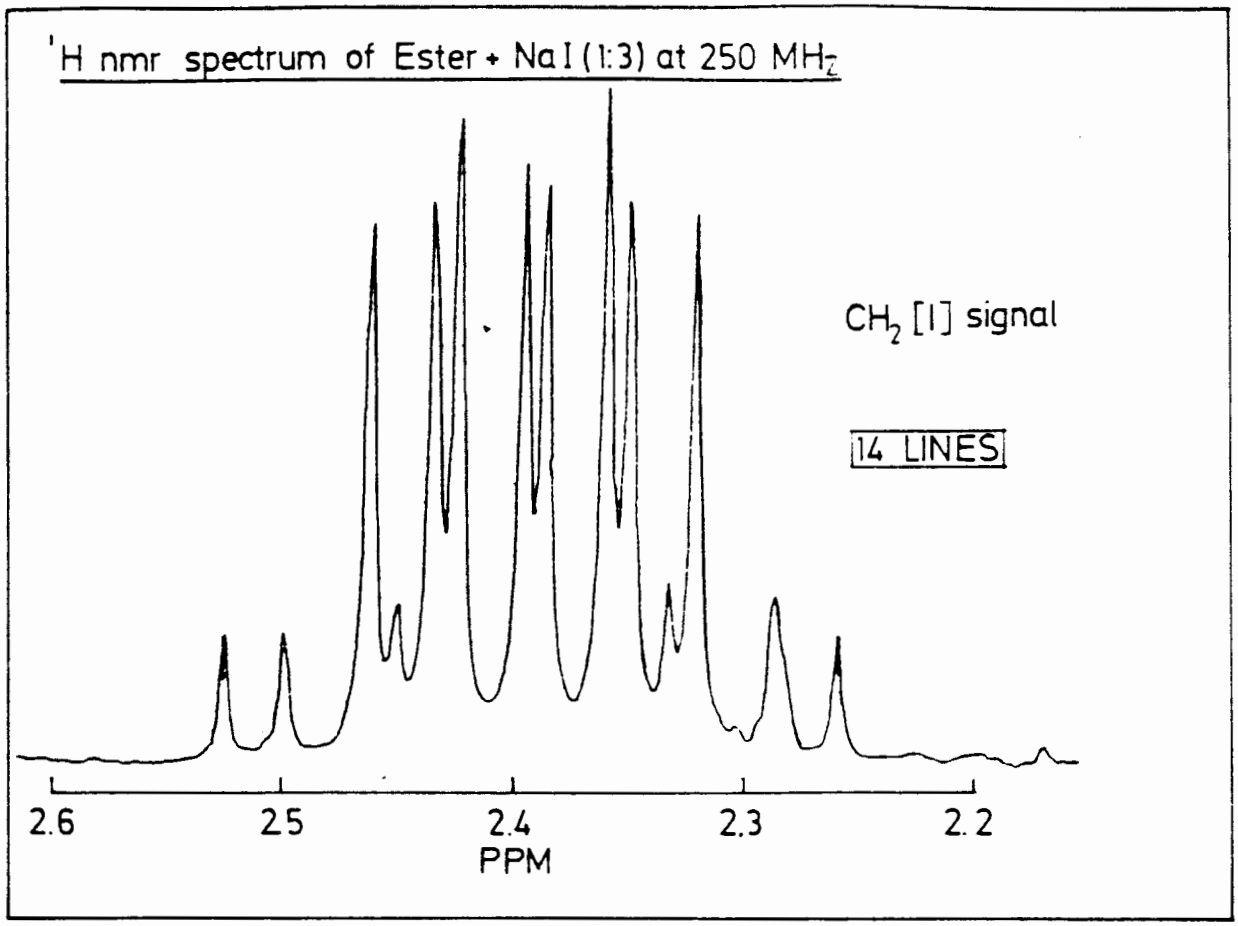
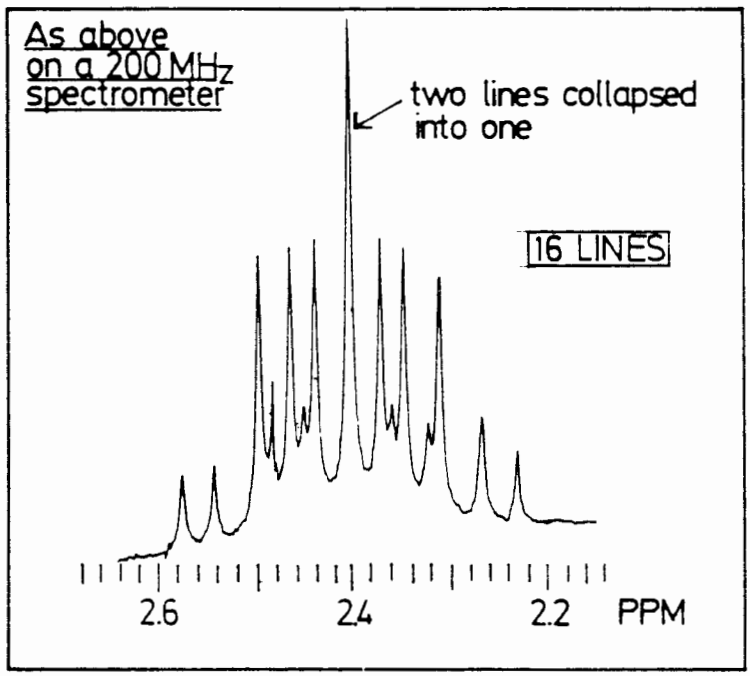
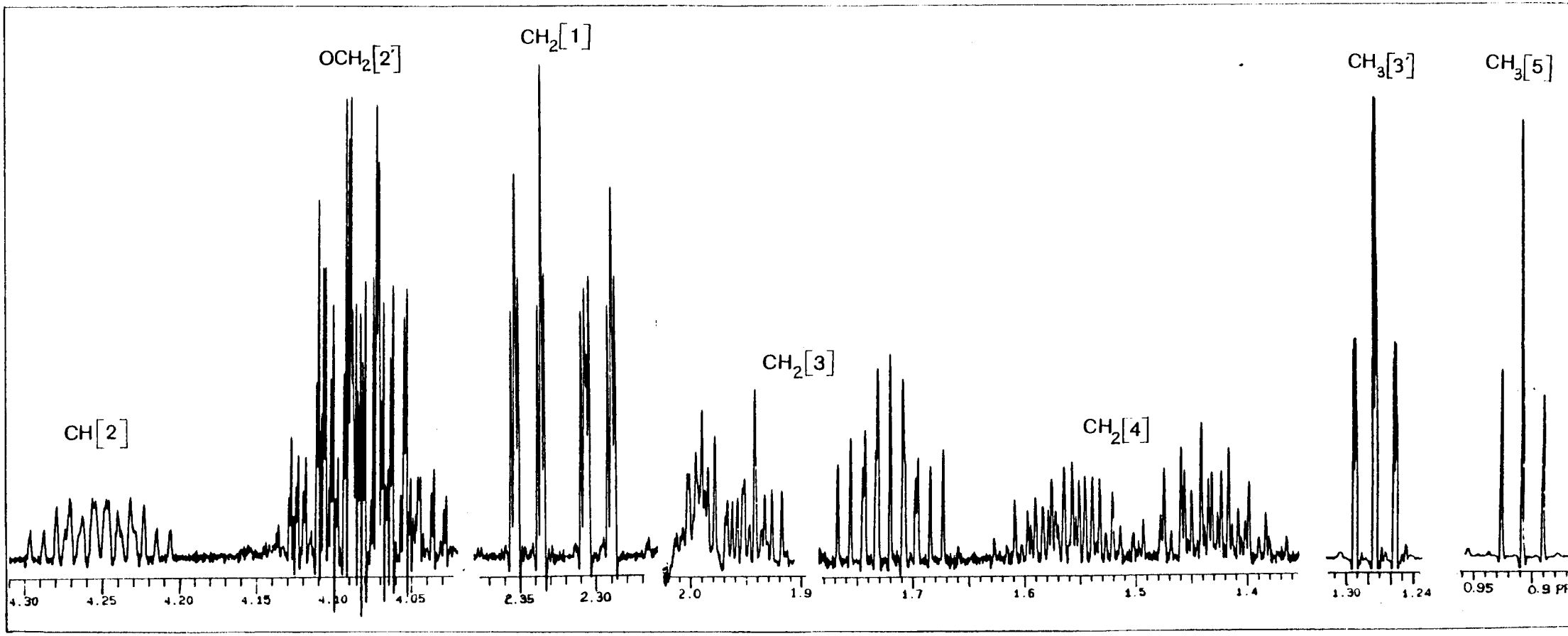


Figure 3.3 CH_2[1] signal of diethyl 2-chloropentylphosphonate





Spectrum 3.7 ^{1}H nmr spectrum at 400 MHz of diethyl 2-chloro=pentylphosphonate + NaI in acetone-d_6

