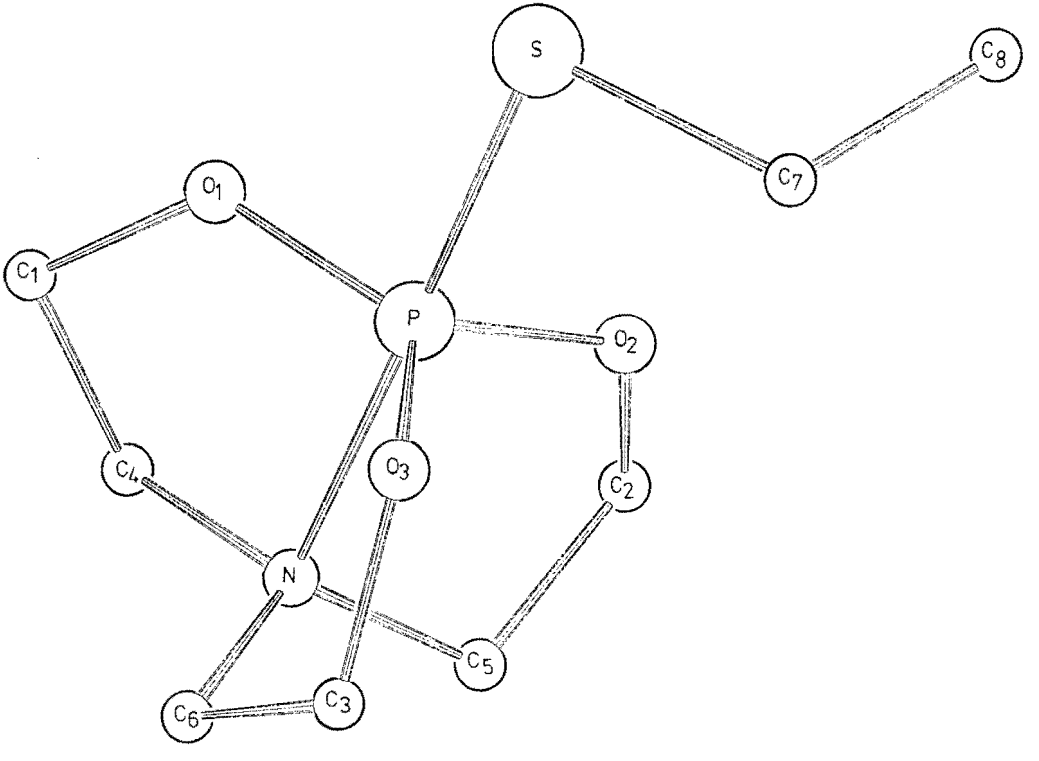
Selectivity in reactions proceeding via five-coordinated phosphorus compounds

SELECTIVITY IN REACTIONS PROCEEDING VIA FIVE-COORDINATED PHOSPHORUS COMPOUNDS



D. VAN AKEN

SELECTIVITY IN REACTIONS PROCEEDING VIA FIVE-COORDINATED PHOSPHORUS COMPOUNDS

PROEFSCHRIFT

ter verkrijging van de graad van doctor in de technische wetenschappen aan de Technische Hogeschool Eindhoven, op gezag van de rector magnificus, prof. ir. J. Erkelens, voor een commissie aangewezen door het college van dekanen in het openbaar te verdedigen op dinsdag 6 januari 1981 te 16.00 uur

door

DIRK VAN AKEN

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DE PROMOTOREN

PROF. DR. H.M. BUCK

EN

PROF. DR. W. DRENTH

Aan mijn ouders

Contents

CHAPTER I

General introduction

I.1 *Recent developments in phosphorus chemistry*

In the past few decades, research in organophosphorus chemistry has developed enormously[1]. The two major reasons for the growing interest in phosphorus are the increasing use of phosphorus reagents in organic synthesis, *e.g.* in the Wittig reaction[1,2] and its modifications, and the study of biochemical processes at a molecular level[1,3,4].

In living cells, "high-energy" phosphates such as adenosine triphosphate (ATP, Fig. I.1) are involved in many processes.

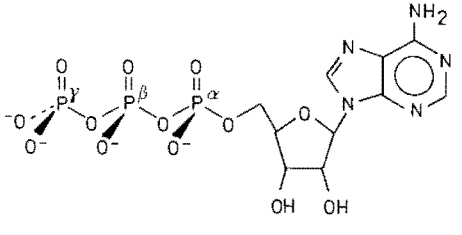
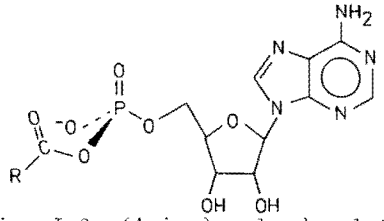


Fig. I.1 Structure of adenosine triphosphate, ATP

ATP is produced by phosphorylation of adenosine diphosphate (ADP) when large molecules taken up by the cell are broken down to smaller fragments[5]. The free enthalpy stored in ATP is used for the biosynthesis of complex molecules, for active transport through membranes, for muscle contraction, etc. The utilization of ATP energy is usually accomplished by transfer of the terminal (γ-)phosphate group to acceptor molecules[6]. In some cases, however, the α-phosphate group with the adenosine

moiety is transferred to the substrate, normally an (amino) acid[7,8]. Thus, fatty acids are first converted to acyl adenylates (Fig. I.2) before their stepwise oxydation to acetyl



RCOOH = fatty acid or amino acid

Fig. I.2 (Amino)acyl adenylate

coenzyme A. Similarly, amino acids are converted to aminoacyl adenylates at the start of protein biosynthesis. The (amino-) acyl adenylates are enzyme-bound intermediates, from which the (amino)acyl group is transferred to an acceptor: coenzyme A in the case of fatty acids, and the appropriate tRNAs for amino acids[7,8].

The two fundamental reactions of phosphorus compounds are *phosphorylation*[9] (*i.e.* substitution at phosphorus) and *group transfer* (*i.e.* substitution at a phosphorus ligand). A very fascinating aspect of these reactions is that they may proceed *via* five-coordinated phosphorus intermediates. It is generally accepted, for instance, that the hydrolysis of polyribonucleotides, catalysed by RNase A, is accomplished by anchimeric assistance of the 2'-OH group of the ribose ring[10-14]. Thus, the first step of the reaction is an intramolecular transphosphorylation resulting in a 2',3'-cyclic phosphate (Fig. I.3). The enzyme catalysis consists of proton abstraction from the O_2,H group by histidine 12, stabilization of the five-coordinated intermediate by hydrogen bonding from protonated lysine 41 to the anionic oxygen ligands, and activation of the leaving group by protonated histidine 119[13,14]. The second step of the reaction, hydrolysis of the 2',3'-cyclic phosphate, is essentially the reverse of the first step.

Model studies by *Westheimer and co-workers*[15-17] have clearly established the importance of five-coordinated inter-

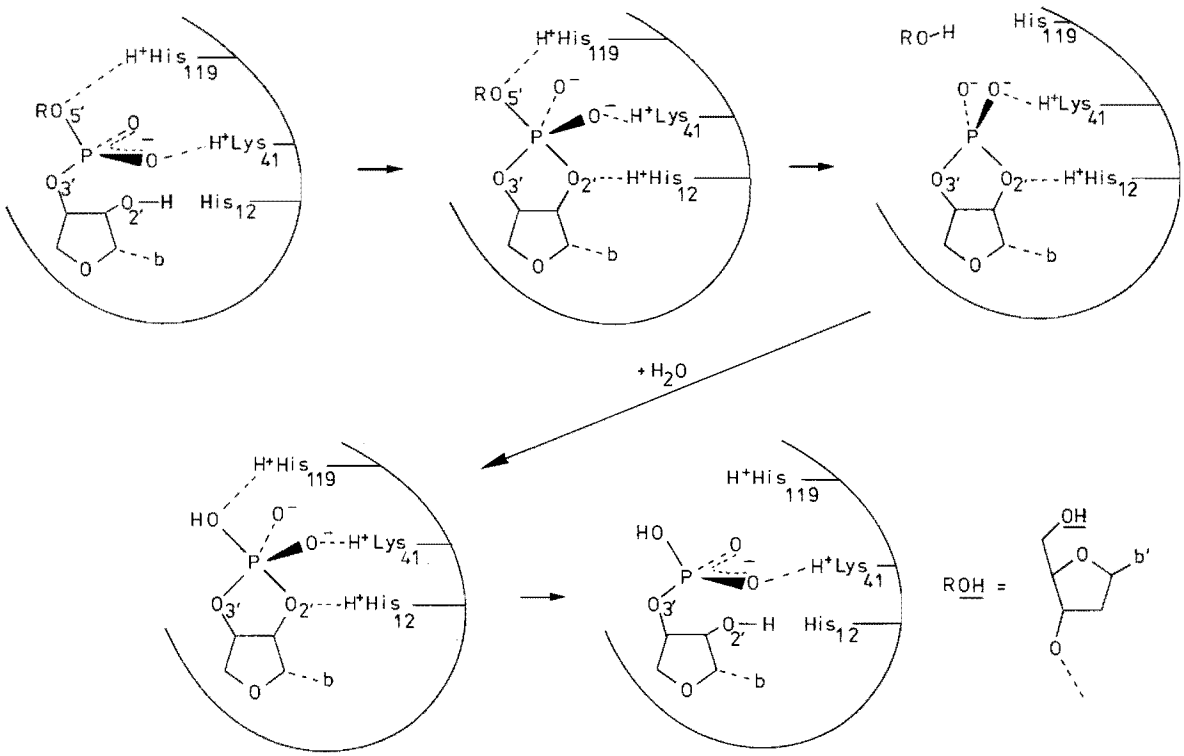


Fig. I.3 Catalytic mechanism of Ribonuclease A

mediates using compounds very similar to the 2',3'-cyclic phosphate. They found that the hydrolysis of five-membered ring phosphates proceeds millions of times faster in comparison to acyclic phosphates[17] (Fig. I.4). This is true not only for the

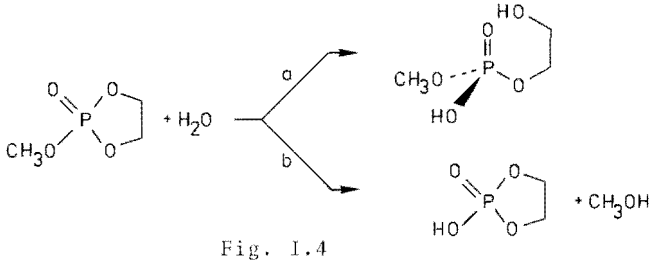


Fig. I.4

ring opening (a) but also for exocyclic cleavage (b). In contrast, a cyclic phosphonate gave only very fast ring opening and no exocyclic hydrolysis[15] (Fig. I.5). A very elegant ex-

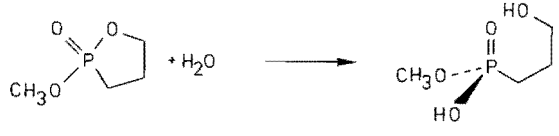


Fig. I.5

planation of these results was based on the presence of five-coordinated intermediates and their capability of ligand reorganizations (*vide infra*).

I.2 *General properties of five-coordinated phosphorus compounds*

An important aspect of five-coordination[18], in contrast to four-coordination, is that the distribution of the ligands about the central atom cannot be spherically symmetrical, *i.e.*, the ligands are not equivalent[19,20]. Two possible structural models are favoured, as shown by X-ray analyses[20-22]: the trigonal bipyramid (TBP) and the tetragonal pyramid (TP), shown in Fig. I.6. Usually, the TBP is encountered, although the energy difference between TBP and TP is often very small (about 6.3 kJ/mol)[19].

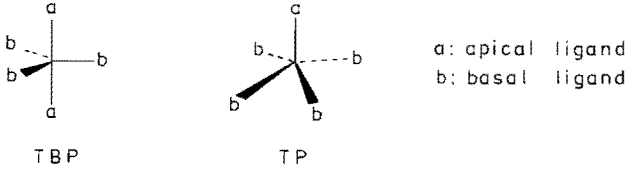


Fig. I.6

In the TBP configuration, the apical (a) bonds are longer and usually weaker than the basal bonds (b)[19,20,23,24]. In addition, apical sites are preferred by electron withdrawing ligands, whereas electron donating ligands tend to occupy basal positions[23-25]. This *polarity rule* has been derived from many experimental data[26,27] and is supported by semiempirical calculations[20-22,28-32]. Furthermore, it has been found that small rings are easily accommodated in the TBP configuration if they span an apical and a basal position. This *strain rule*[16] is a result of the 90^{o} angle between apical and basal bonds in the TBP. In fact, since the TBP is a rather crowded configuration with short non-bonded distances, the presence of rings stabilizes this configuration. As a result, the phosphorus atom is part of one or more rings in most of the known stable phosphoranes.

The assumption that d-orbitals participate in bonding in pentavalent phosphorus compounds provides a rationalization of their properties[33-35], although the exact role of d-orbitals is still a subject of controversy[36-38]. In four- and five-coordinated compounds, *backdonation*[23-25] from the lone pairs of the ligands into the empty d-orbitals of phosphorus gives rise to p_{π}-d_{π} bonds. This backdonation constitutes a substantial contribution to the stability of the phosphoryl (P=O) bond. A TBP configuration can be realized by a hybridization of the p_z and d_{z^2} orbitals to account for the apical bonds, combined with three sp^2 orbitals in the basal plane[33]. The sp^3d hybridization scheme is consistent with the observed difference in length between apical and basal bonds, since pd hybrid orbitals are relatively diffuse resulting in long apical bonds. Moreover,

the polarity rule is explained by this hybridization: the apical pd orbitals interact strongly with electron withdrawing ligands whereas the basal sp^2 orbitals favour donation of electrons from the ligands. In addition, basal ligands are more capable to form d_{π}-p_{π} bonds to phosphorus[23-25]. One of the consequences of the differences in bond strength in a TBP is that leaving groups depart from an apical position[16,31]. Conversely, nucleophilic attack on four-coordinated phosphorus results in a TBP in which the nucleophile occupies an apical position[31], as required by the principle of microscopic reversibility[16].

Another aspect of five-coordination is that the TBP configuration is stereochemically non-rigid[19]. This was first established for PF_5 which has one fluorine resonance in its ^{19}F NMR spectrum[39], although other methods indicate that the fluorine atoms are not equivalent[40]. A plausible explanation for this phenomenon, given by *Berry* [41], is that the positions of the ligands are interconverted fast on the NMR time scale. Thus, every fluorine atom in PF_5 alternately occupies apical and basal positions. This kind of interconversion is called permutational isomerization (PI) which may occur *via* regular (bond deformation) or irregular (bond breaking followed by recombination) pathways[25,35]. Apart from the Berry mechanism (Berry pseudorotation) several other PIs can be distinguished according to the type of permutation[42-44]. In Berry pseudorotation, two basal and both apical ligands change places[41]. The remaining basal ligand is called the pivot. In Fig. I.7,

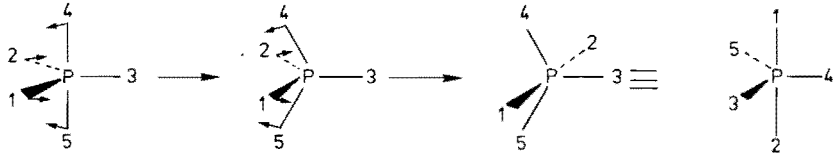
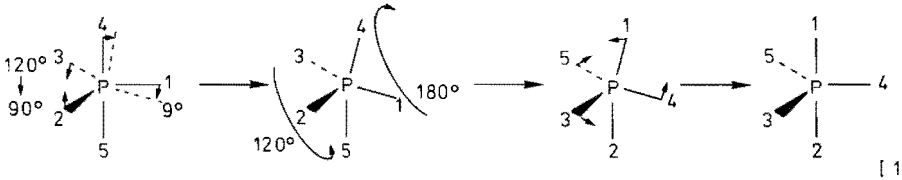


Fig. I.7 Berry pseudorotation

the pivot is ligand 3 and the permutation is (1425). Detailed NMR studies by *Whitesides et al* [45,46] have demonstrated that this type of permutation is actually taking place. Another mechanism which effectuates the same permutation is the Turn-

stile rotation[35,47], which may be favoured in (bi)cyclic phosphoranes (fig. I.8). The energy barrier for pseudorotation may



[1425]

Fig. I.8 Turnstile rotation

be very low, especially if all ligands are identical[19] (*cf.* PF_5). However, pseudorotations which bring electron withdrawing ligands into basal positions are usually unfavourable[24,31]. Furthermore, processes which force small rings to span two apical or two basal sites are unlikely to occur[31].