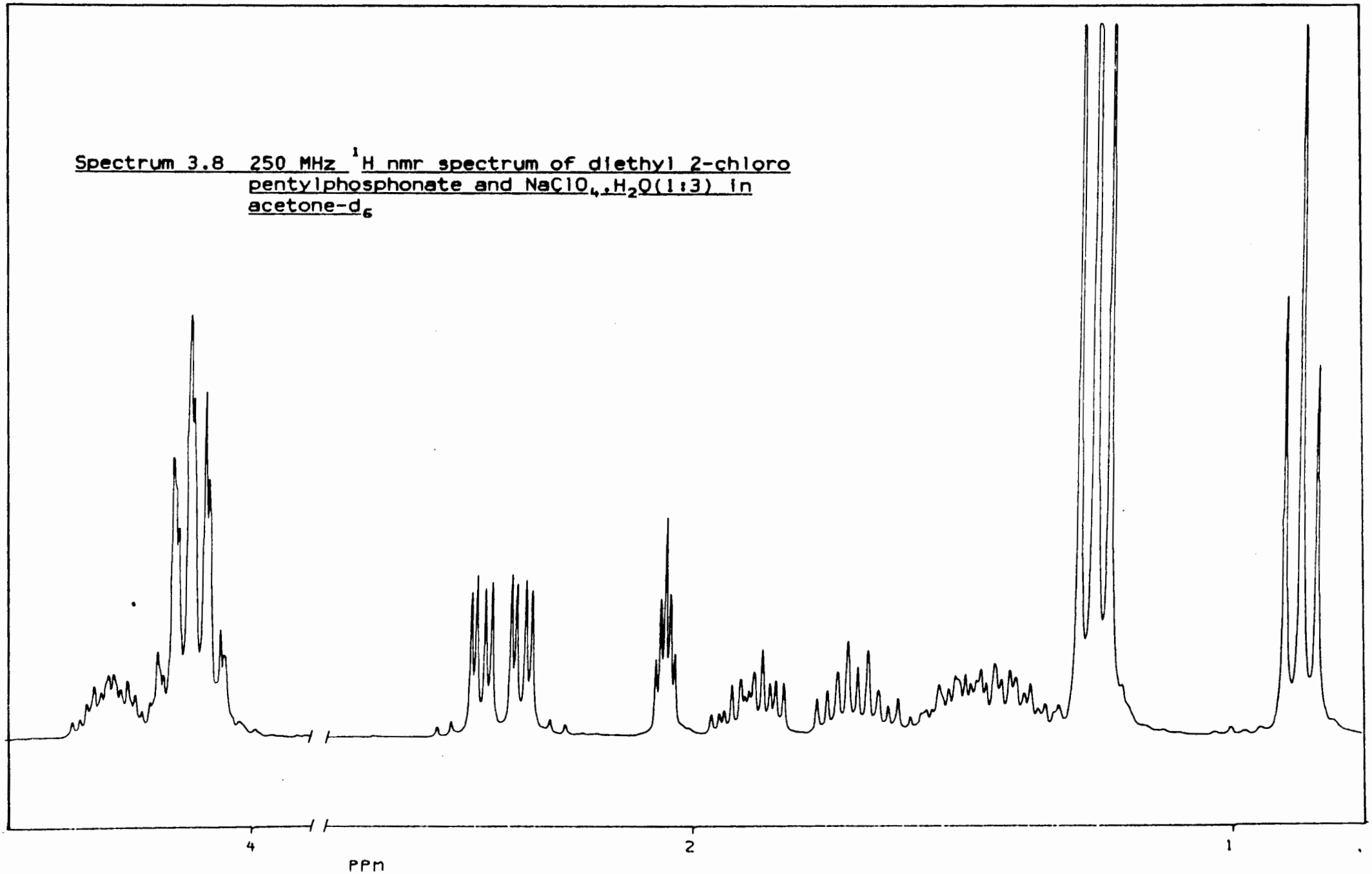
3.5 Spectrum of ester and $NaClO_4.H_2O$ (1:3) in acetone-d_6

This spectrum provides a useful comparison with the spectrum of NaI and ester in acetone-d_6. It is essentially the same as that for the NaI system, with a certain difference in the splitting of the $CH_2(1)$ protons. In the $NaClO_4.H_2O$/ester spectrum, 12 lines are observed, whereas in the NaI case 16 lines (maximum) are seen (see spectrum 3.8). The two patterns are both symmetrical. The $CH_2[1]$ signal in the sodium perchlorate case is not shifted downfield to the same extent as in the NaI case:

	Downfield Shift
NaI/ester (3:1)	0.15 ppm
$NaClO_4.H_2O$/ester (3:1)	0.06 ppm

Another difference in the spectrum of the $NaClO_4.H_2O$/ester spectrum is the upfield shift of the $CH_2[3]$ multiplet which was at δ1.92-δ2.02 ppm to δ1.80-δ1.98 ppm. The $CH_2[4]$ multiplets appear to be shifted closer together as well. This would indicate conformational differences in the propyl end of the molecule which are not observed in the spectrum of the NaI/ester system.

Spectrum 3.8 250 MHz ^{1}H nmr spectrum of diethyl 2-chloro pentylphosphonate and $NaClO_4.H_2O$(1:3) in acetone-d_6



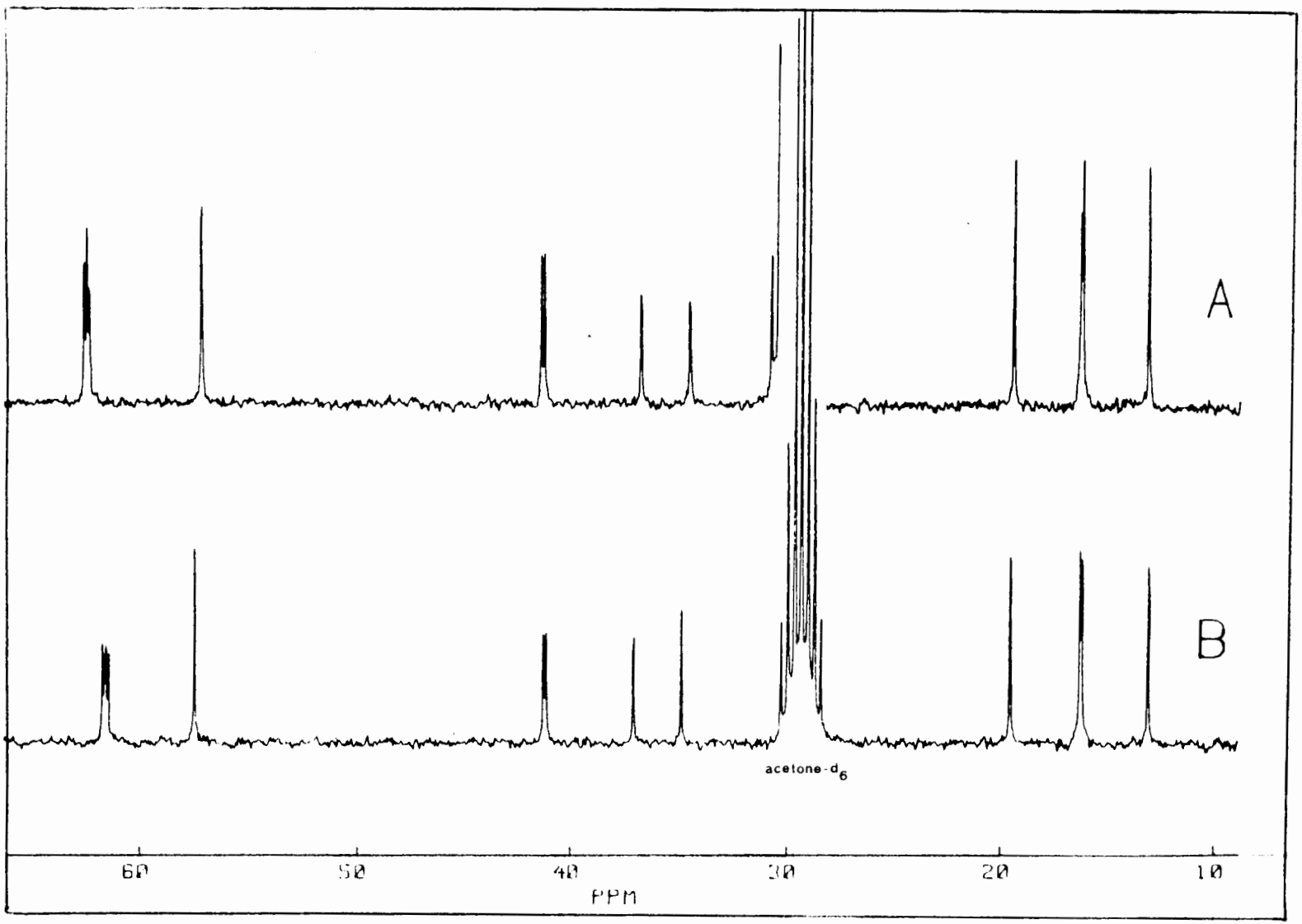
3.6 The effect of NaI on the ^{13}C nmr spectrum of diethyl 2-chloropentylphosphonate in acetone-d_6

The 62.89 MHz ^{13}C nmr spectra of the ester alone and in the presence of 3 moles of NaI were measured in acetone-d_6. Data obtained from the spectra are listed in table 3.5. Two types of spectra were recorded:

(i) Proton decoupled spectrum (Spectrum 3.9)

^{13}C nmr would be a fairly insensitive technique if proton decoupling were not possible. More than one order of magnitude increase in sensitivity is achieved in wide band ^{1}H decoupled ^{13}C nmr spectra compared with the sensitivity of a fully coupled spectrum[48]. Peak heights increase because of the collapse of the C-H spin multiplets to singlets, and because of the increased peak area/height resulting from the nuclear Overhauser effect (NOE), a consequence of proton decoupling experiments. (Irradiation of protons changes the Boltzmann distribution of upper and lower ^{1}H energy levels. This, in turn, effects the population of nuclei in ^{13}C energy levels, resulting in an excess of ^{13}C nuclei in the lower energy level. In real terms, more radio-frequency energy is now absorbed by the ^{13}C nuclei in the lower energy level, resulting in an enhanced signal)

Increasing the sensitivity by proton decoupling means coupling information is lost: all peaks appear as singlets unless they are coupled to another nucleus such as ^{31}P.

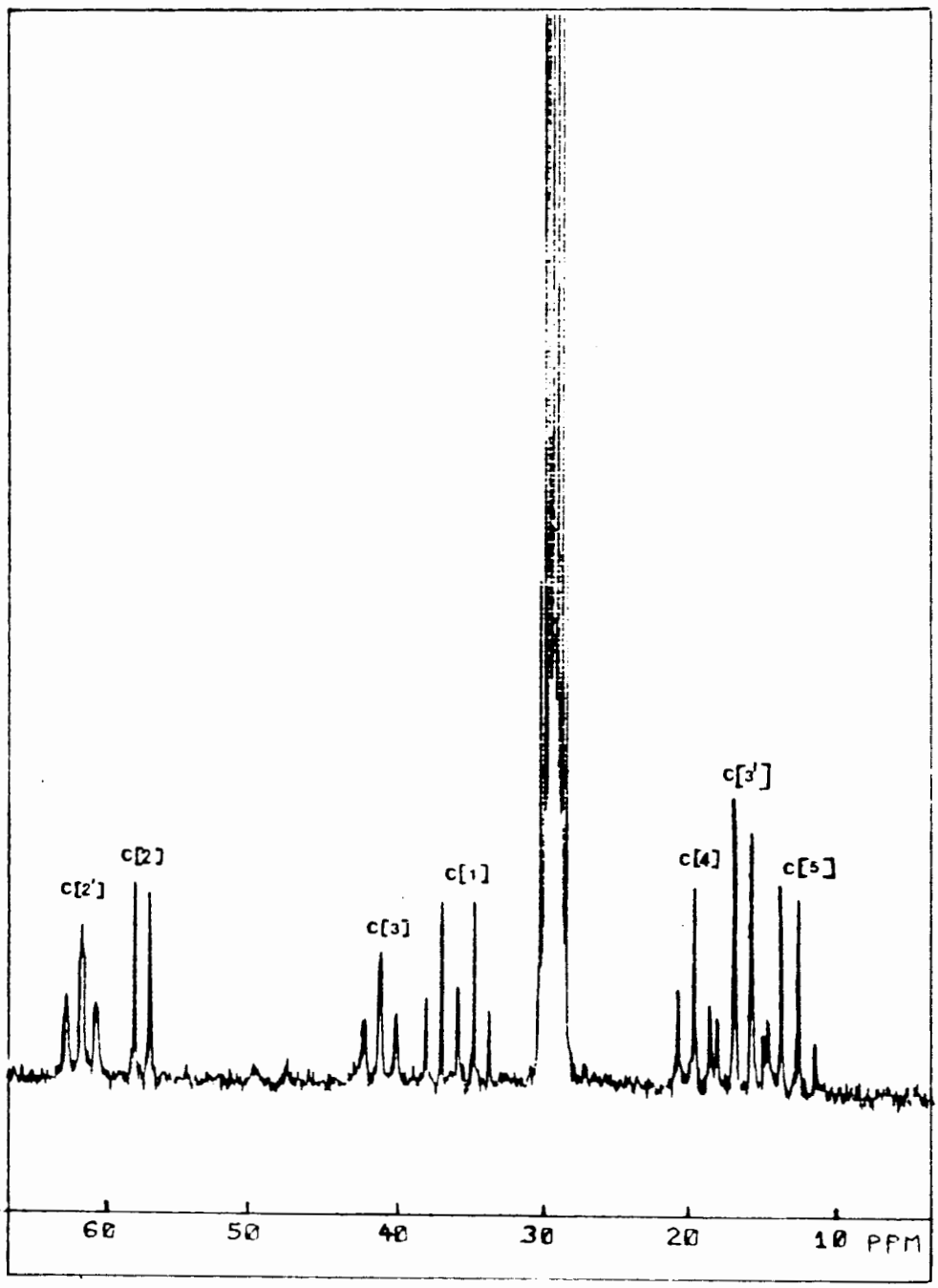


Spectrum 3.9 ^{13}C nmr spectrum proton decoupled spectrum in acetone-d_6
A. of diethyl 2-chloropentylphosphonate
B. of A + 3NaI

(ii) Off resonance decoupled spectrum

This kind of spectrum shows only $^{1}J_{C-H}$ couplings. This technique is still reasonably sensitive, since long-range C-H couplings are not apparent and the NOE still applies. All the protons are irradiated at high power levels some 500 to 1000 Hz away from the actual proton resonances. One bond C-H splitting patterns are evident: the multiplicity of a signal, m, assigns it to a carbon atom attached to (m-1) protons. This makes the task of peak assignments considerably easier than for a completely proton decoupled spectrum. Actual $^{1}J_{C-H}$ coupling constants are reduced in this type of experiment: only residual couplings are seen. An advantage of this is that the multiplets are less likely to overlap.

There are several points to note from table 3.5: The off resonance decoupled spectrum (no. 3.10) allowed unambiguous assignment of peaks. Looking at the completely proton decoupled spectrum (no. 3.9), addition of sodium iodide to the ester in acetone-d_6 seems to make very little difference to any of the resonances. ^{13}C nmr is not as informative as ^{1}H nmr on the effect of NaI on the ester in solution. Small chemical shift differences are seen, however. All peaks move upfield by ca. 0.4-0.8 ppm, except for the C[2'] peak which moves downfield. The C[2'] is also the only signal which shows separate chemical environments for enantiomers. Two separate



Spectrum 3.10 ^{13}C nmr off resonance decoupled spectrum of diethyl 2-chloropentylphosphonate in acetone-d_6

	$\delta(^{13}C)$/ppm relative to acetone-d_6						
SAMPLE	C[1]	C[2]	C[3]	C[4]	C[5]	C[2']^c	C[3']
A. Ester alone	35.86	57.38	41.11	19.44	13.03	61.53 61.71	16.16
B. Ester + 3NaI	35.58	57.16	41.28	19.37	13.13	62.49 62.61	16.24
C. Ester + 3NaI^a corrected	35.06	56.63	40.75	18.89	12.60	61.96 62.08	15.71
D. C-A^b	-0.8	-0.75	-0.36	-0.60	-0.43	+0.43 +0.37	-0.45
E. $^nJ_{C-P}$/Hz	$^1J_{C-P}$ 137.5	$^2J_{C-P}$ ~0	$^3J_{C-P}$ 7.4	-	-	$^2J_{C-P}$ 7.1 6.1	$^3J_{C-P}$ 5.7
F. Off resonance decoupled spectrum	P coupled triplet $-CH_2-$	doublet -CH	triplet $-CH_2-$	triplet $-CH_2-$	quartet $-CH_3$	triplet $-CH_2$	quartet $-CH_3$

Table 3.5 ^{13}C nmr spectrum of diethyl 2-chloropentylphosphonate in acetone-d_6

Notes:
(a) the acetone-d_6 peak in A = 29.2626 ppm, and in B = 29.7906 ppm. The corrected ppm values (C) are obtained by subtracting 0.528 ppm from B.
(b) D is the chemical shift difference C-A. (+) means downfield shift, (-) means upfield shift.
(c) in both A and B there seem to be two C[2'] environments shown as two $^2J_{CH-P}$ coupled doublets.

$^{2}J_{P-C[2']}$ coupled peaks are evident, and the two couplings differ by 1 Hz. The non-equivalence of the C[2'] peaks could perhaps be a result of the chirality of the molecule. Two possibilities are that:

(1) the two ester methylene carbon atoms are equivalent in each enantiomer, but the R and S enantiomers have some conformational difference resulting in the non-equivalence of the C[2'] peaks (i.e. $C[2']_R \neq C[2']_S$).

(2) the ester methylene carbons are non-equivalent on both R and S enantiomers. (R=-S; $C[2']_A \neq C[2']_B$).

The subtle differences shown in the ^{13}C spectra make unambiguous analysis of the two situations difficult. In ^{1}H spectra, the $CH_2[2']$ signal is so complex that analysis is even more difficult. It does appear that the $-OCH_2-$ functional groups of the ester are non equivalent, however. The presence of NaI does not cause any greater change of the chemical shift for this signal than for any of the other signals, nor does the salt affect the $^{2}J_{C-P}$ couplings in any way.

It is not surprising that NaI has little effect on the ^{13}C nmr spectrum of the ester. For instance, it is unlikely that the salt would affect the electron density at ^{13}C nuclei, nor would it change the hybridisation at any of the ^{13}C nuclei. No formal bonding takes place between the ester and the salt either(starting material is recovered in 100% yield when NaI is removed from the sample solution). ^{13}C chemical shifts would

be far more sensitive to these three factors than to conformational changes or weak complexation involving NaI, which is what is most likely occurring in solution.

3.7 The effect of NaI on the ^{31}P nmr spectrum of diethyl 2-chloropentylphosphonate in acetone-d_6

The ^{31}P nmr spectrum of the ester in acetone-d_6 was recorded at a spectral frequency of 101.25 MHz and gave a singlet at δ26.60 ppm (89% H_3PO_4 in D_2O/H_2O was the external reference). On addition of 3 moles of NaI to the sample, the singlet shifted downfield by 1.00 ppm to 27.60 ppm, suggesting that NaI does have some interaction with the phosphonate side of the molecule.

3.8 Interactions between diethyl 2-chloropentylphosphonate and NaI in acetone-d_6 solution observed as changes in the nmr spectrum of the ester.

It is clear that NaI is interacting with the ester, to produce marked spectral changes. It is difficult to be certain of the nature of this interaction, but reviewing the spectral evidence gathered allows the formulation of some postulates on molecular associations in acetone-d_6 solution.

There is no reaction ,as such, with the sodium iodide - starting material is easily recovered at any stage from sample solutions. However, increasing the mole ratio of NaI in solution results in

a concomitant change in chemical shifts and splitting patterns in some of the signals. Clearly it is the salt which is effecting these spectral changes.

Sodium perchlorate has a similar impact on the spectrum of the ester. The conclusion from this is that the interaction is predominantly with the Na cation and is anion independant.

Addition of other cations to the acetone-d_6 solution also bring about changes in the spectrum of the ester. Three moles of K^+ (as the thiocyanate salt) have as marked an effect as one mole of Na^+. Note that K^+ is a larger cation than sodium (ionic radii: Na, 95 ppm; K, 133 ppm),[49] thus the two cations would be expected to have different spatially-dependent associations with the ester. Ca^{2+} brings about large chemical shift differences and changes the splitting pattern of the CH_2[1] ^1H nmr signal considerably. Most likely, the higher charge on the cation results in a stronger association of the ester and Ca^{2+} than the same with monopositive cations.

Reducing the temperature of the nmr sample restricts rotation about single bonds. This trend in spectral changes brought about by lowering the temperature is parallel to that brought about by NaI. It would appear that NaI restricts rotation about single bonds in the ester, particularly the CH_2-P bond. Raising the temperature above room temperature assists rotation

about bonds. Under these conditions, some of the effect of NaI is lost.

When the ester substrate is replaced by 2-bromoethylphosphonate, splitting patterns of its ^{1}H nmr spectrum remain the same as on addition of NaI to the sample. Chemical shifts, however, are significantly changed in the presence of the salt, with the CH_2-Br signal being shifted upfield and most of the other peaks being shifted downfield. Both the CH_2-Br functional group and the phosphonate group appear to be affected by the NaI.

In a sample containing 2-chloropentylphosphonic acid, no NaI effects are observed at all, indicating that the phosphonate group is important for the postulated interaction.

The effects of NaI on the ^{1}H nmr spectrum are less marked in methanol-d_4, but are still apparent. It is likely that methanol-d_4, as a strongly ^{2}H-bonding solvent, complexes with sodium ions with respect to the oxygen atoms of the $P(O)(OEt)_2$ group, and thus reduces the effect observed in a aprotic solvent such as acetone.