Using the properties of phosphoranes, the experiments of *Westheimer et al.*[15-17] are now readily explained assuming phosphorane intermediates. Attack of water on the cyclic phosphate yields the intermediate A (Fig. I.9) in which the ring spans

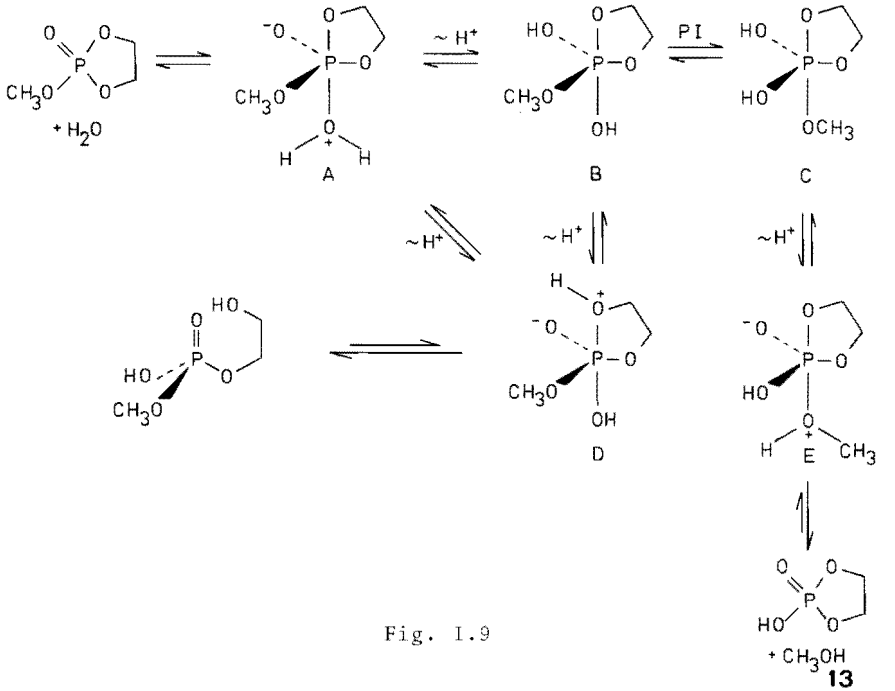


Fig. I.9

an apical and a basal position, while the incoming water molecule occupies the other apical site. Subsequently, intermediate A may undergo proton transfer, either to the endocyclic apical oxygen (D) or to the basal anionic oxygen atom (B). Intermediate D may lead to ring opening while B may undergo PI (B⇌C) to a new intermediate in which the methoxy group is located at an apical position. After proton transfer (C⇌E) methanol cleavage becomes possible.

In contrast to the phosphate hydrolysis, the phosphonate gives rise to an intermediate which may undergo pseudorotation either to an intermediate with the ring oxygen in a basal position, increasing the ring strain, or to an intermediate with the carbon ligand in an apical position, conflicting with the polarity rule (Fig. I.10). Therefore in this phosphorane pseudorotation cannot compete with ring opening.

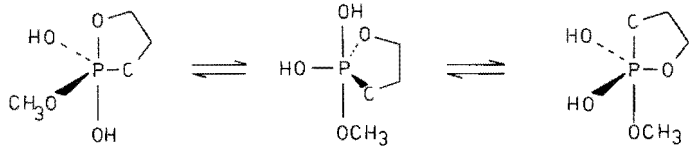


Fig. I.10

According to this mechanism, the very fast rate of both ring opening and exocyclic cleavage is explained by the fact that cyclic four-coordinated phosphorus compounds are more strained than their acyclic analogues, whereas the cyclic phosphorane intermediates are stabilized with respect to acyclic phosphoranes. These factors lower the activation enthalpy for hydrolysis of cyclic compounds substantially[48].

More recently, many other stereochemical and kinetic data in phosphorylation reactions have been rationalized by invoking phosphorane intermediates[49-54]. In group transfer reactions there is less evidence for five-coordinated intermediates, but some examples have been reported[55]. Finally, transient five-coordination of phosphorus in DNA may initiate conformational changes in the helical structure of this molecule[56-58].

I.3 *Scope of this thesis*

In order to obtain a better understanding of enzymatic phosphorylation and group transfer reactions, it is useful to combine the knowledge of phosphorane intermediates with the knowledge of the active sites of enzymes. For example, the formation of five-coordinated intermediates is facilitated by complexation of basal anionic oxygen ligands, which is accomplished by some of the active site residues of RNase A[13,14].

The aim of this thesis is to investigate further the factors favouring the formation of phosphorane intermediates, and to study their role in group transfer reactions. In this study, compounds are used which are capable of intramolecular phosphorylation. In Chapter II, it is shown that intramolecular nucleophilic attack on phosphorus is induced by polarizing the phosphoryl (P=O) bond. The phosphoranes generated in this way have an appreciable stability due to a cage structure. This offers the opportunity, as described in Chapter III, to isolate phosphoranes. The TBP configuration of these compounds was demonstrated by NMR spectroscopy and X-ray analysis.

In Chapter IV, reactions of the caged phosphoranes with nucleophiles are described. Since the cage structure uniquely defines the place of each ligand in the TBP geometry, it is possible to compare reactivities of basal and apical groups in a TBP. It is shown that group transfer from a TBP phosphorane, *i.e.* attack at carbon of an alkoxy ligand with concomitant P=O bond formation, occurs selectively at the basal ligands.

In the cage structures, the nucleophile is fixed in an ideal position for apical entry in the TBP. In Chapter V, other model systems are discussed, with more or less ideal orientations. It is demonstrated that the choice between ring opening and exocyclic hydrolysis of cyclic phosph(on)ates is determined not only by pseudorotation but also by the orientation of the leaving group in the ring opening reaction. A further example of orientational influence is found in the activation parameters for ring closure of several phosphonium ions to protonated

phosphoranes. The introduction of rigidity in the molecule lowers primarily the entropy of activation of the process.

References and Notes

1. For up-to-date reviews on the subject, see the series "Organophosphorus Chemistry" (Specialist Periodical Reports), S. Trippett, ed., The Chemical Society, London.
2. H.J. Bestmann, Pure Appl. Chem., 1980, *52*, 771.
3. H.R. Mahler and E.H. Cordes, "Biological Chemistry", Harper and Row, New York, 1966.
4. A.L. Lehninger, "Biochemistry", Worth Publ., New York, 1975.
5. Ref. 3, p. 488 *et seq.*; ref. 4, p. 546 *et seq.*
6. Ref. 3, p. 377-384; ref. 4, p. 406-411.
7. Ref. 3, p. 592 *et seq.*; ref. 4, p. 933 *et seq.*
8. Ref. 3, p. 914 *et seq.*; ref. 4, p. 387 *et seq.*
9. S.J. Benkovic and K.J. Schray, "Transition States of Biochemical Processes", Chapter 13, R.D. Gandour and R.L. Schowen, eds., Plenum Press, New York, 1978.
10. F.M. Richards and H.W. Wyckoff, "The Enzymes", Vol. IV, P.D. Boyer, ed., Academic Press, New York, 1971.
11. D.G. Gorenstein, A.M. Wyrwycz, and J. Bode, J. Am. Chem. Soc. 1976, *98*, 2308.
12. K.G. Scrimgeour, "Chemistry and Control of Enzyme Reactions", Academic Press, London, 1977, 185.
13. R.R. Holmes, J.A. Deiters, and J.C. Galluci, J. Am. Chem. Soc., 1978, *100*, 7393.
14. C.A. Deakyne and L.C. Allen, J. Am. Chem. Soc., 1979, *101*, 3951.
15. E.A. Dennis and F.H. Westheimer, J. Am. Chem. Soc., 1966, *88*, 3432.
16. F.H. Westheimer, Acc. Chem. Res., 1968, *1*, 70.
17. R. Kluger, F. Covitz, E. Dennis, L.D. Williams, and F.H. Westheimer, J. Am. Chem. Soc., 1969, *91*, 6066.
18. Instead of five-coordinated, the terms pentaco(-)ordinated, quinquecovalent, or pentavalent are often used. To avoid confusion, the term five-coordinated is used throughout this work. Five-coordinated phosphorus compounds are generally named phosphoranes, or oxyphosphoranes if one or more

of the ligands are oxygen atoms.
19. R. Luckenbach, "Dynamic Stereochemistry of Pentaco-ordinated Phosphorus and Related Elements", G. Thieme, Stuttgart, 1973.
20. E.L. Muetterties and R.A. Schunn, Quart. Rev. Chem. Soc., 1966, *20*, 245.
21. T.E Clark, R.O. Day, and R.R. Holmes, Inorg. Chem., 1979, *18*, 1653.
22. T.E. Clark, R.O. Day, and R.R. Holmes, Inorg. Chem., 1979, *18*, 1668.
23. F. Ramirez and I. Ugi, "Advances in Physical Organic Chemistry", Vol. 9, V. Gold, ed., Academic Press, London, 1971.
24. I. Ugi and F. Ramirez, Chem. Br., 1972, *8*, 198.
25. P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E.A. Tsolis, and I. Ugi, Angew. Chem., 1971,*83* , 691.
26. E.L. Muetterties, W. Mahler, and R. Schmutzler, Inorg. Chem., 1963, *2*, 613.
27. E.L. Muetterties, K.J. Packer, and R. Schmutzler, Inorg. Chem., 1964, *3*, 1298.
28. A. Rauk, L.C. Allen, and K. Mislow, J. Am. Chem. Soc., 1972, *94*, 3035.
29. J.B. Florey and L.C. Cusachs, J. Am. Chem. Soc., 1972, *94*, 3040.
30. R. Hoffmann, J.M. Howell, and E.L. Muetterties, J. Am. Chem. Soc., 1972, *94*, 3047.
31. D. Marquarding, F. Ramirez, I. Ugi, and P. Gillespie, Angew. Chem., 1973, *85*, 99.
32. F. Keil and W. Kutzelnigg, J. Am. Chem. Soc., 1975, *97*, 3623.
33. R.F. Hudson and M. Green, Angew. Chem., 1963, *75*, 47.
34. A.J. Kirby and S.G. Warren, "The Organic Chemistry of Phosphorus", Elsevier Publ. Co., Amsterdam, 1967.
35. F. Ramirez, S. Pfohl, E.A. Tsolis, J.F. Pilot, C.P. Smith, I. Ugi, D. Marquarding, P. Gillespie, and P. Hoffmann, Phosphorus, 1971, *1*, 1.
36. D.A. Bochvar, N.P. Gambaryan, and L.M. Epshtein, Russ. Chem. Rev., 1976, *45*, 660.

37. T.A. Halgren, L.D. Brown, D.A. Kleier, and W.N. Lipscomb, J. Am. Chem. Soc., 1977, *99*, 6793.
38. M.A. Ratner and J.R. Sabin, J. Am. Chem. Soc., 1977, *99*, 3954.
39. H.S. Gutowski, D.M. McCall, and C.P. Slichter, J. Chem. Phys., 1953, *21*, 279.
40. H.S. Gutowski and A.D. Liehr, J. Chem. Phys., 1953, *20*, 1652.
41. R.S. Berry, J. Chem. Phys., 1960, *32*, 933.
42. E.L. Muetterties, J. Am. Chem. Soc., 1969, *91*, 1636.
43. E.L. Muetterties, J. Am. Chem. Soc., 1969, *91*, 4115.
44. J.I. Musher, J. Chem. Educ., 1974, *51*, 94.
45. H.L. Mitchell and G.M. Whitesides, J. Am. Chem. Soc., 1969, *91*, 5384.
46. M. Eisenhut, H.L. Mitchell, D.D. Traficante, R.J. Kaufman, J.M. Deutch, and G.M. Whitesides, J. Am. Chem. Soc., 1974, *96*, 5385.
47. I Ugi, D. Marquarding, H. Klusacek, P. Gillespie, and F. Ramirez, Acc. Chem. Res., 1971, *4*, 288.
48. J.A. Gerlt, F.H. Westheimer, and J.M. Sturtevant, J. Biol. Chem., 1975, *250*, 5059.
49. K.E. DeBruin and D.M. Johnson, J. Am. Chem. Soc., 1973, *95*, 4675.
50. D.G. Gorenstein, J. Am. Chem. Soc., 1973, *95*, 8060.
51. K.L. Marsi, J. Org. Chem., 1975, *40*, 1779.
52. A. Schnell and J.C. Tebby, J. Chem. Soc., Perkin I, 1977, 1883.
53. K.L. Marsi and J.L. Jasperse, J. Org. Chem, 1978, *43*, 760.
54. S.J. Kubisen, Jr. and F.H. Westheimer, J. Am. Chem. Soc., 1979, *101*, 5985.
55. A.M.C.F. Castelijns, Thesis Eindhoven, 1979.
56. H.M. Buck, Recl. Trav. Chim. Pays-Bas, 1980, *99*, 181.
57. H.M. Buck, D. van Aken, J.J.C. van Lier, and M.J.H. Kemper, Recl. Trav. Chim. Pays-Bas, 1980, *99*, 183.
58. A.M.C.F. Castelijns, D. van Aken, P. Schipper, J.J.C. van Lier, and H.M. Buck, Recl. Trav. Chim. Pays-Bas, in press.

CHAPTER II

Intramolecular P-N bond formation in phosphoranes as a model for phosphorylation

II.1 *Introduction*

Phosphorylation reactions have been studied extensively in recent years. The search for more efficient phosphorylating reagents and conditions has been stimulated by the *in vitro* synthesis of oligonucleotides[1-5]. In addition, the occurrence of "high-energy" compounds such as ATP has promoted fundamental research in this field in order to elucidate the process of substrate activation by phosphorylation[6-12]. The enormous phosphoryl transfer potential of the "high-energy" phosphates has been attributed to opposing resonance and electrostatic repulsion[7,13], but recent studies have stressed the importance of solvation[14-16].

In general, phosphorylations may proceed *via* a dissociative or an associative mechanism (usually referred to as $S_N1(P)$ and $S_N2(P)$, respectively)[17-21], as shown in Fig. II.1. In the

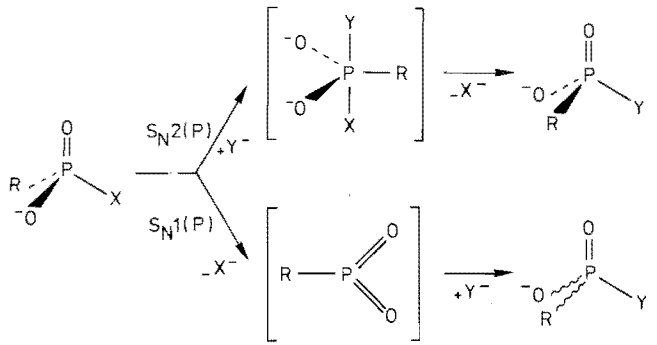


Fig. II.1

$S_N1(P)$ reaction, a monomeric metaphosphate is expelled as an intermediate which reacts with the phosphoryl acceptor. This reaction is characterized by a small, positive entropy of activation[17]. The $S_N2(P)$ reaction involves a five-coordinated transition state or intermediate, which is a crowded configuration leading to a large negative entropy of activation. In case of chiral phosphates the $S_N1(P)$ mechanism leads to racemization since monomeric metaphosphate is achiral, whereas the $S_N2(P)$ mechanism results in inversion at phosphorus unless pseudorotation of the intermediate takes place. Thus, the use of chiral, oxygen-labeled phosphates offers the opportunity to elucidate the mechanism[22,23].

There is much evidence that phosphoranes are intermediates in $S_N2(P)$ phosphorylation reactions. Apart from kinetic or stereochemical evidence[24], phosphoranes have been observed by spectroscopic methods[25], trapped by chemical reaction[26,27] and have recently even been isolated[28-30]. Thus, the phosphoranoxide in Fig. II.2 is formed as a result of an intramolecular nucleo-

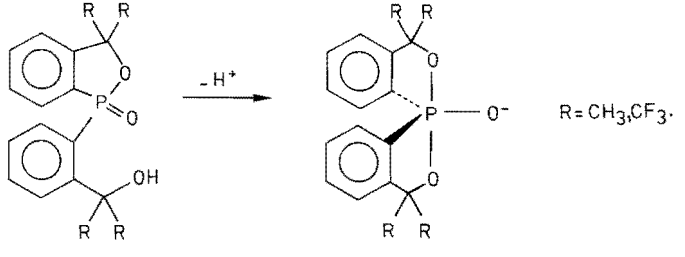


Fig. II.2 Formation of stable phosphoranoxides

philic attack on a phosphinate[30]. It seems possible then to study the first step in phosphorylation if the intermediate is sufficiently stabilized by the presence of small rings. In this connection, a series of compounds reported by *Verkade et al.*[31-34] is of particular interest. These compounds which belong to the class of "atranes"[34-36], are characterized by a cage structure in which nitrogen is located near phosphorus on the principal axis of symmetry (Fig. II.3). In some of these phosphatranes the configuration at phosphorus is tetrahedral whereas the

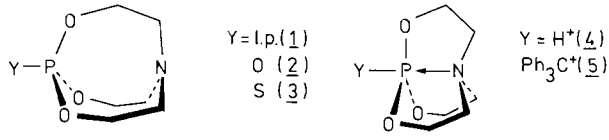


Fig. II.3 Some examples of phosphatranes

others have a TBP configuration. In the latter case a transannular P←N bond is formed due to strong polarization of the P-Y bond towards Y. This situation is found in 4 and 5 where the Y ligand is strongly electron deficient. Since the formation of the P←N bond is in fact an intramolecular phosphorylation, the phosphatranes seem suitable model compounds to study the conditions for phosphorylation and the properties of the intermediates. The previous studies demonstrate that protonation of the phosphite, 1, effectuates the conversion from tetrahedral to TBP phosphorus ($1 + H^+ \rightarrow 4$). Since phosphorylation is normally a reaction of phosphates rather than phosphites, it seems worthwile to investigate whether protonation of the phosphate (2) has the same effect. In order to predict the behaviour of this phosphate upon protonation of the phosphoryl oxygen and to visualize the electron distribution in the tricyclic cage, semiempirical MO calculations were performed. NMR measurements were carried out to verify the theoretical results.

II.2 *CNDO/2 calculations on the relative stabilities of bi- and tricyclic phosphatranes*

II.2.1 Details of the calculation

CNDO/2 calculations[37,38] were performed on several cage structures, both in a bicyclic (A) and a tricyclic (B) configuration (Fig. II.4). Although the CNDO/2 method certainly

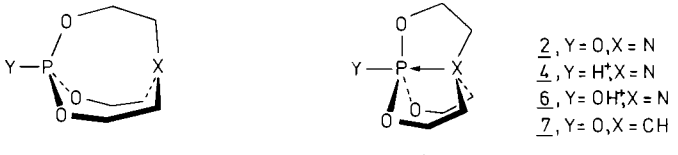


Fig. II.4

has some deficiencies[38,39], it seems a suitable method to be used for these relatively large structures, especially if one looks at trends rather than absolute values.

The geometries A and B used in the calculations are based on X-ray structure determinations of the borane adduct of 1 ($Y=BH_3$)[33], and the salt 4[31], respectively. The cage geometry was not optimized. The hydrogen atoms which were not resolved in the structure determinations were added at fixed distances of 109 pm. The length of the phosphoryl P=O bond was optimized in 5 pm steps. The optimal values of this parameter are 160 pm for A and 175 pm for B. In 7, the nitrogen atom has been replaced by a CH group. Obviously, the configuration around this carbon atom is rather unnatural. In the severely distorted TBP configuration, the $CH_2(X)$ ligands are within a short distance of the apical hydrogen.

II.2.2 Computational results and discussion

The total enthalpies, calculated net charges of relevant atoms, P-N overlap populations and enthalpy differences between the A and B configurations are listed in Table II.1. As evident from the Table, a negative enthalpy difference ΔH (*i.e.* a preference for the B configuration) is found for compounds 2, 4, and 6. Only the carbon analogue, 7, clearly prefers the A configuration. The actual structure of the phosphate, 2, however, is expected to be bicyclic (A) because of the NMR spectral similarity to the thiophosphate (3) for which the A configuration was established by X-ray analysis[32]. This failure of the calculation may be due to the CNDO/2 method, which overestimates bonding interactions between atoms[39]. Nevertheless, the trend in the calculation is that $|\Delta H|$ increases in the order $2 << 4 < 6$. Thus, it may be concluded that 6, just like 4, probably has the tricyclic (B) configuration. The calculations further show that about 0.1 electron unit is transferred from nitrogen to phosphorus upon formation of the transannular bond. The P-N overlap population in the B configuration is lower than

Table II.1 CNDO/2 results for bicyclic and tricyclic phosphatranes

Structure	Enthalpy[a]	Net atomic charge P	X[b]	O[c]	H+	PN[d]	ΔH[a,e]
4A	-126.5148	+0.70	-0.17	-	+0.05	0.0129	-0.1027
4B	-126.6175	+0.56	-0.07	-	+0.01	0.4687	
2A	-144.4136	+0.57	-0.17	-0.32	-		-0.0287
2B	-144.4423	+0.45	-0.07	-0.35	-		
6A	-144.9209	+0.76	-0.17	-0.22	+0.26	0.0128	-0.1191
6B	-145.0400	+0.65	-0.07	-0.27	+0.20	0.4667	
7A	-140.6107	+0.56	+0.06[f]	-0.31	-		+0.0935
7B	-140.5172	+0.44	-0.09[g]	-0.35	-		

[a]Total enthalpy, atomic units (1 a.u.= 2624.92 kJ/mol) [b]X=N except in 7 where X=C. [c]Phosphoryl. [d]Overlap population between P and N. [e]$\Delta H = H_B - H_A$. [f]Net charge on X-H: -0.03. [g]Net charge on X-H: +0.28.

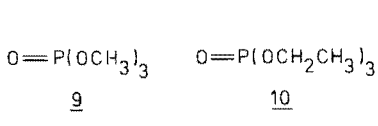
for other bonds, but high compared to the bicyclic cage.

For protonated phosphites an empirical relationship has been found[40,41] between calculated net atomic charges on phosphorus and hydrogen, and the measured coupling constant $^1J_{PH}$. A linear relation is found between $^1J_{PH}$ and the cube of the charges ρ_P and ρ_H as well as the sum of these charges, $(\rho_P+\rho_H)^3$, which can be rationalized by the dominance of the Fermi contact term for one-bond couplings[40,42]. The best correlation is found between $^1J_{PH}$ and $(\rho_P+\rho_H)^3$. From a plot of the coupling constant *vs.* $(\rho_P+\rho_H)^3$ for different protonated phosphites it is possible to estimate the coupling constant for a new phosphite, using the calculated charges. Thus, a coupling constant of 841 Hz[41] was calculated for the A configuration of 4, whereas the B configuration should have a $^1J_{PH}$ of 787 Hz. Since the experimental

value of $^{1}J_{PH}$ is 791 Hz, these results support the assignment of structure B to compound 4.

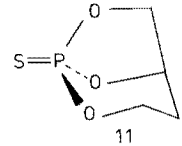
II.3 *Protonation experiments of bicyclic phosphatranes*

In the NMR spectra of the known phosphatranes (*e.g.* 1-5) remarkable differences have been observed between bicyclic and tricyclic compounds[34]. These differences are most evident for the $CH_2(N)$ moiety, where the ^{13}C and ^{1}H signals are split by coupling to phosphorus in tricyclic, but not in bicyclic phosphatranes. These additional couplings in the tricyclic cage are ascribed to the presence of the P←N bond which gives rise to P-N-C and P-N-C-H couplings[34]. Based on these observations, it should be possible to detect P←N bond formation in atranes by NMR. Therefore, the spectra of 2, 3, and the reference compounds 9-11 in acidic solutions were examined.



9

10



11

The ^{1}H NMR spectrum of 2 or 3 in acetic acid was completely analogous to the spectrum of a $CDCl_3$ solution. However, when trifluoroacetic acid (TFA) was used, a significant difference was observed. Instead of one doublet of triplets and one triplet, *two* doublets of triplets appear in TFA (fig. II.5). Both multiplets are shifted to lower field compared to the signals observed in $CDCl_3$ solution (Table II.2). In contrast, the ^{1}H peaks in the spectra of 9, 10 and 11 in TFA show *only* a downfield shift; no additional couplings are observed, although $^{4}J_{PH}$ in 10 seems to be affected somewhat. The additional splitting in the spectra of 2 and 3 in TFA could be due to $H\text{-}N^{+}\text{-}C\text{-}H$ coupling if protonation takes place at nitrogen. In support of this view, the quartet of the CH_2 protons in triethylamine is split into a doublet of quartets in TFA. However, in CF_3COOD

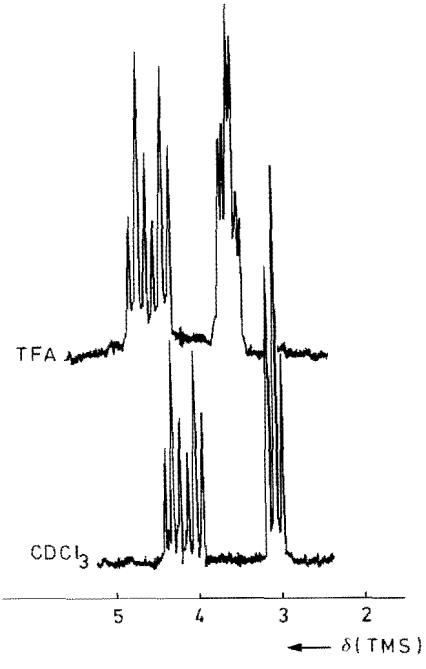


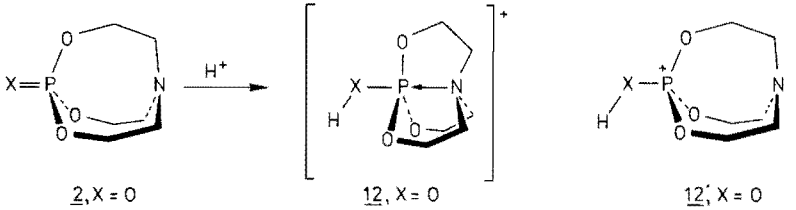
Fig. II.5 ^{1}H NMR spectra of 2 in $CDCl_3$ and in TFA at 35 ^{o}C

Table II.2 ^{1}H NMR data of phosphatranes and triethyl phosphate

Compound	Solvent	CH_2O			CH_2N	
		δ^b	$J_{PH}{}^c$	J_{HH}	δ	J_{PH}
2	$CDCl_3$	4.20	16.0	5.4	3.07	-[d]
2	TFA	4.69	16.5	5.6	3.75	2.0
3	$CDCl_3$	4.09	16.4	5.1	3.03	-[d]
3	TFA	4.51	16.4	5.6	3.63	2.0
10	$CDCl_3$	3.98	8.0	7.0	1.25	0.84
10	TFA	4.19	7.9	7.0	1.37	1.05
4	CD_3CN	4.20	14.0	6.0	3.42	6.0

[a] $C\underline{H}_3C$ for compound 10. [b] Chemical shift in ppm. [c] Coupling constant in HZ. [d] No coupling was resolved.

(d-TFA) the CH_2 resonance of triethylamine is a single quartet whereas the spectra of 2 and 3 still show the additional coupling. It can be concluded that protonation at nitrogen is very unlikely and that the additional coupling is a P-H coupling *via* the P←N bond. Thus, cations 12 and 13 are formed by protonation of 2 and 3, respectively (Fig. II.6). An alternative process, pro-



2, X = O
3, X = S

12, X = O
13, X = S

12', X = O
13', X = S

Fig. II.6

tonation of the P=X bond without the formation of a transannular bond (12' and 13' in Fig. II.6) could hardly account for the new coupling. Moreover, this possibility is excluded by the ^{31}P NMR spectra (*vide infra*).

The ^{31}P NMR shifts of 2 and 3 in TFA are rather upfield with respect to the resonances in $CDCl_3$ (Table II.3). In con-

Table II.3 ^{31}P and ^{13}C NMR data of phosphatranes

Compound	Solvent	P	CO		CN	
		δ[a]	δ	J_{PC}[b]	δ	J_{PC}
2	$CDCl_3$	-6.2	65.9	8.9	49.0	-[c]
2	TFA	-12.9	62.9	6.5	50.7	6.3
3	$CDCl_3$	+60.9	67.7	11.8	50.9	-[c]
3	TFA	+30	64.4	12	52.6	5
4	CD_3CN	-20.9	61.1	11	49.4	13

[a]Chemical shift in ppm. [b]Coupling constant in Hz.
[c]No coupling was resolved. [d]

trast, the reference compounds 9 and 11 give rise to resonances at lower field when dissolved in TFA: $\Delta\delta \simeq 2$ ppm and 0.7 ppm, respectively, where $\Delta\delta = \delta(\text{TFA}) - \delta(CDCl_3)$. The latter differences are normally observed between phosphates and phosphonium ions[43]. Therefore, the upfield shifts observed for 2 and 3 strongly indicate a different process, probably an increase in coordination number of phosphorus from four to five[43], in accordance with structures 12 and 13. The ^{13}C NMR spectra support this interpretation since the C(N) signal is a doublet in TFA, which is characteristic of tricyclic phosphatranes[34].

The ^1H NMR spectrum of 2 in TFA is independent of temperature in the range of -40 to +40 ^oC. Hence, equilibria such as that between 12 and 12' are probably negligible, indicating that only 12 is present in solution.