The most significant changes effected by NaI on the ^{1}H nmr spectrum of the ester are the additional splitting of the $CH_3[3']$ and $CH_2[1]$ signals and the downfield shifts of the $CH_2[1]$ and $CH_2[2']$ signals, best seen at a spectral frequency of

400 MHz. The solvated sodium cation would appear to complex weakly with the phosphonate part of the molecule. This, in turn, may cause some significant conformational changes about the P-C[1] bond, which result in the complication of the deceptively simple CH_2[1] resonance. The loose complex may be as illustrated in figure 3.4.

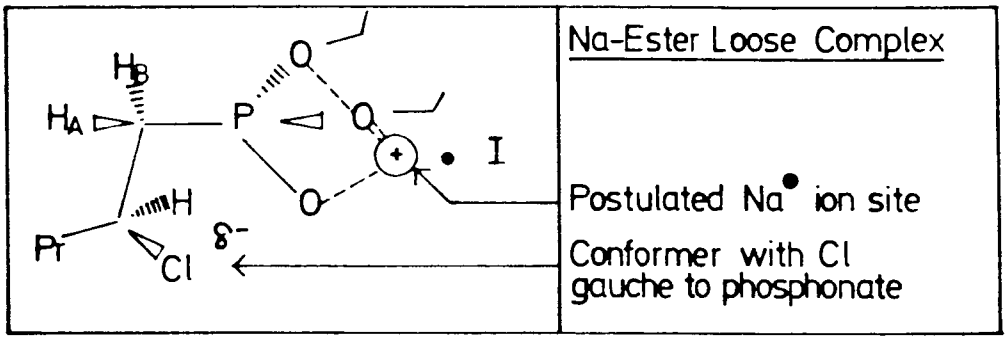


Figure 3.4

Possible stable conformations about the P-C[1] bond are shown below as Newmann projections.

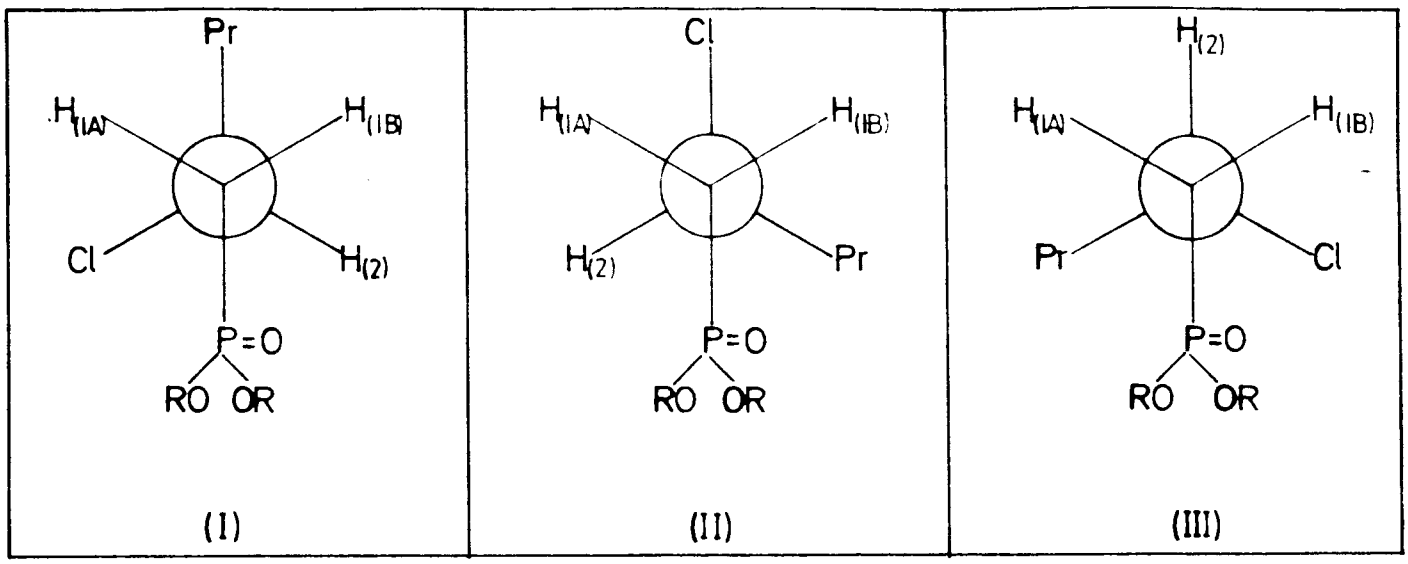


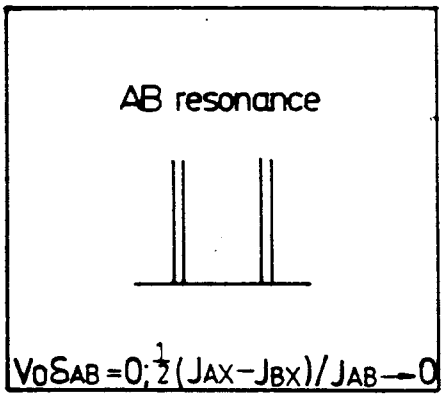
Figure 3.5 Newmann Projections of the stable conformations about the P-C[1] bond.

In conformer (II) the Cl-group is anti to the phosphonate group. It is therefore unlikely that the Cl-group and the sodium cation associated with the phosphonate group would have any interaction in this conformation. However, in conformers (I) and (III) where the Cl-group is gauche to the phosphonate group, some interaction with the sodium ion may be possible, and in fact, strong enough to hold the molecule in the (I) or (III) positions for longer than average. Restriction of rotation around the CH_2-P bond would result in the breakdown of the deceptively simple CH_2[1] into a more complex pattern.

In conformers (I) and (II), $H_{(1A)}$ and $H_{(1B)}$ are magnetically non-equivalent because the coupling constants (angle dependent) $|J_{H(2)-H(1A)}| \neq |J_{H(2)-H(1B)}|$. In conformer (III), $|J_{H(2)-H(1A)}|$ is probably equal to $|J_{H(2)-H(1B)}|$. In all three stable conformations, $|J_{P-H(1A)}|$ probably equals $|J_{P-H(1B)}|$. If rapid rotation around the P-C[1] bond is allowed, as should be the case if there is no NaI in solution, an average $|J_{H(2)-H(1)}|$ can be observed.

The CH_2[1] signal is a four spin system, with H(1A), H(1B), H(2) and P couplings. Conformers (I) and (II) are probably AA'MX or ABMX systems, depending on whether H(1A) and H(1B) have coincident chemical shifts (M = H(2); X = P). Conformer (III) is probably an A_2MX system in which H(1A) and H(1B) are effectively magnetically equivalent. Selective homonuclear irradiation at δ4.25 ppm (at the CH[2] signal) would collapse

the spin system to AA'X, A_2X or ABX[50]. The appearance of the AB part of the spectrum is as in figure 3.6 for the condition where $V_o\delta AB$, the chemical shift difference between A and B in Hz is equal to zero and $(J_{AX}-J_{BX})/2J_{AB}$ tends to zero.[51]



The signals in figure 3.6 are tending towards the CH_2[1] doublet which appears as result of decoupling the CH[2] proton.

Figure 3.6 Theoretical ABX spectrum[51]

A four spin system such as the one being studied has a possibility of 56 transitions, 32 of which would be seen (for the most general case, ABCD). Simpler 4 spin systems like AA'MX and ABMX still produce complex patterns which require computer analysis to be understood fully. Figure 3.7, although for an AA'BB' system, shows how the splitting pattern of the spectrum changes from two separate resonances to a symmetrical multiplet depending on the chemical shift difference between A and B nuclei.

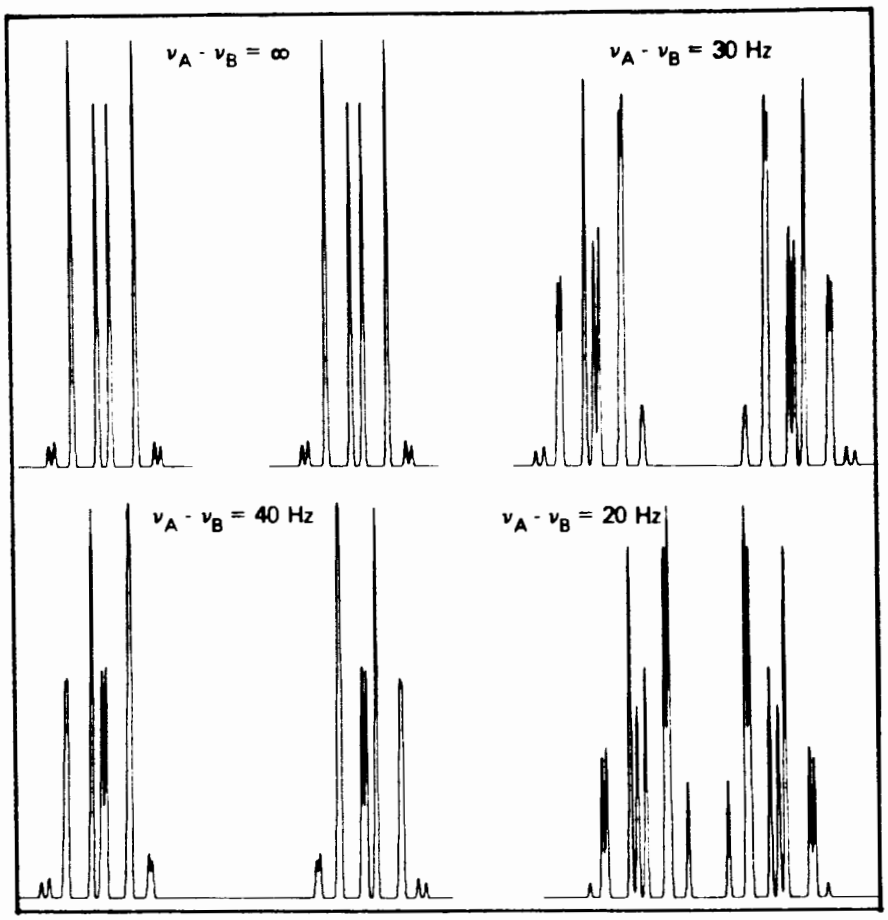
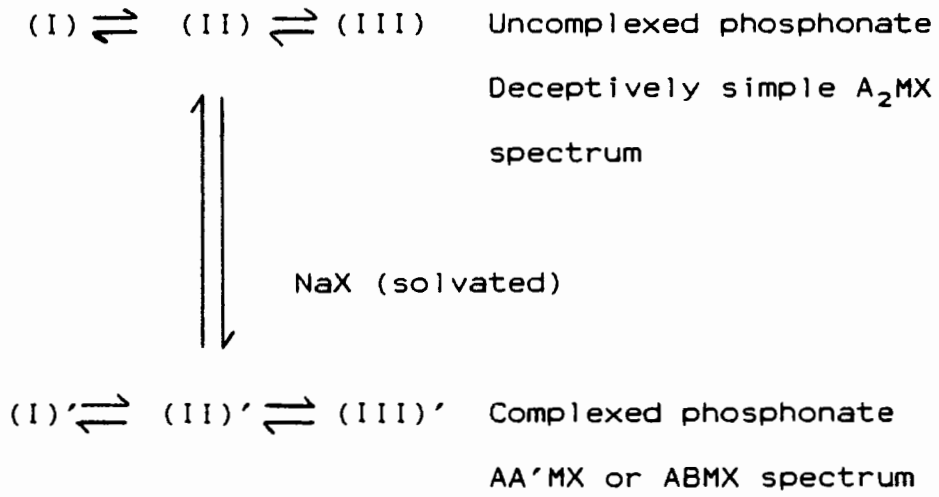