After the observation of hydroxyphosphoranes in solution, attempts were made to isolate these compounds. However, evaporation of a TFA solution of 2 did not yield 12 in pure form, although the oily residue has the same spectra as 12. The reaction of 3 with HBF_4 in CH_2Cl_2 solution yielded a crystalline 1:1 adduct which was characterized by a complex ^1H NMR spectrum

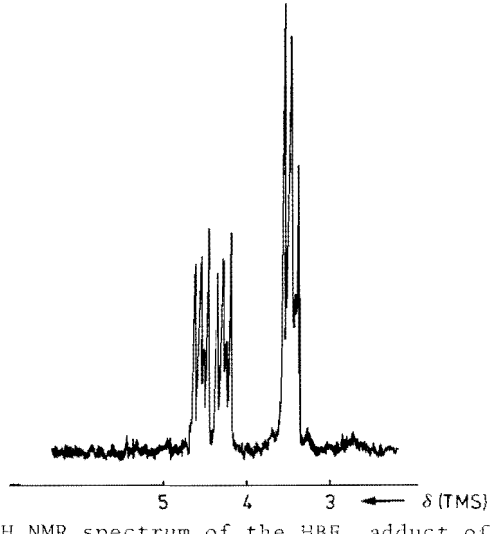
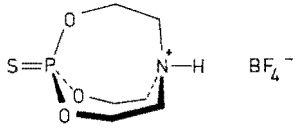


Fig. II.7 ^1H NMR spectrum of the HBF_4 adduct of 3

(Fig. II.7) similar to the spectra of $SP(OCH_2CH_2)_3N^+CH_3\ I^-$ [34] and $(HOCH_2CH_2)_3N^+H\ Br^-$ [45]. In addition, the ^{31}P resonance was at +57.4 ppm, only slightly upfield from 3 (*cf.* the value for 13, or 3 in TFA, in Table II.3). These data are in accordance with a *N*-protonated salt, 14.



14

A tentative explanation for the formation of different products in TFA and in CH_2Cl_2/HBF_4 is that nitrogen, being the most basic site, is protonated initially. In the CH_2Cl_2 experiment, the product formed precipitates rapidly, yielding 14. In TFA, however, the product remains in solution which may result in proton transfer *via* the weakly basic CF_3COO^- anions to other sites of the phosphatrane. Apparently, a more stable product is formed when the chalcogen atom is protonated, since this is the product observed in the latter experiment.

In the experiments described above, either an *O*-(*S*-) or an *N*-protonated product is formed. However, mention should be made of the fact that *Verkade and coworkers* observed several other, still unidentified, products upon dissolving 2 or 3 in TFA. They observed as many as six ^{31}P resonances[46] depending on the concentration. Presumably, multiple protonation is one of the processes which account for this observation.

II.4 *Discussion*

In accordance with the CNDO/2 calculations, protonation of the exocyclic phosphorus ligand in phosphatranes 2 and 3 effectuates the intramolecular nucleophilic attack of nitrogen on phosphorus resulting in a TBP configuration. The cation 12 seems to be the first example of a positively charged hydroxyphosphorane observed in solution. The relative stability of

this type of oxyphosphorane can be attributed to the cage structure in which three five-membered rings are present after P←N bond formation. These small rings fit very well in the TBP since they span an apical and a basal site[47], thus stabilizing the TBP configuration.

From these protonation studies in combination with the calculated charge densities it can be inferred that the first step in phosphorylation, *i.e.* nucleophilic attack on phosphorus, is facilitated by a greater positive charge on phosphorus. As noted by *Deakyne and Allen*[48], activation of the leaving group is more important in the second step (breakdown of the phosphorane intermediate). One of the implications of these findings is that protonation, or electrophilic complexation, of the phosphoryl bond is especially effective in the first step of phosphorylation, which is usually the rate-determining step. Thus, acid[49] or metal ion[50,51] catalyzed phosphorylations may be rationalized by complexation of the phosphoryl bond facilitating the formation of a phosphorane intermediate. Moreover, protonation may determine which TBP is formed. Nucleophilic attack opposite the phosphoryl oxygen atom without protonation leads to an apical O^- ligand which is unfavourable in a TBP (Fig. II.8). However, after protonation an OH ligand

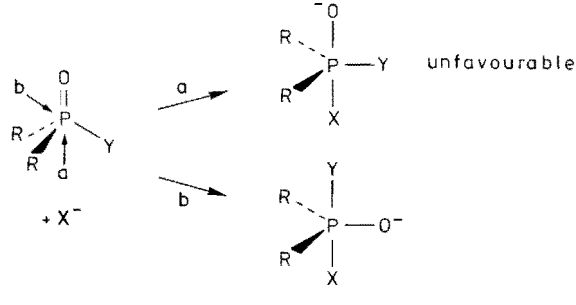


Fig. II.8

is formed which is not unfavourable at an apical site. Since attack opposite the phosphoryl bond is kinetically favoured[52], acid-catalyzed and non-catalyzed reactions may proceed *via*

different intermediates. Hence, acid catalysis may affect the stereochemistry of the phosphorylation[49].

It seems reasonable to assume that protonation or complexation becomes more important as the phosphate group is more ionised, particularly in biological phosphorylations. Thus, the negative charges in ATP[53], although accounting in part for the large negative $\Delta G^{\ominus}$ of hydrolysis[7,54], hamper a nucleophilic attack on the phosphorus atoms. Therefore, one of the functions of phosphorylating enzymes must be the sufficient shielding of these negative charges, accomplished by the obligatory metal ions[20,55]. Furthermore, some important enzymatic phosphorylations are controlled by protons. The phosphorylation of ADP to form ATP by mitochondrial ATPase is driven by high proton concentration[56,57]. In addition, in the RNase reaction protonated amino acid residues activate the phosphate group as well as the nucleophile and the leaving group[48,58,59].

II.5 *Experimental*

► *Apparatus*

^{1}H NMR spectra were recorded either on a Varian T-60A spectrometer equipped with a variable temperature unit, or on a Varian EM-360A apparatus. ^{13}C and ^{31}P NMR spectra were obtained using a Bruker HX 90 spectrometer interfaced with a Digilab-FT-NMR-3 computer. Standards were TMS (internal) for ^{1}H and ^{13}C NMR and 85% H_3PO_4 (external) for ^{31}P NMR. In all cases, downfield shifts (δ) are designated as positive.

► *Materials and preparations*

Trifluoroacetic acid (TFA) was refluxed with P_2O_5 and subsequently distilled from the same flask.

Trimethyl phosphate and triethyl phosphate of commercially available purity were used without further purification.

Phosphate 2 and thiophosphate 3 were prepared according to literature procedures[34]. However, crystallization of the

products from the evaporated reaction mixture was accomplished by dissolving the oil in CH_2Cl_2 and slowly evaporating the solution. Yields were variable and did not exceed 15%; mp of 2: 240 °C dec. (lit.[34] 208-212 °C dec.); mp of 3: 237-239 °C dec. (lit.[34] 218-220 °C dec.)

A sample of thiophosphate 11 was kindly supplied by dr. A.C. Bellaart of our laboratory.

► *Protonation studies*

NMR samples were prepared by weighing about 50 mg of the (thio) phosphate in a sample tube and adding 0.35 ml of solvent. The tube was shaken and gently warmed until a clear solution resulted. The data of compounds 2, 3 and 10 are listed in Tables II.2 and II.3. Other data are as follows:

^{1}H NMR of 11 ($CDCl_3$): δ 1.75 (d of m, 16 Hz, 1 H); δ 2.57 (q of m, 12 Hz, 1 H); δ 4.0-4.6 (m, 4 H); δ 5.0 (d of m, 22 Hz, 1 H).

(TFA) : δ 1.87 (d of m, 16 Hz, 1 H); δ 2.65 (q of m, 12 Hz, 1 H); δ 4.1-4.9 (m, 4 H); δ 5.2 (d of m, 22 Hz, 1 H).

^{31}P NMR of 9 ($CDCl_3$): -1.1 ppm

(TFA) : +1.24 ppm

^{31}P NMR of 11 ($CDCl_3$): +76.8 ppm

(TFA) : +77.5 ppm

Evaporation of a sample of 2 in TFA by means of a stream of dry nitrogen yielded an oily residue which was soluble in CD_3CN. The spectra obtained from this new sample were identical with the original spectra.

Upon addition of small amounts of TFA or d-TFA to a CD_3CN solution of 2 the new splitting of the CH_2N triplet was only observed when an excess of acid was present, *e.g.* 50 µl of TFA (0.67 mmol) with 63 mg 2 (0.32 mmol).

When a TFA solution of 2 was cooled, no changes were observed in the ^{1}H NMR spectrum apart from some line broadening due to poorer resolution and solubility. Below -40 °C the phosphate began to precipitate from the solution.

► *Isolation of the HBF_4 adduct of* 5

To a stirred solution of 0.5 g 5 in 15 ml CH_2Cl_2 and 5 ml ether, 1 ml of a 50% solution of HBF_4 in water was added in one portion at room temperature. While stirring was continued for 1 h, a white solid precipitated. An additional 10 ml of ether was added to separate the product completely. The solid was filtered off and washed three times with CH_2Cl_2. The crude product was recrystallized from hot acetonitrile, mp 205 °C. Anal. Calcd. for $C_6H_{13}NO_3PSBF_4$: C, 24.26; H, 4.41; N, 4.72. Found: C, 24.60; H, 4.51; N, 4.91.

^1H NMR (CD_3CN): δ 3.44 (m, 6 H, CH_2N); δ 4.40 (d of m, 16.4 Hz, 6 H, CH_2O); δ 7.5 (broad s, *ca.* 1 H, NH).

References and Notes

1. F. Ramirez, E. Evangelidou-Tsolis, A. Jankowski, and J.F. Marecek, J. Org. Chem., 1977, *42*, 3144.
2. L.A. Slotin, Synthesis, 1977, 737.
3. K.K. Ogilvie, N. Theriault, and R.L. Sadana, J. Am. Chem. Soc., 1977, *99*, 7741.
4. C.B. Reese, Tetrahedron, 1978, *34*, 3143.
5. R. Arentzen and C.B. Reese, J. Chem. Soc., Perkin I, 1977, 445.
6. R.F. Hudson and M. Green, Angew. Chem., 1965, *75*, 47.
7. D.B. Boyd, Thesis Harvard, 1967, and references cited.
8. F.H. Westheimer, Acc. Chem. Res., 1968, *1*, 70.
9. K.J. Schray and S.J. Benkovic, J. Am. Chem. Soc., 1971, *93*, 2522.
10. A. Williams and R.A. Naylor, J. Chem. Soc., B, 1971, 1973.
11. F. Ramirez, Y.F. Chaw, J.F. Marecek, and I. Ugi, J. Am. Chem. Soc., 1974, *96*, 2429.
12. F. Ramirez and J.F. Marecek, Pure Appl. Chem., 1980, *52*, 2213.
13. H.R. Mahler and E.H. Cordes, "Biological Chemistry", Harper and Row, New York, 1966.
14. P. George, R.J. Witowsky, M. Trachtman, C. Wu, W. Dorwart, L. Richman, W. Richman, F. Shurayh, and B. Lentz, Biochim. Biophys. Act., 1970, *223*, 1.
15. D.M. Hayes, G.L. Kenyon, and P.A. Kollman, J. Am. Chem. Soc., 1975, *97*, 4762.
16. D.M. Hayes, G.L. Kenyon, and P.A. Kollman, J. Am. Chem. Soc., 1978, *100*, 4331.
17. D.G. Gorenstein and Y.-G. Lee, J. Am. Chem. Soc., 1977, *99*, 2258.
18. J.P. Guthrie, J. Am. Chem. Soc., 1977, *99*, 3991.
19. G. Lowe and B.S. Sproat, J. Chem. Soc., Chem. Commun., 1978, 783.
20. S.J. Benkovic and K.J. Schray, "Transition States of Biochemical Processes", Chapter 13, R.D. Gandour and R.L.

Schowen, eds., Plenum Press, New York, 1978.
21. F. Ramirez and J.F. Marecek, J. Am. Chem. Soc., 1979, *101*, 1460.
22. S.J. Abbott, S.R. Jones, S.A. Weinman, and J.R. Knowles, J. Am. Chem. Soc., 1978, *100*, 2558.
23. M.-D. Tsai and T.-T. Chang, J. Am. Chem. Soc., 1980, *102*, 5416.
24. See ref. 8, and refs. 49-54 of Chapter I.
25. F. Ramirez, M. Nowakowski, and J.F. Marecek, J. Am. Chem. Soc., 1977, *99*, 4515.
26. G. Kemp and S. Trippett, Tetrahedron Lett., 1976, 4381.
27. G. Kemp and S. Trippett, J. Chem. Soc., Perkin I, 1979, 879.
28. A. Munoz, B. Garrigues, and M. Koenig, J. Chem. Soc., Chem. Commun., 1978, 219.
29. I. Granoth and J.C. Martin, J. Am. Chem. Soc., 1978, *100*, 5229.
30. E.F. Perozzi and J.C. Martin, J. Am. Chem. Soc., 1979, *101*, 1591.
31. J.C. Clardy, D.S. Milbrath, J.P. Springer, and J.G. Verkade, J. Am. Chem. Soc., 1976, *98*, 623.
32. J.C. Clardy, D.S. Milbrath, and J.G. Verkade, J. Am. Chem. Soc., 1977, *99*, 631.
33. J.C. Clardy, D.S. Milbrath, and J.G. Verkade, Inorg. Chem., 1977, *16*, 2135.
34. D.S. Milbrath and J.G. Verkade, J. Am. Chem. Soc., 1977, *99*, 6607.
35. M.G. Voronkov, O.A. Osipov, V.A. Kogan, V.A. Chetverikova, and A.E. Lapsin, Khim. Geterotsikl. Soedin., 1967, 35; Chem. Abstr., 1967, 64320v.
36. M.G. Voronkov and F.D. Faitel'son, Khim. Geterotsikl. Soedin., 1967, 39; Chem. Abstr., 1967, 64321w.
37. J.A. Pople and D.L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, 1970; QCPE Program no. 141.
38. J.N. Murrell and A.J. Harget, "Semi-empirical Self-consistent Field Molecular Orbital Theory of Molecules", Wiley

Interscience, London, 1972.
39. A.R. Gregory and M.N. Paddon-Row, J. Am. Chem. Soc., 1976, *98*, 7521.
40. L.J. VandeGriend, J.G. Verkade, J.F.M. Pennings, and H.M. Buck, J. Am. Chem. Soc., 1977, *99*, 2459.
41. D. van Aken, A.M.C.F. Castelijns, J.G. Verkade, and H.M. Buck, Recl. Trav. Chim. Pays-Bas, 1979, *98*, 12.
42. G.A. Gray and T.A. Albright, J. Am. Chem. Soc., 1977, *99*, 3243.
43. M. Murray, R. Schmutzler, E. Gründemann, and H. Teichmann, J. Chem. Soc., B, 1971, 1714.
44. M.M. Crutchfield, C.H. Dungan, J.H. Letcher, V. Mark, and J.R. Van Wazer, "^{31}P Nuclear Magnetic Resonance", Interscience Publ., New York, 1967, p.173.
45. Prepared from triethanolamine and HBr.
46. J.G. Verkade, personal communication.
47. *cf.* Chapter 1, Section I.2.
48. C.A. Deakyne and L.C. Allen, J. Am. Chem. Soc., 1979, *101*, 3951.
49. M.J.P. Harger, J. Chem. Soc., Perkin I, 1977, 2057.
50. H.A. Nunez and R. Barker, Biochemistry, 1976, *15*, 3843.
51. B. Anderson, R.M. Milburn, J. McB. Harrowfield, G.B. Robertson, and A.M. Sargeson, J. Am. Chem. Soc., 1977, *99*, 2652.
52. D. Marquarding, F. Ramirez, I. Ugi, and P. Gillespie, Angew. Chem., 1973, *85*, 99.
53. Since at pH 7 three OH groups of ATP are fully ionized and the fourth (pK 6.95) about 50%, there are on the average 3.5 O^- ligands in ATP at this pH (*cf.* ref. 54).
54. A.L. Lehninger, "Biochemistry", Worth Publ., New York, 1975.
55. See ref. 13, pp. 384, 595, 919, *etc.*
56. P. Mitchell, Biochem. Soc. Trans., 1976, *4*, 399.
57. P.C. Hinkle and R.E. McCarthy, Sci. Am., 1978, *238*, 104.
58. D.G. Gorenstein, A.M. Wyrwycz, and J. Bode, J. Am. Chem. Soc., 1976, *98*, 2308.
59. R.R. Holmes, J.A. Deiters, and J.C. Galluci, J. Am. Chem. Soc., 1978, *100*, 7393.

CHAPTER III

Preparation and characterization of tricyclic phosphatranes bearing apical alkoxy (alkylthio) groups

III.3 *Introduction*

In recent literature, several stable oxyphosphoranes have been reported[1-4] in which one of the phosphorus ligands is negatively charged (Fig. III.1). These compounds can be

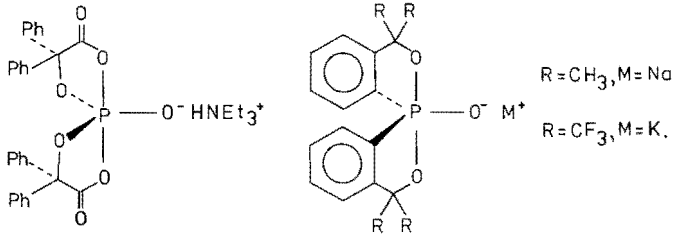


Fig. III.1

regarded as models for phosphorylation by anionic nucleophiles[5] (Fig. III.2). In contrast, relatively little is known about

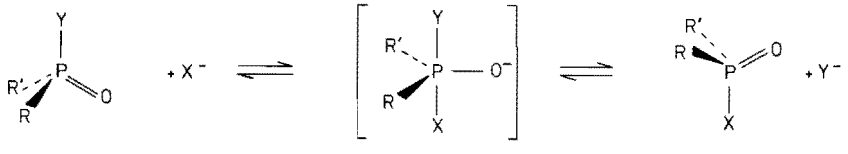


Fig. III.2

phosphoranes bearing positively charged ligands. In the acid-induced equilibria between cyclic phosphoranes and phosphonium ions, protonated oxyphosphoranes have been postulated[6,7] as intermediates (Fig. III.3). These studies show that the equilibrium: protonated oxyphosphorane⇌phosphonium ion, usually

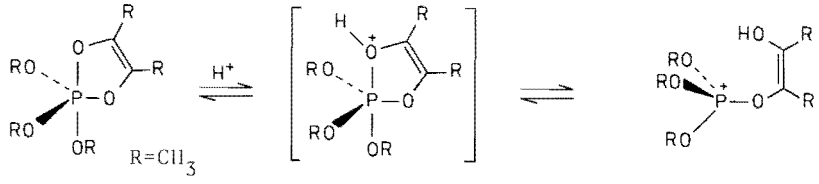
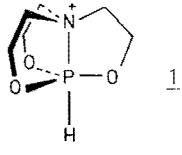


Fig. III.3

lies on the side of the phosphonium ion. The first example of the opposite situation was reported by *Verkade et al.*[8] (Fig. III.4): the tricyclic phosphatrane structure 1 is more stable



1

Fig. III.4

than its phosphonium isomer. Similar intermediates may be involved in attack by a neutral nucleophile on a phosphonium ion[9-15], or on a phosphate where the developing negative charge is shielded. The latter case is often encountered in enzymatic reactions[16-18] (Fig. III.5). In addition, the ^{18}O exchange in

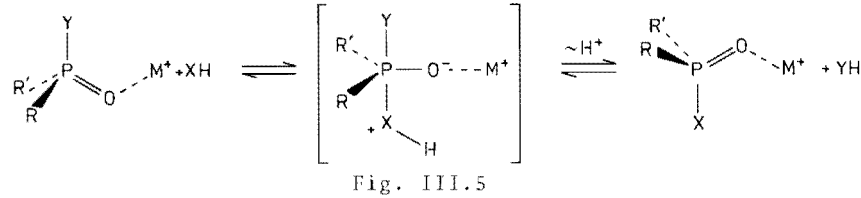


Fig. III.5

the acid-catalyzed hydrolysis of ethylene phosphate[19] can be attributed to the pseudorotation of protonated intermediates (Fig. III.6).

The isolation of further stable phosphoranes of this type might lead to a better understanding of their role in the reactions described above. Since the tricyclic phosphatranes offer a strongly stabilized structure[20], they seem a promising starting point for the preparation of such phosphoranes. As

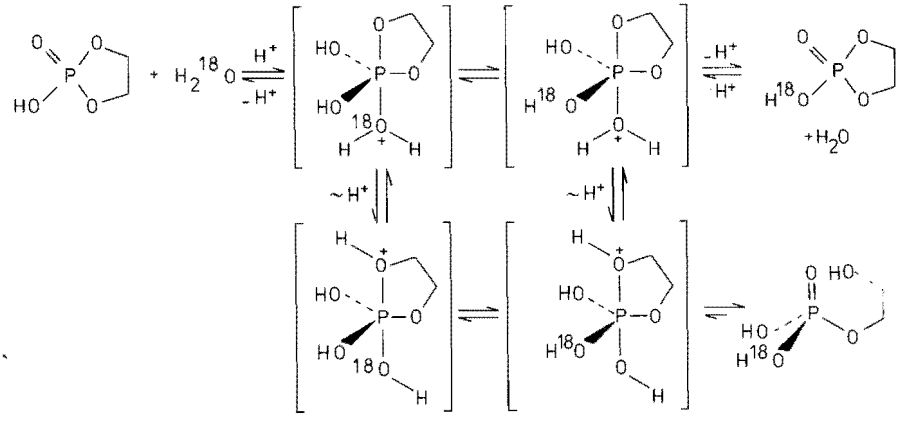
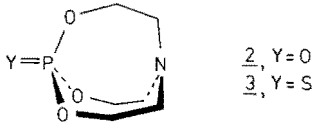


Fig. III.6 ^{18}O exchange accompanying ring opening in ethylene phosphate hydrolysis

described in Chapter II, the introduction of an electrophilic group at the phosphoryl oxygen or sulfur atom of the bicyclic phosphatranes 2 and 3 leads to the formation of phosphatranes



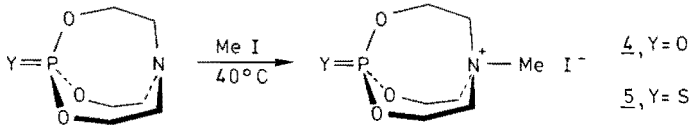
2, Y = O
3, Y = S

similar to 1. Moreover, the replacement of the apical hydrogen ligand in 1 by an alkoxy or alkylthio group would yield good models for the intermediates of phosphorylation reactions. Therefore, the alkylation of 2 and 3 was examined.

III.2 *Alkylation of phosphatranes*

In the bicyclic phosphatranes 2 and 3, two nucleophilic sites can be distinguished, *viz.* the nitrogen atom and the phosphoryl chalcogen atom. The X-ray analysis of 3 has revealed that the configuration around the nitrogen atom in this cage is almost trigonal planar[20,21]. The relatively low nucleophilicity of 3 towards methyl iodide may be the result of this configuration which causes steric hindrance by the adjacent

CH_2 protons[20]. Nevertheless, methylation by methyl iodide takes place at nitrogen (Fig. III.7), since trialkyl phosphates and



4, Y=O

5, Y=S

Fig. III.7 *N*-alkylation of bicyclic phosphatranes

thiophosphates do not react with methyl iodide under these conditions[22]. In order to alkylate the chalcogen atom of 2 or 3, it is necessary to use a stronger alkylating agent. *Murray et al.*[23] have reported the alkylation of phosphoryl bonds using trialkyloxonium salts. These reagents have the advantage that a low reaction temperature is possible and that no anionic nucleophile is produced. Since the nitrogen atom is more sterically hindered than the chalcogen atom, the *N*-alkylation reaction probably has a higher entropy of activation. Hence, a low reaction temperature is expected to decrease the amount of *N*-alkylated product. Therefore, the phosphatranes 2 and 3 were treated with triethyl- and trimethyloxonium tetrafluoroborate. The products of these reactions were obtained as crystalline salts, soluble in acetonitrile (4 and 5 are virtually insoluble in this solvent). The NMR data of these compounds, 6-10, are listed in Tables III.1 and III.2. As an example, the ^1H NMR spectrum of 8 is shown in Fig. III.8.

From the ^1H NMR data (Table III.1) it is evident that the cage resonances all shift to lower field upon alkylation, indicating the introduction of a positively charged group. The shift is more pronounced for the CH_2N than for the CH_2O protons. In addition, the signals of the exocyclic group are split by coupling to phosphorus, similar to the J_{POCH} for the cage protons, which is evidence for *O*-(*S*-)alkylation (*cf.* the singlet from the methyl group in 4). Furthermore, the CH_2N resonances of 6-10 are doublets of triplets, characteristic of a tricyclic cage with a P←N bond. The P-N-C-H coupling constant in these compounds is similar to the corresponding parameter in 1.

Table III.1 ^{1}H NMR data of alkylated phosphatranes and their precursors[a]

	YR	CH_2O			CH_2N		CH_nY	
		δ[b]	J_{PH}[c]	J_{HH}	δ	J_{PH}	δ	J_{PH}
2[d]	O	4.20	16.0	5.4	3.07	-[e]		
3[d]	S	4.09	16.4	5.1	3.03	-[e]		
6	OEt	4.28	17.0	6.0	3.34	4.0	3.91[f]	7.0
7	OMe	4.35	16.6	6.2	3.39	4.0	3.63	11.5
8	SEt	4.28	16.0	5.8	3.40	5.0	2.77[g]	14.5
9	SMe	4.38	17.0	6.0	3.43	5.0	2.23	16.0
10	S^+Me_2	4.63	16.0	6.0	3.77	6.5	2.80	11.4
1	H	4.20	14.0	6.0	3.42	6.0	5.9[h]	790[h]
4[i]	O;Me(N)	4.77	16	-[j]	4.13	-[e]	3.49	-[e]

[a]Solvent CD_3CN unless indicated otherwise. [b]Chemical shift in ppm, reference TMS. [c]Coupling constant in Hz. [d]Solvent $CDCl_3$. [e]No coupling resolved. [f]$C\underline{H}_3C$: δ 1.18, J_{PH} 2.0, J_{HH} 7.0. [g]$C\underline{H}_3C$: δ 1.23, J_{PH} 1.6, J_{HH} 7.2. [h]δ and J for H-P. [i]Solvent $(CD_3)_2SO$. [j]Complex (A_2B_2) multiplets.

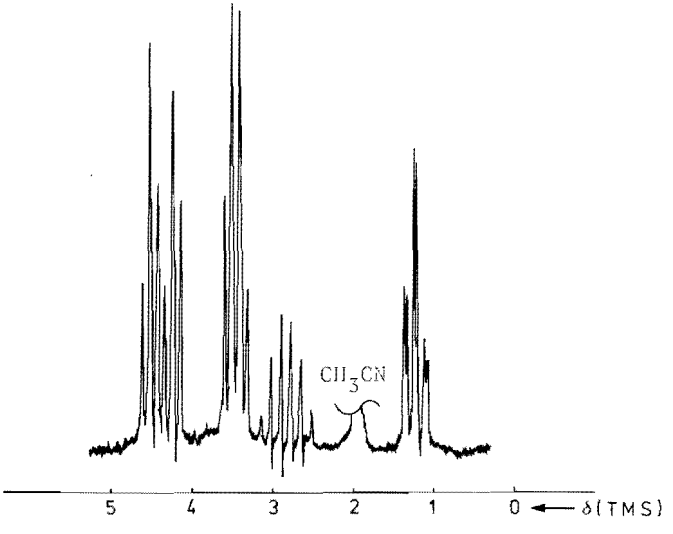


Fig. III.8 ^{1}H NMR spectrum of 8

Table III.2 ^{13}C and ^{31}P NMR data of alkylated Phosphatranes and their precursors[a]

	Cage atoms					Exocyclic group			
	P	CO		CN		CX		C-CX	
	δ[b]	δ	J_{PC}[c]	δ	J_{PC}	δ	J_{PC}	δ	J_{PC}
2[d]	-6.2	65.9	8.9	49.0	-[e]				
3[d]	+60.7	67.7	11.8	50.9	-[e]				
6	-20.6	61.9	5	47.9	12	63.0	7	15.3	9
7	-20.2	62.0	5	48.1	13	54.0	7		
8	+5.6	64.1	13	49.3	14	25.9	6	15.3	9
9	+5.2	64.2	13	49.5	13	13.8	6		
1	-20.9	61.0	11	49.4	13				

[a]Solvent CD_3CN unless indicated otherwise. [b]Chemical shift in ppm; reference 85% H_3PO_4 for ^{31}P, TMS for ^{13}C NMR. [c]Coupling constant in Hz. [d]Solvent $CDCl_3$. [e]No coupling resolved.

The ^{13}C and ^{31}P NMR spectra are in support of the tricyclic structure (Table III.2). First, the upfield shift of the ^{31}P resonance of 6-9 (relative to the parent compounds, 2 and 3) is strong evidence for an increase in the coordination number of phosphorus resulting from the formation of the P←N bond[24]. In addition, all ^{13}C resonances of the alkylated products are doublets, indicating that the chalcogen atom is alkylated and that a tricyclic cage is formed. In conclusion, the alkylation by trialkyloxonium salts yields the products shown in Fig. III.9.

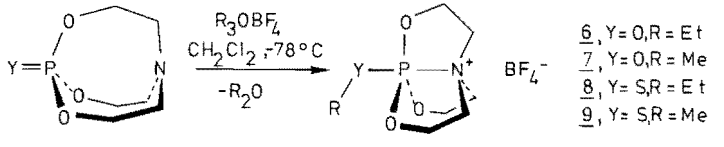


Fig. III.9 *O*-(*S*-)alkylation of phosphatranes

An interesting aspect of the methylation of 3 is that the reaction is not terminated at the monoalkylated stage (9). A doubly methylated salt, $[Me_2SP(OCH_2CH_2)_3N]^{2+}(BF_4^-)_2$, 10, was obtained as a by-product. In the ^1H NMR spectrum of 10 (Table III.1), the resonances are downfield with respect to 9 and the doublet of the Me-S groups corresponds to six protons. Thus, the well-known tendency of sulfur to attain three-coordination [25] is not completely suppressed in 9, in spite of the overall positive charge. Presumably, the apical position of the sulfur atom reduces the influence of the positive charge (*vide infra*).

III.3 *X-ray structure determination of 8*

The crystallinity of the alkylation products offers the possibility to undertake an X-ray structure determination of these compounds in order to verify if the structure in solution, inferred from the NMR data, corresponds to the solid phase structure. Therefore, single crystals were prepared of 8 which seems to be the most stable member of the series: crystals of 8 could be left standing for several days in the open air without significant decomposition. The crystals belong to the monoclinic crystal system with a= 845.7(9), b= 1826.8(13), c= 935.8(5) pm, β= 93.08°(8), numbers in parentheses referring to standard deviations in the last digit. The space group is $P2_1/n$ and there are 4 molecules per unit cell. Details of the structure determination are given in the Experimental. Computer drawings [26] of the unit cell and of the cation are shown in Fig. III.10 and III.11, respectively. Intramolecular bond distances and angles are listed in Tables III.3 and III.4.