Figure 3.7 Simulated AA'BB' spectra with variation in $\nu_A - \nu_B$. The coupling constants are fixed at $J_{AB} = 7.5$, $J_{AA'} = 0.5$, $J_{AB'} = 2.0$, and $J_{BB'} = 7.0$ (all in Hz).

In our system a deceptively simple spectrum is broken down, supposedly by weak complexation of the sodium ion to the phosphonate, to yield, with varying quantities of salt, a pair of multiplets which in the limiting case (maximum NaI interaction) become a symmetrical multiplet. Protons $H_{(1A)}$ and $H_{(1B)}$, which were isochronous now have different chemical shifts with respect to each other.

In addition to weak complex formation, the NaI may induce a change in the equilibrium between stable conformers:



The shift in equilibrium may be due to restricted rotation or shift in the distribution of rotamers at room temperature because of sodium complexation.

The effect of changing the medium in which nmr samples are recorded from acetone-d_6 to acetone-d_6 + NaI in terms of magnetic susceptibility and viscosity differences must not be ignored entirely, although these effects would be small.

A downfield shift is observed in the ^{31}P resonance of the phosphonate when in the presence of NaI. There are reports of changes in the ^{31}P chemical shifts of biological compounds

induced by singly charged cations such as Na^+.[53,54] In one report,[53] the effect of the Na^+ ion is attributed to short range shielding/deshielding of " unbalanced p and d electrons " of the P atom, brought about by changes induced in its electronic interactions with adjacent atoms. These in turn are affected by local changes in their environment, such as weak complexation with sodium.

The nature of the complexation postulated for diethyl 2-chloropentylphosphonate would imply an increase in electrophilicity of the P atom, since negative charge would be drawn to the oxygen atoms of the phosphonate group to counteract the positive charge of the sodium ion. The increase in the electrophilicity would be expected to shift the ^{31}P signal downfield, and this is indeed what happens. ^{31}P resonances are known to be dependent on oxygen-phosphorous-oxygen bond angles.[55] Perhaps the penetration of the sodium cation into the solvation sphere of the phosphonate changes these bond angles to an extent which is observable as a shift in the ^{31}P resonance.

It is strange that such a "hard" positive centre as the sodium cation seems to have some chelating properties particularly with respect to a centre such as the chlorine group. However, alkali metals have been known to associate with phosphorus functionalities[56-58] and the CH-Cl group of the ester being studied here does appear to be part of the salt interaction.

Buncel et al.[59] give the kinetic evidence of the effect of alkali ions on the rate of nucleophilic displacement at the phosphoryl centre. With increasing alkali ion concentration, first order rate constants of the reaction increase sharply. Rate retardation is effected by addition of crown ether and cryptand complexing agents, which trap the alkali ions, preventing them from interacting as they did when free in solution. The explanation given for their observations was that strong interactions between the alkali ion and the phosphoryl group increases the electrophilicity of P. The alkali ion, by this interaction, serves as a catalyst for the reaction.

It would seem, therefore, that the sodium ion, normally not considered a complexing metal, has some complexing properties with diethyl 2-chloropentylphosphonate in acetone-d_6 solution.

CHAPTER 4

CONCLUSIONS

The chemical model of compound 1, β-trimethylammonioethylphosphonic acid, does not undergo Maynard and Swan fragmentation, even in very basic conditions at 100°C. It is, therefore, most unlikely that compound 1 would undergo similar fragmentation at physiological pH and temperature. If compound 1 was absorbed into a plant system, no intracellular fragmentation would occur and 2-(3,4-dichlorophenoxy)ethyldialkylamine and ethylene, the two biologically active species, would not be released. The studies undertaken in this project indicate that compound 1 would be an unsuitable plant growth regulator.

While attempting to modify the model compound in such a way that it would be susceptible to Maynard and Swan fragmentation, aspects of the chemistry of β-substituted alkylphosphonates came to light.

The rate of fragmentation of these substituted alkylphosphonates can be accelerated to a marked degree by the introduction of an alkyl group at the β-position of the substrate. The alkyl substituent is thought to provide added stabilization of the transition state of the reaction.

An esterified β-substituted phosphonic acid such as diethyl 2-chloropentylphosphonate is protected by its ester groups from Maynard and Swan fragmentation in alkali solution (eg. reaction with Me_3N), but, at the same time, is susceptible to base catalysed elimination of HCl to form diethyl 1-pentenylphosphonate as the major product. This is achieved under the mildest conditions, indicating that diethyl 1-pentenylphosphonate is a thermodynamically more stable system. Substitution of trimethylamine for chlorine at the 2-position is very much a secondary reaction even when conditions are adjusted to favour such a reaction.

Reaction of diethyl 2-chloropentylphosphonate with nucleophiles such as Br^- and I^- produces similar results to those obtained by reaction with a base such as trimethylamine.

It is interesting to note that diethyl 2-chloroethylphosphonate is easily converted to diethyl 2-iodoethylphosphonate (see experimental section 5.10) by reaction with excess NaI in acetone solution at 36°C for 4 days. There is no evidence for the formation of diethyl vinylphosphonate (by elimination of HCl). It would appear therefore that while the addition of an alkyl group to the β-position of a β-substituted alkylphosphonic acid enhances the rate of Maynard and Swan fragmentation, it hampers substitution of Br or I at the same time. For this reason, no acceptable synthesis of a modified model compound, β-trimethylammoniopentylphosphonic acid was achieved.

(Alternative synthetic pathways to those described in this thesis were not explored due to time limitations).

It may be that the 2-position on these alkylphosphonates has become less accessible to substitution by the addition of alkyl groups which are more bulky than a single hydrogen atom. It may also be energetically more favourable for a long-chain β-substituted alkylphosphonate to undergo elimination rather than substitution- the opposite may be the case for the short-chain β-substituted ethylphosphonate.

There is convincing evidence that, while no reaction of the diethyl 2-chloropentylphosphonate with NaI takes place, associations of the phosphonate part of the molecule with the sodium cation in acetone solution are strong enough to cause changes in the chemical shifts and splitting patterns of the signals in the nmr spectrum of the substrate.

A loose complex of the sodium cation co-ordinated with the three electronegative oxygens of the phosphonate moeity is postulated. To a certain extent, this results in added rigidity of the rest of the molecule as seen by the complication of the deceptively simple CH_2[I] ^{1}H nmr resonance. This unexpected result is not limited to NaI. Other simple salts such as $NaClO_4$, CaI_2, KSCN, not usually thought of as complexing agents, produce similar results.

CHAPTER 5

EXPERIMENTAL

General

NMR spectra were recorded on the following spectrometers: 60 MHz VARIAN EM 360A, 90 MHz BRUCKER WH90, 200 MHz VARIAN VXR200. Samples were sent to West Germany for spectroscopy on a 250 MHz BRUCKER spectrometer and a 400 MHz VARIAN spectrometer. Internal references used were tetramethyl silane (TMS) and the sodium salt of 3(trimethylsilyl)-propanesulfonic acid (DSS) for ^{1}H nmr ; TMS and acetone-d_6 for ^{13}C nmr; 89% H_3PO_4 for ^{31}P nmr. Mass spectra were recorded on a VG Micromass 16F spectrometer. C, H, N analyses were determined using a Heraeus Universal combustion analyzer. Melting points of solid products were obtained using a Fischer-Johns m.p. apparatus. Thin layer chromatography was carried out on aluminium backed silica gel plates (MERCK, Kieselgel 60 F_{254}, Art. 5554) and silica gel (MERCK, Kieselgel 60 F_{254}, Art. 9385, Korngroße 0.063-0.200 mm, 70-230 mesh ASTM) was used for column chromatography. Fine suspensions were filtered by using CELITE filter aid.

Reagents

Triethyl phosphite, 1,2-dibromoethane, isopropanol, thionyl chloride, triethyl orthoformate, diethyl phosphite and ethyl iodide were distilled before use.

Sodium carbonate, methyl iodide, 10M hydrochloric acid, hydrogen sulphide, 40% NaOD solution(spectroscopic grade), 25% Me_4NOH buffer, potassium hydroxide, phosphorus pentachloride, phosphorus pentoxide, magnesium sulphate, 1-pentene, conc. sulphuric acid, sodium iodide, 57% hydriodic acid, sodium, bromine, iodine, silver nitrate, sodium hydroxide, sodium thiosulphate, calcium iodide, potassium thiocyanate, sodium perchlorate, magnesium, acetone-d_6, methanol-d_4, chloroform-d, and D_2O were used as supplied.

A 4.36M solution of dimethylamine in absolute ethanol was made up by heating 40% aqueous dimethylamine and allowing the volatile dimethylamine to be bubbled through a KOH drying tower into absolute ethanol. The solution was standardized with 0.05M HCl using methyl red as indicator.

Silver oxide (Ag_2O) was prepared by reaction of 1 equivalent of silver nitrate with 1 equivalent of sodium hydroxide in aqueous solution at room temperature. The precipitate (Ag_2O) which came out of solution was washed with water until the washings were neutral and dried in a dessicator.

A 0.03g.ml^{-1} solution of sodium thiosulphate was made up (w/v) using distilled water.

Sodium hydride (packaged as a 50% suspension in oil) was washed with dry petroleum ether in a dry N_2 atmosphere before use.

Absolute ethanol was prepared by reaction with dry magnesium turnings and iodine and subsequent distillation.[60]

A 3.75M solution of triethylamine in acetonitrile was standardised by titration against 0.5N HCl solution using methyl red as indicator.

Solvents were dried according to standard procedures and all water used in reactions was glass distilled. Nitrogen was dried over P_2O_5 and conc. H_2SO_4.

Reactions

5.1 Synthesis of β-trimethylammonioethylphosphonic acid[34]

Step(i) Preparation of diethyl β-bromoethylphosphonate[35]

A mixture of 1,2-dibromoethane (136g) and triethyl phosphite (30g) was heated at 145°C for three hours. A condenser was fitted above the reaction vessel and water heated to a temperature of 50°C was pumped through it. The ~~departed~~ EtBr formed was collected in a cold trap (60% yield). The remaining reaction mixture was distilled under high vacuum. (77% yield; b.p. 99-106°C at 1 mmHg). Calculated for $C_6H_{14}O_3PBr$: C, 29.4; H, 5.8%. Found: C, 29.35; H, 5.7%. ^1H nmr (CCl_4): δ1.3 (t; J_{H-H} = 7Hz; 6 protons; CH_3), δ1.7-δ2.6 (m; J_{H-H} = 7Hz; J_{H-P} = 18Hz; 2 protons; CH_2P), δ3.46 (m; J_{H-H} = 7Hz; 2 protons; CH_2-Br), δ4.06 (quintet; $J_{H-H} = J_{H-P}$ = 7Hz; 4 protons; OCH_2)

Step(ii) Preparation of diethyl β-dimethylaminoethyl-phosphonate.

To 118 ml of a 4.36 M solution of dimethylamine in absolute ethanol, 31.6 g of diethyl β-bromoethylphosphonate was added. The reaction, which is exothermic at first, was allowed to proceed at room temperature, with stirring, for 2 days. The reaction mixture was then stripped of solvent, leaving a viscous liquid, $Me_2N-CH_2CH_2P(O)(OEt)_2$ and some solid $Me_2N^+H-CH_2CH_2P(O)(OEt)_2Br^-$, as residue. The viscous liquid was then

taken up in ether, 7.4 g of Na_2CO_3 was added to it, and the mixture was filtered to remove all solid material. Once all solvent had been removed on a rotary evaporator, a clear liquid remained as residue. (83% yield; b.p. 93-95°C at 0.9 mmHg). ^1H nmr (CCl_4): δ1.33 (t; J_{H-H} = 8Hz; 6 protons; ester-CH_3), δ1.53-δ2.93 (m; 4 protons; CH_2CH_2), δ2.2 (s; 6 protons, Me_2N), δ4.0 (quintet; $J_{H-H} = J_{H-P}$ = 8 Hz; 4 protons; O-CH_2)

Step(iii) Quaternization of diethyl β-dimethylaminoethylphosphonate to diethyl β-trimethylammonioethylphosphonate iodide.

Approximately 200 ml of CCl_4 containing 22.4g of Me_2N-$CH_2CH_2P(O)(OEt)_2$ and 45.7g of MeI was stirred together, with cooling. After a few minutes, the precipitate was filtered off and recrystallized from ethyl acetate and methanol (60% yield; m.p. 156-159°C. Calculated for the monohydrate $C_9H_{23}O_3PNI$: C, 30.78; H, 6.60; N, 3.98%. Found: C, 30.7; H, 6.3; N, 3.95%. ^1H nmr (D_2O): δ1.33 (t; J_{H-H} = 7 Hz; 6 protons; ester-CH_3), δ1.90-δ2.96 (m; 2 protons; CH_2P), δ3.15 (s; 9 protons; Me_3N^+-), δ3.32-δ3.90 (m; 2 protons; CH_2N-), δ4.20 (quintet; $J_{H-H} = J_{H-P}$ = 7Hz; 4 protons; OCH_2).

Step(iv) Hydrolysis of diethyl β-trimethylammonioethyl-phosphonate iodide to zwitterionic β-trimethylammonioethyl-phosphonic acid

A solution of 22.4g of $Me_2N^+-CH_2CH_2P(O)(OEt)_2I^-$ in 100 ml 10 M HCl was heated to reflux for 22 hours. Excess HCl was removed first by a rotary evaporator and then by a high vacuum pump for 3 hours. The semi-crystalline orange residue remaining was added to an aqueous solution containing 23g Ag_2O. A grey precipitate separated out, which was filtered off by vacuum filtration using CELITE filter aid. The filtrate then had H_2S bubbled through it for 15 minutes. After the reaction mixture had been concentrated to approximately half its volume, the Ag_2S precipitate was filtered off. Further concentration produced 9g of a white solid, $Me_2N^+-CH_2CH_2P(O)(OH)(O^-)$ which was recrystallized from from ethanol and methanol. (76% yield; m.p. 252°C). Calculated for the monohydrate $C_5H_{16}O_4PN$: C, 32.4; H,8.6; N,7.6%. Found: C,32.2; H, 8.25; N, 7.65%. ^1H nmr (D_2O): δ1.9-δ2.4 (m; J_{H-H} = 6Hz; 2 protons; CH_2-P), δ3.12 (s; 9 protons; $(CH_3)_3N^+$), δ3.52 (m; J_{H-H} = 6Hz; 2 protons; CH_2-N).

5.2 Reaction of β-trimethylammonioethylphosphonic acid with sodium deuteroxide in D_2O.

One hundred mg of $Me_2N^+-CH_2CH_2P(O)(OH)O^-.H_2O$ was dissolved in 0.5 ml D_2O containing 50 µl 25 % Me_4NOH, in an nmr tube. ^1H nmr in D_2O was identical to that obtained in step(iv) of the

synthesis of $Me_3N^+-CH_2CH_2P(O)(OH)O^-.H_2O$ with additional peak: δ3.16 (s; 12 protons; Me_4N-). The reaction solution was made basic by the addition of 100 µl of NaOD (a 40% solution). After 24 hours with no apparent change in the nmr spectrum, the tube was incubated at 60°C. No fragmentation products were observed in the nmr spectrum even over a period of days.

5.3 Reaction of β-trimethylammonioethylphosphonic acid with sodium hydride in dimethylsulfoxide.

β-trimethylammoniumethylphosphonic acid (1g) was added to a solution of 0.288g NaH (i.e. 0.576g of a 50% suspension in oil) in 15 ml freshly distilled DMSO. Reagents were added slowly, with cooling, under a flow of dry N_2 gas. The β-trimethylammoniumethylphosphonic acid was reluctant to dissolve, but after some time formed a fine suspension. The N_2 flow was stopped and a tube connecting the the reaction vessel to a water-filled inverted flask in a water bath was attached to collect any ethylene or trimethylamine gas which may evolve. Over a period of 5 days at both room temperature and at 100°C, no reaction took place. No gas evolved and the pH of the water bath remained neutral.

5.4 Attempted synthesis of 2-chloropropylphosphonic acid[22]

Concentrated sulphuric acid (225ml) was added dropwise to 128 ml isopropanol in a 1 liter round bottomed flask. During this

procedure, the solution was stirred with cooling. This flask was connected via a sulphuric acid drying tower to another round bottomed flask containing 70.5g of PCl_5 suspended in 150ml of benzene. The isopropanol/H_2SO_4 solution was heated with stirring at such a rate that an even flow of propene gas was produced. The propene was allowed to pass into the PCl_5/benzene solution, which was kept at 0-5°C in an ice-salt bath for 8 hours. The mixture was left to stand overnight, then, after the addition of 15.51g P_2O_5g, was stirred for 4 hours while being heated to 50°C. The P_2O_5 did not dissolve completely and the reaction mixture turned dark. The solution was filtered and distilled to yield two fractions: benzene, b.p.80-82°C; $POCl_3$, b.p 100-105°C. According to the literature, another fraction, 2-chloropropylphosphonic dichloride, remains(b.p. 88-92°C at 12 mmHg). However, here only a small amount of black, tarry residue was left after distillation. The dichloride is supposed to be added dropwise to distilled water, then dried by evaporation to form 2-chloropropylphosphonic acid in 74% yield (m.p. 85-87°C when recystallized from toluene). This stage in the preparation was never reached.

5.5 Synthesis of 2-chloropentylphosphonic acid[22]

A benzene solution (250ml) containing 58ml 1-pentene and a suspension of 222g of phosphorus pentachloride was stirred overnight at room temperature. The mixture was then poured

slowly into 250g of ice and left to cool and separated into benzene and aqueous phases. The layers were separated and the aqueous phase was washed with 50ml of benzene. This washing was added to the benzene layer which was then dried with $MgSO_4$, and stripped of solvent on a rotary evaporator. Petroleum ether (b.p. 60-80°C) was added to the remaining oily residue, precipitating a soft-grey brown solid which was recrystallized from boiling chloroform by pouring the solution into chilled petroleum ether (b.p. 30-40°C) (White solid; m.p. 87-89°C; 13% yield).

Calculated for the monohydrate, $C_5H_{14}O_4PCl$: C, 29.35; H, 6.90%. Found: C, 29.05; H, 6.05%. ^1H nmr (D_2O): δ0.90 (t; J_{H-H} = 7 Hz; 3 protons; CH_3), δ1.48 (m; 2 protons; CH_2 adjacent to CH_3), δ1.77 (m; 2 protons; CH_2), δ2.34 (doublet of doublets; J_{H-P} = 18 Hz; J_{H-H} = 7 Hz; 2 protons; CH_2-P), δ4.30 (m, 1 proton; CH(Cl)).

5.6 Attempted formation of diethyl 2-chloropentylphosphonate via 2-chloropentylphosphonic dichloride.

One gram of 2-chloropentylphosphonic acid was dissolved in 10ml freshly distilled thionyl chloride. The mixture was allowed to reflux overnight. The thionyl chloride was removed by a rotary evaporator leaving an oily residue assumed to be $C_3H_7CH(Cl)CH_2P(O)Cl_2$ (64% yield). ^1H nmr (CCl_4): δ0.40-δ1.30 (m; CH_3), δ1.30-δ2.43 (m; CH_2CH_2), δ2.43-δ3.87 (m; CH_2-P), δ3.87-δ5.13 (m; CHCl). All signals were poorly resolved, but assignments were made by comparison with starting material.