The O-P-S, O-P-O, and O-P-N angles in Table III.4 clearly prove that the configuration of phosphorus is a TBP. For comparison, in the thiophosphate 3 the average S-P-O angle is 110.8° and the O-P-O angle 108.1°. The P-S distance is enlarged from 193 pm in 3 to 210 pm in 8, whereas the P-N distance is diminished from 313 pm to 206 pm (In 1 the P-N distance is 199 pm). Obviously, the formation of the TBP is accompanied

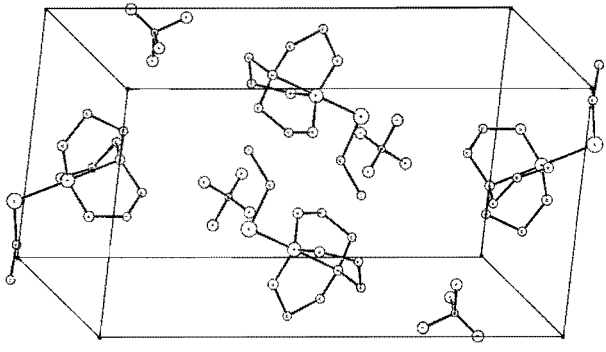


Fig. III.10 Unit cell of 8

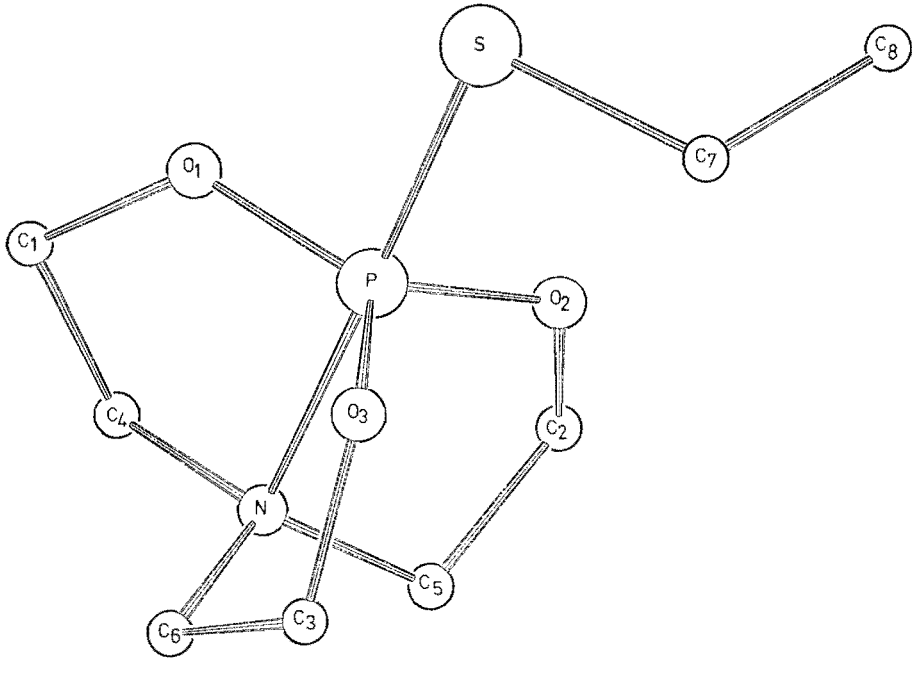


Fig. III.11 Structure of the cation of 8

Table III.3 Intramolecular bond distances in $[EtSP(OCH_2CH_2)_3N]^+$

Atoms[a]	Distance/pm	Atoms	Distance/pm
P -S	210(2)[b]	C_1-C_4	151(4)
P -O_1	157(2)	C_2-C_5	146(3)
P -O_2	163(1)	C_3-C_6	150(2)
P -O_3	159(2)	C_4-N	149(3)
P -N	206(3)	C_5-N	143(2)
O_1-C_1	146(2)	C_6-N	152(1)
O_2-C_2	140(4)	S -C_7	189(2)
O_3-C_3	150(4)	C_7-C_8	156(3)

[a]Atom numbering corresponds to Fig. III.11.
[b]Standard deviations in the last digit are given in parentheses.

Table III.4 Bond angles in $[EtSP(OCH_2CH_2)_3N]^+$

Atoms[a]	Angle/degrees	Atoms	Angle/degrees
S -P -O_1	93.0(11)[b]	P -O_2-C_2	120.7(14)
S -P -O_2	94.2 (9)	P -O_3-C_3	119.8(14)
S -P -O_3	94.0 (9)	O_1-C_1-C_4	101.4(12)
S -P -N	178.1 (7)	O_2-C_2-C_5	107.1(19)
O_1-P -O_2	118.9(11)	O_3-C_3-C_6	106.8(16)
O_1-P -O_3	120.8(12)	C_1-C_4-N	112.3(19)
O_2-P -O_3	119.1(10)	C_2-C_5-N	109.2(18)
O_1-P -N	85.4(10)	C_3-C_6-N	104.4(13)
O_2-P -N	85.5(10)	C_4-N -P	102.7(17)
O_3-P -N	87.8(10)	C_5-N -P	102.1(13)
P -S -C_7	98.8(13)	C_6-N -P	102 9(10)
P -O_1-C_1	128.3(16)	S -C_7-C_8	111.0(18)

[a]Atom numbering corresponds to Fig. III.11. [b]Standard deviations in the last digit are given in parentheses.

by a compression of the bond angles of the cage which is most pronounced for the O-C-C angles (average in 3: 116.6°). The conformation of the S-P bond is trans: viewed along the TBP axis, C_7 is located in the middle between O_2 and O_3.

III.4 *Discussion*

The presence of two nucleophilic sites in the bicyclic phosphatranes 2 and 3 clearly results in different alkylation products, depending on the reagent and the conditions. Two factors determining the site of alkylation are probably the planar configuration of nitrogen and the nucleophilicity of the leaving group (I^- *vs.* a dialkyl ether). Thus, the steric hindrance of the CH_2N protons causes a high negative entropy of activation for *N*-alkylation, increasing the free enthalpy of activation: $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$. Therefore, *N*-alkylation is hampered at low temperature. At higher temperature, however, both *N*- and *O*-(*S*-) alkylation are possible. Since the latter reaction is probably reversible as a result of the nucleophilicity of I^-, the *N*-alkylated product, which is apparently more stable, is found exclusively.

Both the NMR data and the X-ray structure determination clearly demonstrate that compounds 6-10 have tricyclic cations in which a P←N bond effects the five-coordination of phosphorus. The configuration of phosphorus is a nearly perfect TBP, with a tertiary amine and an alkoxy (alkylthio) group as apical ligands. A very important property of these compounds is their rigid configuration, *i.e.* the tricyclic structure precludes any permutational isomerization[27]. As demonstrated in Fig. III.12, the products of Berry pseudorotation[28] must have at least one five-membered ring spanning two basal sites which leads to excessive activation enthalpies.

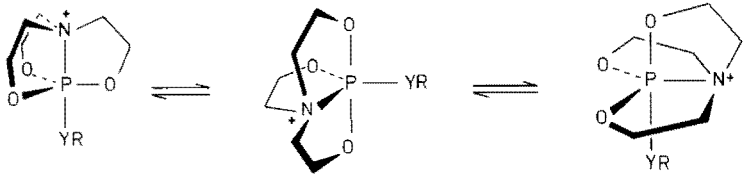


Fig. III.12

III.5 *Experimental*

► *Apparatus*

^{1}H NMR spectra were recorded either on a Varian T-60A or on a Varian EM-360A spectrometer. ^{13}C, ^{31}P, and 90 MHz ^{1}H NMR spectra were obtained using a Bruker HX90 spectrometer interfaced with a Digilab-FT-NMR-3 computer. Standards were TMS (internal) for ^{13}C and ^{1}H NMR, and 85% H_3PO_4 (external) for ^{31}P NMR. In all cases, downfield shifts (δ) are designated as positive.

Melting points were measured using a Mettler FP1 apparatus with recorder.

► *Materials and preparations*

All solvents were dried before use. Dichloromethane and acetonitrile were stored over 4 Å molecular sieves. Trimethyloxonium tetrafluoroborate (Me_3OBF_4) was stored in an exsiccator filled with nitrogen gas and kept at 4 °C. All moisture-sensitive compounds, especially the trialkyloxonium salts, were handled in a dry nitrogen atmosphere. Compounds 1-5 were prepared according to literature procedures[26]. Alternative synthesis of the parent phosphite starting from trimethyl phosphite and triethanolamine was not successful due to the tendency of the product to polymerize. Triethyloxonium tetrafluoroborate (Et_3OBF_4) was prepared *via* the *Meerwein* procedure[29] and stored in the cold.

► *1-ethoxy-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane tetrafluoroborate (6)*

To a stirred solution of 0.5 g 2 (26 mmol) in 5 ml CH_2Cl_2, cooled to -78 °C, a CH_2Cl_2 solution of Et_3OBF_4 (0.5 g in 5 ml) was added dropwise. The solution was allowed to warm to room temperature, and evaporated by means of a dry N_2 stream. The resulting white solid still contained some oxonium salt which was removed by trituration with CH_2Cl_2 on an ice bath. In the

^{1}H NMR spectrum at 60 MHz, the CH_2O multiplets from endo- and exocyclic groups partially overlapped. A 90 MHz spectrum revealed that the CH_2O (exo) signal was a quasi-quintet, indicating that $J_{PH}=J_{HH}$. Anal. Calcd. for $C_8H_{17}NO_4PBF_4$: C, 31.09; H, 5.55; N, 4.53. Found: C, 30.07; H, 5.41; N, 4.26.

► *1-methoxy-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane tetrafluoroborate (7)*

A solution of 1.3 g 2 (6.7 mmol) in 10 ml of CH_2Cl_2 was cooled to -78 °C. With stirring, a solution of 1.0 g Me_3OBF_4 (6.7 mmol) in 3 ml CH_3CN and 5 ml $CH_2Cl_2$was added dropwise. After the addition, the mixture was allowed to warm overnight. A white solid was removed by filtration in a nitrogen atmosphere and washed several times with CH_2Cl_2. The filtrate and washings were evaporated. The residue was dissolved in a minimum amount of acetonitrile. The solution was evaporated *slowly* by passing over a stream of dry nitrogen, until only a fourth part of the original volume was left. The crystals which had formed were isolated by decanting the slightly yellow solution.

► *1-ethylthio-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane tetrafluoroborate (8)*

A stirred CH_2Cl_2 solution of 3 (1 g, 4.7 mmol) was cooled to -78 °C. A solution of 1 g Et_3OBF_4 in CH_2Cl_2 was added dropwise, after which the mixture was allowed to warm. The precipitated product was isolated by filtration on a glass filter and washed three times with dry CH_2Cl_2. The salt was soluble in CH_3CN; it was recrystallized by slow evaporation of a CH_3CN solution under nitrogen: needles, mp 164-6 °C, dec. The density was determined by the flotation method: flotation occurred in a 1:0.65 mixture (v/v) of CCl_4 (ρ= 1.59 g/cm^3) and CH_2Cl_2 (ρ= 1.32 g/cm^3). Thus, the density of this mixture (and of the crystals) is 1.48 g/cm^3. Anal. Calcd. for $C_8H_{17}NO_3PSBF_4$: C, 29.56; H, 5.27; N, 4.31. Found: C, 29.30; H, 5.37; N, 4.26.

► *1-methylthio-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane tetrafluoroborate (9) and 1-dimethylthio-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane bis(tetrafluoroborate) (10)*

0.51 g of Me_3OBF_4 (4.3 mmol) was dissolved in a small amount of CH_3CN. CH_2Cl_2 was added until the salt began to precipitate. After cooling to -78 °C, a solution of 0.9 g (4.3 mmol) of 2 in CH_2Cl_2 was added dropwise. The stirred suspension was allowed to warm to room temperature. Stirring was continued for several h. A white solid was removed by filtration and washed three times with CH_2Cl_2. This product was found to be 5. The filtrate and washings contained unreacted thiophosphate and two *S*-alkylated products as indicated by the presence of two Me-S-P doublets in the ^1H NMR spectrum. Upon slow evaporation of the solution, one of the alkylated products (10) precipitated first. The other product and 3 were difficult to separate. However, very slow evaporation of a CD_3CN solution yielded 9 in >90% purity.

Compound 10, characterized by poor solubility in CH_3CN and a Me-S-P doublet of large intensity in the ^1H NMR spectrum, was obtained in better yield when the reaction was carried out in CH_2Cl_2 suspension without CH_3CN. The solid formed in this reaction consisted of nearly pure 10. Anal. Calcd. for $C_8H_{18}O_3PSB_2F_8$: C, 23.27; H, 4.39; N, 3.39. Found: C, 23.04; H, 4.35; N, 3.27.

► *X-ray structure determination of 8*

Single crystals of 8 were obtained by slow evaporation of a concentrated CH_3CN solution under a stream of dry nitrogen. They belong to the monoclinic crystal system with a= 845.7(9), b= 1826.8(13), c= 935.8(5) pm, β= 93.08°(8). Systematically absent reflections are: 0k0, k odd; and h0ℓ, (h+ℓ) odd, indicating space group $P2_1/n$. Because of β being close to 90°, this space group was chosen rather than the equivalent $P2_1/c$. The calculated density is 1.49 g/cm³, assuming 4 molecules per cell, the experimental value (flotation method) is 1.48 g/cm³.

A set of 972 unique reflections with intensities above the 3σ level was obtained on a Nonius CAD4 automatic diffractometer using Mo radiation. No absorption correction was applied. Intensity statistics indicated a centre of symmetry, in accordance with the space group.

The structure was solved by direct methods using the MULTAN[30] program. In the subsequent refining by means of difference sythesis there appeared to be some disorder in the position of the BF_4 anion. The organic cation showing up well, however, it was decided not to continue refinement after an R value of 14.8% was reached.

The X-ray data were collected at the University of Utrecht by prof. dr. J.C. Schoone. The evaluation and structure determination was made by dr. A.S. Koster of the department of Physical Chemistry, while the ORTEP drawings were obtained with the assistance of dr. G.J. Visser of the Computing Centre at Eindhoven University of Technology.