The oily residue (0.7g) was taken up in dry benzene and added dropwise to a chilled, stirred solution of 0.4 ml of dry ethanol and 0.87 ml of dry triethylamine in benzene. A water-cooled reflux condenser was fitted above the reaction vessel and the mixture was warmed on a hot water bath for 2 hours. A fine precipitate formed which was removed by vacuum filtration. Benzene was removed by evaporation from the filtrate to leave a small amount of dark oily residue (21% crude yield), which gave a poorly resolved ^{1}H nmr spectrum and charred on distillation, even under high vacuum.

5.7 Synthesis of diethyl 2-chloropentylphosphonate

A solution of 17.9g 2-chloropentylphosphonic acid in 40ml triethyl orthoformate was heated in an oil bath to 105°C for 2 hours. Volatile byproducts of the reaction, namely ethanol and ethyl formate were allowed to escape through a fractionating column fitted above the reaction vessel, and were condensed in a water-cooled condenser and collected in an ice-cooled trap. During the course of the reaction, the temperature at the still head rose to 69-71°C and after 2 hours dropped to 40°C after which volatiles stopped collecting. The last traces of low boiling components of low boiling components were removed from the reaction mixture using a rotary evaporator, leaving behind a residue of mass 17.58g (75% crude yield). The required product was isolated from this residue by column chromatography. Using Silica gel and a mixed eluting solvent (80% $CHCl_3$; 15% $(CH_3)_2CO$;

5% toluene), 96% of the applied sample was recovered from the column. (Colourless liquid; b.p. 99-102°C at 0.1 mmHg). Thin layer chromatography: R_f = 0.7, using the eluting solvent above. Calculated for $C_9H_{20}O_3PCl$: C,44.54; H, 8.31%. Found: C,44.40; H, 8.05%. ^1H nmr (acetone-d_6) for $C_3H_7CH(Cl)CH_2P(O)(OCH_2CH_3)_2$, numbering carbon atoms 1-5 down the pentyl carbon chain away from the phosphorus group: δ0.92 (t; J_{H-H} = 8Hz; 3 protons; CH_3[5]), δ1.27 (t; J_{H-H} = 8Hz; 6 protons; CH_3 of ester group), δ1.56 (m; 2 protons; CH_2[4]), δ1.88 (m; 2 protons; CH_2[3]), δ2.29 (doublet of doublets; J_{H-P} = 20 Hz; J_{H-H} = 8Hz; 2 protons; CH_2[1]), δ4.05 (m; J_{H-H} = 8Hz; 4 protons; CH_2 of ester group), δ4.26 (m; 1 proton; CH(Cl)). ^{13}C nmr (acetone-d_6): δ13.03 (quartet; C[5]), δ16.16 (quartet; $^3J_{P-C}$ = 5.7Hz; methyl C of ester group), δ19.44 (t; C[4]), δ35.86 (^{31}P coupled triplet; $^1J_{P-C}$ = 137.5 Hz; C[1]), δ41.11 (t; $^3J_{P-C}$ = 7.4 Hz; C[3]), δ57.38 (doublet; $^2J_{P-C}$ ~ 0; C[2]), δ61.53 (t; $^2J_{P-C}$ = 7.1 Hz; one methylene C of ester group), δ61.71 (t; $^2J_{P-C}$ = 6.1 Hz; the other methylene C of ester group). (Multiplicities of ^{13}C signals quoted here were derived in a separate off-resonance decoupling experiment). ^{31}P nmr ($CDCl_3$): δ26.60 ppm w.r.t. 89% H_3PO_4.

5.8 Reaction of NMe_3 with diethyl 2-chloropentylphosphonate

Diethyl 2-chloropentylphosphonate (0.4g) was placed in a 3ml ampoule partially filled with freshly dried acetonitrile. The ampoule was chilled in a dry ice bath, then 0.73ml of 3.75M

solution of trimethylamine in acetonitrile was added to the mixture. The tube was sealed and placed in a 60°C water bath. After 24 hours, white, needle-like crystals had formed and the solution had turned yellow. The precipitated crystals (Me_3NHCl) were separated from the reaction solution and washed with cold, dry solvent, then dried under high vacuum, since they were hygroscopic. ^1H nmr (D_2O): δ2.92 (s; 10 protons; Me_3NHCl). The remaining reaction mixture was stripped of solvent on a rotary evaporator. The oily residue was washed with D_2O and extracted into $CDCl_3$. The $CDCl_3$ layer, dried with $MgSO_4$, contained $C_3H_7CH{=}CH{-}P(O)(OEt)_2$ (60% yield). ^1H nmr ($CDCl_3$): δ0.90 (t; J_{H-H} = 7Hz; 3 protons; CH_3[5]), δ1.33 (t; J_{H-H} = 7Hz; 6 protons; CH_3 of ester group), δ1.72 (m; J_{H-H} = 7Hz; 2 protons; CH_2[3]), δ4.06 (quintet; J_{H-H} = J_{H-P} = 7Hz; 4 protons; CH_2 of ester group), δ5.60 (m; J_{H-P} = 18 Hz; 1 proton; CH[1]), δ6.70 (m; J_{H-H} = 7 Hz; 1 proton; CH[2]). The D_2O layer contained mainly Me_3NHCl and traces of what is probably $C_3H_7CH(N^+Me_3)CH_2P(O)(OEt)_2$. ^1H nmr (D_2O): δ1.27 (m; 9 protons; CH_3 groups on phosphonate), δ2.90 (s; 10 protons; Me_3NHCl), δ3.08 (s; 9 protons; Me_3N^+-), δ3.56 (m; 11 protons; remaining CH_2, CH groups on phosphonate). Ratio of proposed products in D_2O phase: 82% Me_3NHCl: 18% $C_3H_7CH(N^+Me_3)CH_2P(O)(OEt)_2$.

5.9 Attempted conversion of diethyl 2-chloropentylphosphonate to diethyl 2-iodopentylphosphonate by reaction with sodium iodide

A five-fold excess of dried NaI (3.67g), dissolved in dry acetone, was heated under reflux with 1.32g of diethyl 2-chloropentylphosphonate for 24 hours, then filtered and distilled to dryness. The semi-solid residue was taken up in chloroform and filtered ~~gravitationally~~ under gravity. The filtrate was centrifuged for 15 minutes, then the solvent was removed from the supernatant by a rotatory evaporator to yield a red oil. Subsequent characterization of this product indicated that starting material had been recovered (75% yield). Calculated for $C_9H_{20}O_3PI$: C, 32.35; H, 6.03%. Calculated for $C_9H_{20}O_3PCl$: C, 44.54; H, 8.31%. Found C, 45.95; H, 7.85%. ^1H nmr (acetone-d_6): as for diethyl 2-chloropentylphosphonate (see experimental section (no.5.7)). ^1H nmr (acetone-d_6) When NaI is present in sample: the CH_2-P signal (δ2.30) shifts to δ2.44 ppm, with additional splitting.

5.10 Synthesis of diethyl 2-iodoethylphosphonate

A solution consisting of 0.46g dry NaI and 0.25g diethyl 2-bromoethylphosphonate dissolved in acetone was placed in a water bath at 36°C for 4 days. The acetone was removed on a rotary evaporator,then the residue was partitioned between chloroform and water. The chloroform layer was separated and dried with $MgSO_4$. The solvent was removed, leaving a yellow liquid,

$(EtO)_2P(O)CH_2CH_2I$. Calculated for $C_6H_{14}PO_3I$: C, 24.67; H, 4.83%. Found: C, 24.60; H, 4.83%. ^1H nmr (acetone-d_6): δ1.92 (t, J_{H-H} = 8Hz; 6 protons; CH_3), δ2.30-δ2.76 (m; 2 protons; CH_2-P), δ3.22-δ3.50 (m; 2 protons; CH_2-Br), δ4.14 (quintet; J_{H-H} = J_{H-P} = 8Hz; 4 protons; OCH_2).

5.11 Attempted conversion of 2-chloropentylphosphonic acid to 2-iodopentylphosphonic acid by reaction with sodium iodide

Sodium iodide (0.422g) was dissolved in 0.5ml acetone-d_6 containing 0.1102g of 2-chloropentylphosphonic acid. The mixture was placed in a water bath at 36°C for 24 hours. The nmr spectrum of the mixture was recorded several times during this period to monitor the progress of the reaction. ^1H nmr in acetone d_6 was essentially the same as that recorded for starting material.

5.12 Attempted conversion of 2-chloropentylphosphonic acid to 2-iodopentylphosphonic acid by reaction with hydriodic acid[43]

One gram of 2-chloropentylphosphonic acid was allowed to reflux in 2ml of a 57% solution of hydriodic acid for 17 hours. Unreacted HI was removed first by a rotary evaporator, then by a high vacuum pump for over 8 hours. The remaining dark, oily residue was taken up in 3ml diethyl ether and washed four times with 3ml quantities of a $0.03g.ml^{-1}$ solution of sodium thiosulphate until decolourized. The ethereal layer was then

dried over $MgSO_4$, decanted and the product recrystallized from diethyl ether and petroleum ether (b.p. 30-40°C). Calculated for $C_5H_{12}O_3PI$: C,21.60; H, 4.35%. Found: C, 23.35; H, 4.65%. ^1H nmr (acetone-d_6): There was evidence that all required peaks were present, but the spectrum was poorly resolved.

5.13 Esterification of crude 2-iodopentylphosphonic acid

Crude 2-iodopentylphosphonic acid (1.49g) was dissolved in 4.5ml triethyl orthoformate and heated on an oil bath at 140°C for 3 hours. A still head, condenser and icetrap were connected to the reaction vessel in order to trap escaping volatile byproducts. The reaction mixture was stripped of the last traces of volatiles on a rotary evaporator, leaving 0.14g of a red oil. This was applied to a silica gel column with eluting solvent chloroform:acetone (4:1). Fractions of 3ml volume were collected, and most of the sample was recovered between fractions 3 to 8, as a yellow liquid. Calculated for $C_9H_{20}O_3PI$: C, 32.35; H, 6.03%. Calculated for $C_9H_{20}O_3Cl$: C, 44.54; H, 8.31%. Found: C, 44.7; H, 8.35%. ^1H nmr ($CDCl_3$): δ0.94 (t; J_{H-H} = 8 Hz; CH_3[5]), δ1.32 (t; J_{H-H} = 8Hz; 6 protons; ester-CH_3), δ1.46-δ2.11 (m; 4 protons; CH_2CH_2), δ2.11-δ2.46 (doublet of doublets; J_{H-H} = 8 Hz; J_{H-P} = 20 Hz; 2 protons; CH_2-P), δ3.81-δ4.37 (m; 5 protons; CH[2] and OCH_2), δ5.3-δ7.0 (m; trace amount; CH=CH of C_3H_7-CH=CH-P(O)(OEt)$_2$.