References and Notes

1. A. Munoz, B. Garrigues, and M. Koenig, J. Chem. Soc., Chem. Commun., 1978, 219.
2. I. Granoth and J.C. Martin, J. Am. Chem. Soc., 1978, *100*, 5229.
3. I. Granoth and J.C. Martin, J. Am. Chem. Soc., 1978, *100*, 7434.
4. E.F. Perozzi and J.C. Martin, J. Am. Chem. Soc., 1979, *101*, 1591.
5. D. Marquarding, F. Ramirez, I. Ugi, and P. Gillespie, Angew. Chem., 1973, *85*, 99.
6. A.M.C.F. Castelijns, P. Schipper, and H.M. Buck, J. Chem. Soc., Chem. Commun., 1978, 382.
7. A.M.C.F. Castelijns, Thesis Eindhoven, 1979.
8. J.C. Clardy, D.S. Milbrath, J.P. Springer, and J.G. Verkade, J. Am. Chem. Soc., 1976, *98*, 623.
9. K.E. DeBruin and D.M. Johnson, J. Am. Chem. Soc., 1973, *95*, 4675.
10. D.G. Gorenstein, J. Am. Chem. Soc., 1973, *95*, 8060.
11. K.L. Marsi, J. Org. Chem., 1975, *40*, 1779.
12. G.A. Aksnes, F.Y. Khalil, and P.J. Majewski, Phosphorus, 1977, *3*, 6157.
13. A.Schnell and J.C. Tebby, J.Chem. Soc., Perkin 1, 1977, 1883.
14. K.L. Marsi, J. Org. Chem., 1978, *43*, 760.
15. S.J. Kubisen, Jr. and F.H. Westheimer, J. Am. Chem. Soc., 1979, *101*, 5985.
16. S.J. Benkovic and K.J. Schray, "The Enzymes", Vol. VIII, P.D. Boyer, ed., Academic Press, New York, 1973.
17. S.J. Benkovic and K.J. Schray, "Transition States of Biochemical Processes", R.D. Gandour and R.L. Schowen, eds., Plenum Press, New York, 1978, p.493.
18. K.G. Scrimgeour, "Chemistry and Control of Enzymatic Reactions", Academic Press, London, 1977, p. 185.
19. P.C. Haake and F.H. Westheimer, J. Am. Chem. Soc., 1961,

83, 1102.
20. D.S. Milbrath and J.G. Verkade, J. Am. Chem. Soc., 1977, *99*, 6607.
21. J.C. Clardy, D.S. Milbrath, and J.G. Verkade, Inorg. Chem., 1977, *16*, 2135.
22. C. Walling and R. Rabinowitz, J. Am. Chem. Soc., 1959, *81*, 1243.
23. M. Murray, R. Schmutzler, E. Gründemann, and H. Teichmann, J. Chem. Soc., B, 1971, 1714.
24. M.M. Crutchfield, C.H. Dungan, J.H. Letcher, V. Mark, and J.R. Van Wazer, "^{31}P Nuclear Magnetic Resonance", Interscience Publ., New York, 1967, p.173.
25. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, Ltd., Tokyo, 1968, p. 329.
26. Program: C. Johnson, "ORTEP, a Fortran Thermal-ellipsoid Plot Program", US Atomic Energy Commission Report, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
27. I. Ugi and F. Ramirez, Chem. Br., 1972, *8*, 198.
28. R.S. Berry, J. Chem. Phys., 1960, *32*, 933.
29. H. Meerwein, "Houben-Weyl, Methoden der Organischen Chemie", Vol. IV/3, Sauerstoff I, Teil 3, E. Müller, ed., G. Thieme Verlag, Stuttgart, 1965, p. 336.
30. Program: MULTAN 78. P. Main, S.E. Hull, L. Lessinger, G. Germain, J.-P. Declerq, M.M. Woolfson, Dept. of Physics, University of York, York, England.

CHAPTER IV

Selectivity in group transfer reactions from tricyclic phosphatranes

IV.1 *Introduction*

In general, group transfer reactions of phosphate esters can be described as nucleophilic substitutions in which phosphate is the leaving group. The substrate which is transferred may be an acyl group, as in many biochemical reactions[1,2], or an alkyl group[3] (Fig. IV.1). Thus, the hydrolysis of phosphate

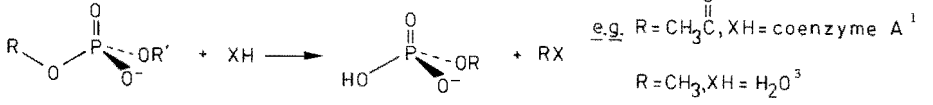


Fig. IV.1 Group transfer reaction

esters *with C-O bond breaking*[3-5] is in fact a group transfer reaction. Another example of group transfer is found in the Arbuzov reaction, which is usually assumed to involve nucleophilic displacement at the carbon atom of an alkoxyphosphonium ion[6-9] (Fig. IV.2). The dealkylation step is an S_N2 reaction

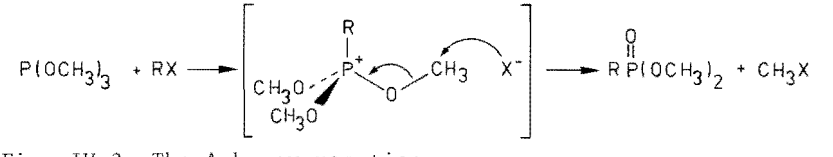


Fig. IV.2 The Arbuzov reaction

with inversion at carbon[6,7]. Closely related to the Arbuzov reaction are the reactions of cyclic oxyphosphoranes with acids[10-13]. It has been established that these reactions proceed by protonation of the apical ring oxygen atom[10,11] yielding a phosphonium ion, followed by dealkylation by the anion

of the acid (Fig. IV.3)[12,13]. Under low nucleophilic conditions,

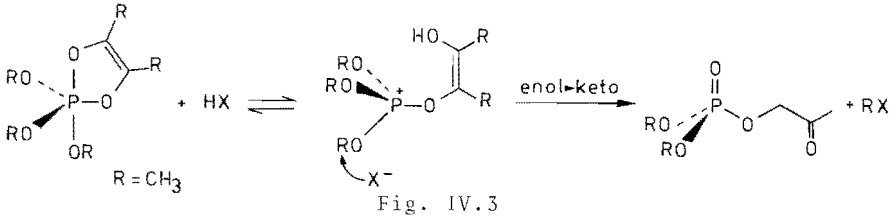


Fig. IV.3

equilibria have been studied of these phosphonium ions with the parent oxyphosphoranes[12,13].

In phosphate esters and alkoxyphosphonium ions, nucleophiles generally have the choice between attack on carbon or on phosphorus[3-5,14-21]. The latter reaction leads to oxyphosphoranes, which have indeed been observed as intermediates in the Arbuzov reaction[22,23]. As yet it is not clear, however, whether the actual group transfer occurs from the four- or the five-coordinated configuration. Reaction *via* an oxyphosphorane intermediate could imply selectivity, since the five ligands are not equivalent in this case[24]. *Thus, the position of a ligand in the TBP configuration may be more important than its intrinsic reactivity, whereas in a phosphonium ion the most reactive group is transferred.* In early work on this subject[10,11], it was presumed that the apical ligands in the TBP configuration are more reactive than the basal ligands as a result of their weaker bonding to phosphorus. In contrast, the transfer of a methyl group from a cyclic oxyphosphorane apparently occurs from a basal site (Fig. IV.4), since the phosphate group must

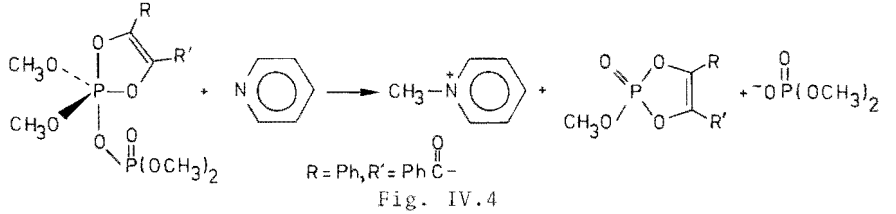


Fig. IV.4

depart from an apical position while a ring oxygen occupies the other apical site[13]. It should be pointed out, however,

that the apical and basal ligands are not comparable in this case, and furthermore, that pseudorotation in this compound may result in a fast exchange of the ligands[25]. In order to detect selectivity in group transfer from five-coordinated intermediates, oxyphosphoranes should be considered with comparable apical and basal groups which are not interconverted by pseudorotation. Since the tricyclic phosphatranes discussed in the previous Chapters fulfil these conditions, it seems worthwhile to investigate their reactions with nucleophiles. The products of the 1-*H*-phosphatrane with various nucleophiles, which have been characterized before, may serve as reference compounds for the products derived from 1-alkoxy-(1-alkylthio-)phosphatranes. Therefore, it seems useful to recall first the data reported for the former compounds (Section IV.2) before the reactions of the alkoxy and alkylthio derivatives are described.

IV.2 *Reaction of 1-H-phosphatrane with various nucleophiles*

It has been observed by *Verkade et al.*[26] that the apical hydrogen atom in 1 (Fig. IV.5)[27] cannot be removed, even by very strong bases. They concluded that the cage structure was affected, without describing the products which were formed. As reported later by *Castelijns*[13], the reaction of 1 with strong nucleophiles (lithium methoxide, sodium acetate, or sodium hydroxide) yields products 2-4 (Fig. IV.5) which were

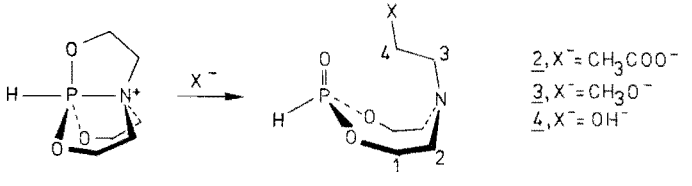


Fig. IV.5 Nucleophilic attack on 1-*H*-phosphatrane

characterized by NMR (Table IV.1 and IV.2).

In the ^{1}H NMR spectrum of 2-4, the doublet with large coupling ($^1J_{PH}$ = 790 Hz) has been replaced by a new doublet

Table IV.1 ^{1}H NMR data of the products derived from 1[a]

Compound	H_1[b]	H_2	H_3	H_4	H-P	
	δ	δ	δ	δ	δ	J_{PH}
2	4.0	2.8	2.8	3.5	6.6	740
3	4.0	2.9	2.9	3.5	6.6	730
4	4.0	2.8	2.8	3.4	6.5	720

[a]Solvent CD_3CN, δ in ppm, J in Hz.
[b]Numbering corresponds to Fig. IV.5.

Table IV.2 ^{31}P and ^{13}C NMR data of the products derived from 1

Compound	P	C_1[b]		C_2	C_3	C_4	C(X)
	δ	δ	J_{PC}	δ	δ	δ	δ
2	+4.4	68.5	10	56.1	60.4	61.0	58.3
3	+5.7	68.3	9	56.5	60.2	61.8	174.9[c]
							21.2[d]

[a]Solvent CD_3CN, δ in ppm, J in Hz. [b]Numbering corresponds to Fig. IV.5. [c]$\underline{C}(O)CH_3$. [d]$C(O)\underline{C}H_3$.

with somewhat smaller coupling ($^{1}J_{PH} \simeq 730$ Hz), which indicates that the P-H bond is preserved in this reaction. In addition, the signals of the cage hydrogen atoms have drastically been changed, since the P-H coupling of the CH_2N groups disappears and the H-H splitting pattern becomes more complex (Fig. IV.6). In the ^{13}C NMR spectrum, the two doublets of 1 are replaced by four signals from the cage atoms. The absence of P-C couplings in three of the signals indicates the breaking of the P-N bond (Table IV.2). Finally, the ^{31}P NMR shifts of 2-4 are in the range expected for dialkyl phosphites.

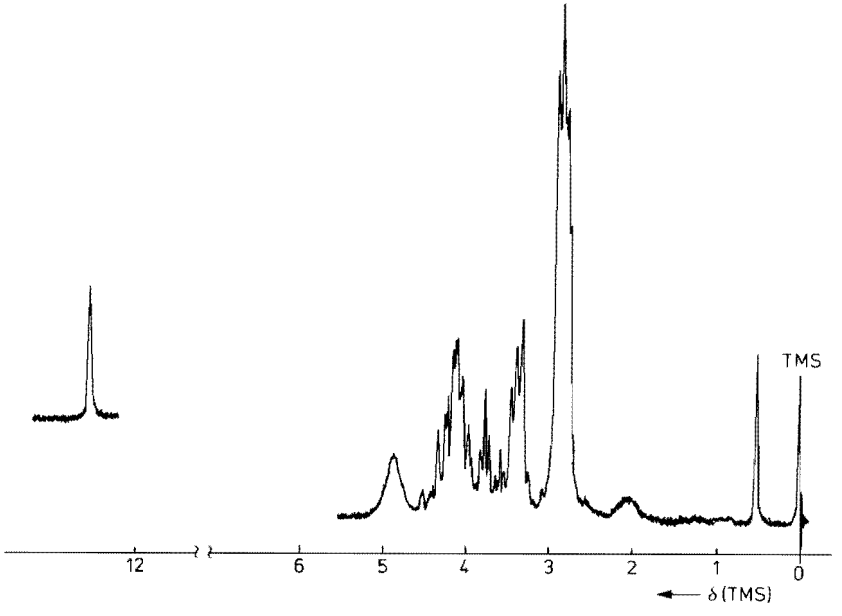
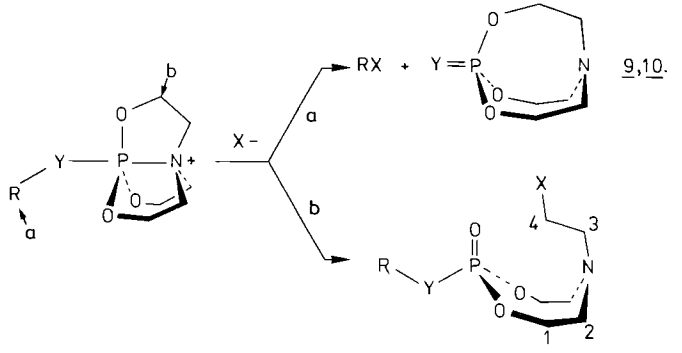


Fig. IV.6 ^{1}H NMR spectrum of 4

IV.3 *Reaction of 1-alkoxy-(alkylthio-)phosphatranes with nucleophiles*

The X-ray analysis of compound 7 (Fig. IV.7) and the NMR data have clearly established that the cations of 5-8 have a tricyclic structure with the exocyclic alkoxy or alkylthio group in an apical position (*cf.* Chapter III). Since the basal ligands are alkoxy groups, two obvious reaction paths can be distinguished for the reaction with nucleophiles (Fig. IV.7). Pseudo-apical nucleophilic attack (a) results in transfer of the alkylgroup, R, with recovery of the bicyclic phosphatranes 9 (Y=O) and 10 (Y=S), whereas pseudo-basal attack (b) yields monocyclic products (11-14). The terms pseudo-apical and pseudo--basal are used to indicate that nucleophilic attack does not take place on the oxygen (or sulfur) atom directly bonded to phosphorus.



Numbering:

Y	R	
O	Et	5,11
O	Me	6,12
S	Et	7,13
S	Me	8,14

Fig. IV.7

The salts 5-8 were treated with aqueous base. The ^{1}H NMR spectra of the products show a striking resemblance to the spectra of compounds 2-4 (Fig. IV.8), indicating that the

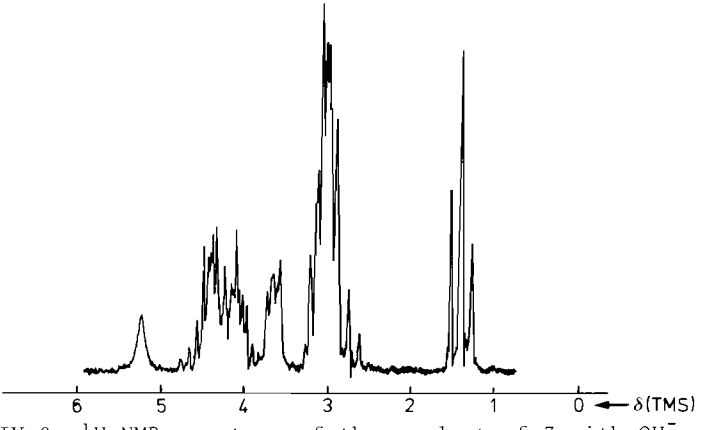


Fig. IV.8 ^{1}H NMR spectrum of the product of 7 with OH^-

reaction proceeds *via* path b. The NMR data are listed in Tables IV.3 and IV.4. Phosphorus couplings in the signals from the exocyclic RY group (^{1}H and ^{13}C) indicate that the P-Y bond is not broken in this reaction which excludes path a. The phosphorus resonances confirm these conclusions. The products of 5 and 6 are phosphates (δ_P near 0 ppm) whereas

Table IV.3 ^{1}H NMR data of alkaline hydrolysis products of 5-8[a]

Compound	H_1[b]	H_2	H_3	H_4	CH_nY	CH_3C
11	4.2	2.9	2.9	3.5	4.0	1.31[c]
12	4.1	2.9	2.9	3.5	3.7[d]	
13	4.2	2.9	2.9	3.5	2.7	1.29[e]
14	4.1	2.9	2.9	3.5	2.6[f]	

[a] δ in ppm, solvent $CDCl_3$. [b] Numbering corresponds to Fig. IV.7. [c] J_{POCCH}: 1 Hz, J_{HCCH}(exo): 7 Hz. [d] J_{POCH}: 11 Hz. [e] J_{POCCH} not resolved, J_{HCCH}(exo): 7 Hz. [f] J_{PSCH}: 16 Hz.