5.14 Preparation of 1,2-diiodopentane[45]

Iodine (12.69g) was added in small quantities to 7.013g of 1-pentene, while the solution was stirred and chilled in an ice-salt bath. Once all the iodine had dissolved, the solution was allowed to stir at room temperature for an hour. The colourless mixture proved to consist of 50% 1,2-diiodopentane and 50% 1-pentene. ^{1}H nmr (CCl_4): δ1.0 (t; J_{H-H} = 6Hz; CH_3 of diiodopentane and 1-pentene superimposed), δ1.17-δ2.36 (m; CH_2CH_2 of 1,2-diiodopentane and 1-pentene superimposed), δ3.40-δ4.63 (m; 3 protons; -CH(I)CH_2(I)), δ4.63-δ6.12 (m; 3 protons; -$CH{=}CH_2$).

5.15 Attempted synthesis of diethyl 2-iodopentylphosphonate via the Michaelis-Becker reaction[29,44]

Distilled diethyl phosphite (6.44ml; b.p. 86-91^{o}C at 20mmHg) was stirred with 25ml sodium-dried hexane under a flow of dry nitrogen. Freshly cut sodium metal (1.15g) was added to the mixture, in small quantities which were allowed to be absorbed into the solution before further additions were made. The reaction solution was heated gently to hasten the absorption of the last pieces into the solution. The mixture was cooled to room temperature, the 12.69g of I_2 and 7.013g of 1-pentene, which had been stirred together for 1 hour (see experimental section no.(5.14)), were added dropwise to it. The mixture was allowed to reflux for 3 hours, then was left to stand overnight.

After the addition of a small volume of water, the mixture was shaken and the aqueous and organic layers were allowed to separate out. The aqueous layer was washed three times with chloroform. These chloroform washings were combined with the organic layer, which was dried with $MgSO_4$, was filtered and then stripped of solvent by a rotary evaporator, to yield 0.61g of an oily residue. This appeared to consist of 74% diethyl phosphite and 26% of the required product. Calculated for $C_9H_{20}O_3PI$: C, 32.35; H, 6.03%. Found: C,23.35; H, 5.45%. ^1H nmr ($CDCl_3$): δ0.66-δ1.11 (m; 3 protons; CH_3[5]), δ1.36 (t; J_{H-H} = 6Hz; ester-CH_3 of product and CH_3 of diethyl phosphite), δ1.58-δ2.88 (m; 6 protons; CH_2CH_2 and CH_2-P of product), δ3.54-δ4.64 (m; OCH_2 groups of diethyl phosphite and product; -CH[2] of product). Assignments are tentative, however, since the nmr was poorly resolved.

5.16 Preparation of 1,2-dibromopentane

Bromine liquid (4.7ml) was added very slowly to 10ml 1-pentene with stirring and cooling in an ice-salt bath. After the addition was completed, the mixture was left to stir at room temperature for 1 hour (Colourless liquid; 100% yield). Calculated for $C_5H_{10}Br_2$: C, 26.2; H,4.38%. Found: C, 25.95; H, 4.45%. ^1H nmr ($CDCl_3$): δ1.16 (t; J_{H-H} = 6Hz; 3 protons; CH_3), δ1.20-δ2.48 (m; 4 protons; CH_2CH_2), δ3.33-δ4.70 (m; 3 protons; CH(Br)-CH_2Br). ^{13}C nmr($CDCl_3$): δ13.315 (C[5]); δ20.208 C([4]); δ36.420 (C[3]); δ38.119 (C[1]); δ52.827(C[2]).

5.17 Attempted synthesis of diethyl 2-bromopentylphosphonate via the Michaelis-Becker reaction

Diethyl phosphite (7.3ml) in 40ml hexane was stirred at room temperature while 1.04g of sodium was added in small quantities. The last pieces of sodium required heating of the mixture to reflux temperature before being absorbed. The solution was then cooled and 6ml of 1,2-dibromopentane were added slowly, with stirring. The solution was allowed to reflux for 3 hours and left to stand. A white precipitate formed overnight. The reaction mixture was washed with water and the organic layer was dried and stripped of solvent (liquid residue, 44.6% yield). Calculated for $C_9H_{20}O_3PBr$: C, 37.65; H, 7.02%. Calculated for $C_5H_{10}Br$: C, 26.12; H, 4.38%. Found: C, 29.4; H, 5.1%. ^1H nmr ($CDCl_3$): as for 1,2-dibromopentane (see experimental, Section no.(5.16)), δ2.46-δ3.03 (broad multiplet; trace amount of uncharacterized species).

5.18 Attempted synthesis of diethyl 2-~~chloro~~bromopentylphosphonate via the Arbuzov reaction

Freshly distilled triethyl phosphite (8.44g) and 11.73 of 1,2-dibromopentane were stirred together for 1 day, while being heated in an oil bath to 200°C. The volatile byproduct, EtBr, was allowed to escape through a water condenser which had water heated to 50°C pumped through it. The EtBr was subsequently

condensed and trapped in a dry ice/acetone bath (62% yield). The reaction mixture was stripped of the last traces of the volatiles on a rotary evaporator, leaving a yellow liquid residue (95% crude yield). Calculated for $C_9H_{20}O_3PBr$: C, 37.65; H, 7.02%. Found: C, 36.50; H, 7.30%. The evaporated reaction mixture was applied to a silica gel column, using chloroform as eluting solvent, and was recovered in 73% yield. Fractions were collected in volumes of 5ml, and the maximum masses of recovered solvent eluted in the tenth and sixteenth fractions, the former consisting of 1,2-dibromopentane and the latter of what seems to be 52% $C_3H_7CH=CHP(O)(OEt)_2$ and 48% $C_3H_7CH(Br)CH_2P(O)(OEt)_2$. ^1H nmr of fraction 16 ($CDCl_3$): δ0.93 (t; J_{H-H} = 7Hz; C[5] methyl group of both products superimposed), δ1.32 (t; J_{H-H} = 7 Hz; CH_3 of ester groups of both products superimposed), δ1.44-δ2.76 (m; 6 protons; CH_2CH_2 and CH_2-P of $C_3H_7CH(Br)CH_2P(O)(OEt)_2$), δ3.72-δ4.38 (m; OCH_2 groups of both products superimposed, CH-Br), δ5.29-δ7.07 (m; 2 protons; CH=CH).

5.19 Isomerisation of triethyl phosphite to diethyl ethylphosphonate

Freshly distilled ethyl iodide (5.96g; b.p. 72-76°C) was mixed with 7g of triethyl phosphite and allowed to reflux gently for 4 hours. The ethyl iodide was then distilled off under atmospheric pressure, leaving diethyl ethylphosphonate (95% yield) which was distilled under reduced pressure (b.p. 96-98°C

at 15 mmHg). ^{1}H nmr ($CDCl_3$): δ0.98 (t; J_{H-H} = 8Hz; 3 protons; CH_3 of ethyl-P group), δ1.33 (t; J_{H-H} = 7 Hz; 6 protons; CH_3 of ester groups), δ1.52-δ2.05 (m; 2 protons; CH_2-P), δ4.13 (quintet; J_{H-H} = J_{H-P} = 7Hz; $-OCH_2$).

APPENDIX

Mass Spectra

Mass spectra were obtained from a VG Micromass 16F spectrometer at 70eV and 200°C.

1. Diethyl 2-chloropentylphosphonate $C_3H_7CH(Cl)CH_2P(O)(OEt)_2$

Fragment	m/e	% abundance
$M^{+\cdot}$	243	21
$C_3H_7\overset{+}{C}HCH_2P(O)(OEt)_2$	207	100
$C_3H_7\overset{+}{C}HCH_2\text{-}P(O)(OH)OEt$	179	15
$C_3H_7\overset{+}{C}HCH_2P(O)(OH)_2$	151	43
$[CH_3CH_2P(O)(OH)OEt]^{+\cdot}$	138	41
$\overset{+}{P}(O)(OH)_2$	81	15
$C_5H_9^{+}$	69	35
$C_3H_5^{+}$	41	29

2. Diethyl 1-pentenylphosphonate ($C_3H_7CH=CH-P(O)(OEt)_2$)

	Fragment	m/e	% abundance
	$M^{+\cdot}$	206	11
	$\overset{+}{C}H_2CH_2CH=CHP(O)(OEt)_2$	191	20
	$\overset{+}{C}H_2-CH=CHP(O)(OEt)_2$	177	44
	$\overset{+}{C}H=CHP(O)(OEt)_2$	163	97
OR	$\overset{+}{C}H_2-CH_2-CH=CHP(O)(OH)OEt$		
	$\overset{+}{C}H_2=CH-P(O)(OH)OEt$	135	100
OR	$\overset{+}{C}H_2-CH_2-CH=CH-P(O)(OH)_2$		
	$\overset{+}{C}H_2-CH=CH-P(O)(OH)_2$	121	19
	$\overset{+}{P}(O)(OH)_2$	81	15
	$C_5H_5^+$	65	31
	$C_3H_5^+$	41	51

3. Diethyl 2-bromoethylphosphonate ($BrCH_2CH_2P(O)(OEt)_2$)

Fragment	m/e	% abundance
$M^{+\cdot}$	245	62
$[BrCH_2CH_2P(O)(OH)OEt]^{+\cdot}$	217	17
$[BrCH_2CH_2P(O)(OH)_2]^{+\cdot}$	189	26
$\overset{+}{C}H_2CH_2P(O)(OEt)_2$	165	100
$\overset{+}{C}H_2CH_2P(O)(OH)OEt$	137	29
$\overset{+}{C}H_2CH_2P(O)(OH)_2$	109	79
$\overset{+}{P}(O)(OH)_2$	81	47
~~$C_5H_5^+$~~ $\overset{+}{P}(OH)_2$	65	25

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