Table IV.4 ^{31}P and ^{13}C NMR data of alkaline hydrolysis products of 5-8[a]

	P	C_1[b]		C_2	C_3	C_4	CH_nY		CH_3C	
Compound	δ	δ	J_{PC}	δ	δ	δ	δ	J_{PC}	δ	J_{PC}
11	-0.21	64.2	6	57.7	61.0	62.9	70.3	7	16.7	7
12	+0.3	69.7	8	55.5	59.4	60.6	69.7[c]	(8)		
13	+31.2	70.3	10	57.4	61.3	63.4	26.1	4	17.3	7
14	+30.7									

[a] in ppm, J in Hz, solvent $CDCl_3$. [b] Numbering corresponds to Fig. IV.7. [c] Coincident with C_1 doublet.

7 and 8 yield thiolphosphates ($\delta_P \simeq 30$ ppm)[28]. It is worth noting that a small amount of bicyclic phosphatrane 9 or 10 was observed by ^{31}P NMR in some reaction products. However, the salts 5-8 were usually contaminated with similar amounts of 9 or 10, since it is very difficult to remove these precursors completely. No evidence was found for the generation of 9 or 10 in the reaction of 5-8 with OH^-.

IV.4 *Discussion*

The NMR data of the products demonstrate that in all investigated tricyclic phosphatranes nucleophilic attack occurs on the psuedo-basal carbon atoms. This is a remarkable result, since at least in compounds 5 and 6 some pseudo-apical group transfer might be expected. If the secondary carbon atom of the apical group in 5 would be equally reactive with respect to the pseudo-basal carbon atoms, a 25% pseudo-apical group transfer would occur. Moreover, compound 6 is expected to react *via* path a even better than compound 5 (Fig. IV.7), since in S_N2 reactions primary alkyl groups are about 30 times more reactive than secondary alkyl groups[29]. Actually, no pseudo-apical attack is detected by NMR, indicating that less than 5% of the reaction proceeds by path a, *i.e.*, the pseudo-basal sites are apparently about 20 times more reactive than the pseudo-apical site. Since in compound 6 a factor of 10 (30:3) in favour of the apical site is predicted by S_N2 reactivity, it can be concluded that the basal cage ligands are *at least* 200 times more reactive than estimated. Two factors which could be responsible for this difference are ring strain which could favour ring opening (path b), and the difference in bonding between apical and basal ligands in the TBP. Since the reaction is exothermic, the Hammond postulate[30] states that the transition state (TS) may be rather similar to the starting compound. If this is the case, the relief of ring strain may not be an important factor since most of the strain present in the starting compound will also occur in the TS. Moreover, the conformation of the five-membered rings in the tricyclic phosphatranes is highly puckered, as evident from the X-ray analysis of 7, which diminishes ring strain resulting from eclipsing of vicinal protons. Thus, the reactions provide evidence that the apical or basal position of a ligand, at least partially, determines whether nucleophilic attack occurs: P=O bond formation from basal oxygen ligands seems to be favoured.

When dealkylations of phosphonium ions are compared to the reactions described here, it is evident that always the most reactive group (*e.g.* primary alkyl) is transferred from phosphonium ions, whereas oxyphosphoranes may show reversed reactivity, *e.g.* if a primary alkyl group occupies an apical position. On the other hand, if an apical site is occupied by a group which usually is less reactive than the basal ligands, little difference is observed between oxyphosphoranes and phosphonium ions. This situation is probably found in compounds 1, 7, and 8, since phosphonium ions which contain a hydrogen or alkylthio ligand as well as alkoxy ligands always transfer the alkyl group bound *via* oxygen[31-34] (Fig. IV.9).

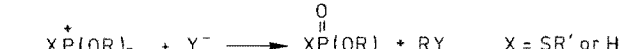


Fig. IV.9

Preferential pseudo-basal group transfer from oxyphosphoranes may be rationalized by the theoretical description of phosphorus in a TBP configuration (*cf.* Chapter I, Section I.2). Thus, it is known that the apical ligands accumulate more electron density than the basal ligands as a result of the pd hybridization of the apical bonds and backdonation from the basal ligands[35]. Due to the backdonation the basal bonds can be considered as partial double bonds, which is reflected in a shorter bond length and a higher barrier for rotation around these bonds[36]. Since the transition state probably resembles the TBP configuration, these factors favour the formation of a P=O bond from a basal alkoxy ligand, *i.e.* pseudo-basal group transfer. Evidently, a complete description of the reactivity of a TBP should include the basal formation of P=O bonds besides apical entry and departure of ligands[37]. This scheme can be applied to various reactions in which five-coordinated intermediates play a role. For instance, in the recently reported methanolysis of diazaoxaphospholenes a pseudo-basal group transfer from an oxyphosphorane intermedi-

ate was postulated[38] (Fig. IV.10). Furthermore, basal P=O

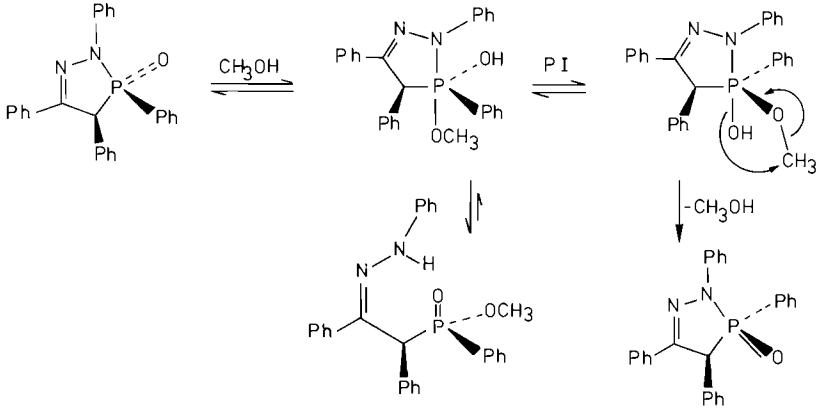


Fig. IV.10

bond formation may be important in the Wittig reaction. It has been established that a five-coordinated cyclic intermediate is involved in this reaction[39-42]. According to recent theoretical investigations[43,44], the oxygen ligand in the intermediate initially occupies an apical site whereas the products are formed from the isomer with a basal oxygen atom (Fig. IV.11).

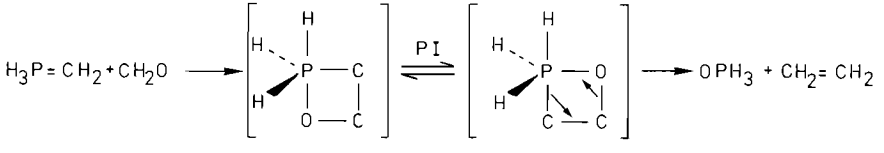


Fig. IV.11 Tentative mechanism of the Wittig r action, based on *ab initio* calculations

The proposed mechanism, involving a permutational isomerization, is in accordance with basal P=O bond formation as well as apical departure since an apical P-C bond is broken.

It has not been elucidated yet if phosphoranes are intermediates in enzymatic group transfer reactions. The introduction of an enzyme site as the fifth ligand might lead to five-coordinated intermediates which are stabilized by shiel-

ding of the basal anionic oxygen ligands[10,11]. However, acyl ligands which are most relevant in biochemistry[1] are expected to occupy an apical site in a TBP, making group transfer unfavourable. A solution to this problem may be that the enzyme site enters the TBP adjacent to the acyl group (Fig. IV.12),

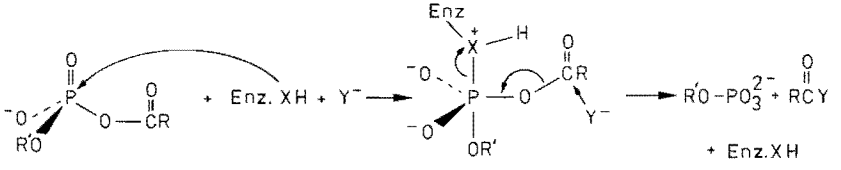


Fig. IV.12

bringing this ligand in a basal position, or that the acyl group is reactive enough to be transferred even from an apical site. Another proposal is that phosphoranes are formed as intermediates in acyl transfer as a result of intramolecular phosphorylation by the anionic oxygen of the acyl group[12,13] (Fig. IV.13). This mechanism, which is in accordance with

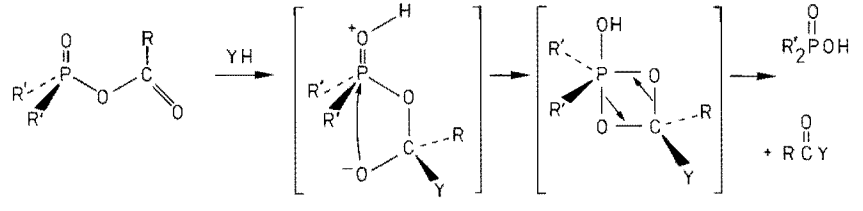


Fig. IV.13

P=O bond formation from a basal ligand, could account partially for the high reactivity of acyl phosphates since breaking of the C-O bond is facilitated when the oxygen atom occupies a basal position.

IV.5 *Experimental*

Preparations and reactions

Tricyclic phosphatrane 1 was prepared according to the literature procedure[26]. The preparation of the salts 5-8 has

been described in Chapter III.

► *Reaction of 1 with nucleophiles*

NMR samples were prepared by dissolving 50 mg of 1 in 0.35 ml of CD_3CN. The nucleophile (solid sodium acetate or lithium methoxide, or a 1 mol/l NaOH solution) was added with shaking and warming. The reaction could be monitored by ^1H NMR: the doublet, $^1J_{PH}$= 790 Hz, of 1 was gradually replaced by a new doublet with smaller coupling (720-740 Hz). When the reaction was completed, ^{13}C and ^{31}P NMR spectra were recorded to characterize the products.

► *Reaction of 5-8 with OH^-*

An NMR sample of the phosphatrane was prepared by dissolving about 50 mg in 0.35 ml of CD_3CN. A few drops of a 1 mol/l NaOH solution were added, and the NMR sample tube was shaken to obtain a clear solution. The reaction could be monitored by ^1H NMR. In all cases, no more changes were observed after one day of reaction. The products were isolated by pouring the NMR sample in a few ml of water, extracting with chloroform, drying the chloroform layer on $MgSO_4$, and evaporating the chloroform *in vacuo*. The residue was dissolved in $CDCl_3$ and ^1H, ^{13}C and ^{31}P NMR spectra were recorded. The products were obtained as oils with no tendency to crystallize.

The reaction of 7 with OH^- was monitored by ^{31}P NMR. Before the addition of the nucleophile, both 7 and some thiophosphate 10 were observed in the mixture. During the reaction, no significant change in the amount of 10 was found, whereas the signal of 7 was gradually replaced by a new peak, δ +30.7 ppm, attributed to 13.

References and Notes

1. H.R. Mahler and E.H. Cordes, "Biological Chemistry", Harper and Row, New York, 1971, pp. 510, 595, 918, *etc.*
2. M.-D. Tsai, Biochemistry, 1979, *18*, 1468.
3. P.C. Haake and F.H. Westheimer, J. Am. Chem. Soc., 1961, *83*, 1102.
4. G. DiSabato and W.P. Jencks, J. Am. Chem. Soc., 1961, *83*, 4393.
5. V.E. Bel'skii, Russ. Chem. Rev., 1977, *46*, 828.
6. A.J. Kirby and S.G. Warren, "The Organic Chemistry of Phosphorus", Elsevier, Amsterdam, 1967, p. 37 *et seq.*
7. W. Gerrard and W.J. Green, J. Chem. Soc., 1951, 2550.
8. G.M. Kosolapoff and L. Maier, "Organic Phosphorus Compounds", Vol. 7, Wiley, New York, 1976, p. 23 *et seq.*
9. K.S. Colle and E.S. Lewis, J. Org. Chem., 1978, *43*, 571.
10. W.G. Voncken and H.M. Buck, Recl. Trav. Chim. Pays-Bas, 1974, *93*, 210.
11. W.G. Voncken, Thesis Eindhoven, 1976.
12. A.M.C.F. Castelijns, P. Schipper, and H.M. Buck, J. Chem. Soc., Chem. Commun., 1978, 382.
13. A.M.C.F. Castelijns, Thesis Eindhoven, 1979.
14. M. Revel, J. Navech, and F. Mathis, Bull. Soc. Chim. Fr., 1971, 105.
15. K.E. DeBruin and D.M. Johnson, J. Am. Chem. Soc., 1973, *95*, 4675.
16. K.E. DeBruin, A.G. Padilla, and M.-T. Campbell, J. Am. Chem. Soc., 1973, *95*, 4681.
17. D.G. Gorenstein, J. Am. Chem. Soc., 1973, *95*, 8060.
18. F. Ramirez, S.L. Glaser, P. Stern, I. Ugi, and P. Lemmen, Tetrahedron, 1973, *29*, 3741.
19. K.L. Marsi, J. Org. Chem., 1975, *40*, 1779.
20. K.L. Marsi and J.L. Jasperse, J. Org. Chem., 1978, *43*, 760.
21. S.J. Kubisen and F.H. Westheimer, J. Am. Chem. Soc., 1979, *101*, 5985.
22. A. Skowronska, J. Mikołajczak, and J. Michalski, J. Chem.

Soc., Chem. Commun., 1975, 791.
23. G. Bauer and G. Hägele, Angew. Chem., 1977, *89*, 493.
24. I. Ugi and F. Ramirez, Chem. Br., 1972, *8*, 198.
25. F. Ramirez, S. Pfohl, E.A. Tsolis, J.F. Pilot, C.P. Smith, I. Ugi, D. Marquarding, P. Gillespie, and P. Hoffmann, Phosphorus, 1971, *1*, 1.
26. D.S. Milbrath and J.G. Verkade, J. Am. Chem. Soc., 1977, *99*, 6607.
27. J.C. Clardy, D.S. Milbrath, J.P. Springer, and J.G. Verkade, J. Am. Chem. Soc., 1976, *98*, 623.
28. M.M. Crutchfield, C.H. Dungan, J.H. Letcher, V. Mark, and J.R. Van Wazer, "^{31}P Nuclear Magnetic Resonance", Interscience, New York, 1967.
29. A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, 1962, p. 13.
30. T.H. Lowry and K. Schueller Richardson, "Mechanism and Theory in Organic Chemistry", Harper and Row, New York, 1976, p. 102.
31. D.C. Morrison, J. Am. Chem. Soc., 1955, *77*, 181.
32. M. Mikołajczyk, J. Krzywanski, and B. Ziemnicka, J. Org. Chem., 1977, *42*, 191.
33. G.M. Kosolapoff and L. Maier, "Organic Phosphorus Compounds", Vol. 5, Wiley, New York, 1973, p. 55.
34. R. Weiss, L.J. VandeGriend, and J.G. Verkade, J. Org. Chem., 1979, *44*, 1860.
35. P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E.A. Tsolis, and I. Ugi, Angew. Chem., 1971, *83*, 691.
36. J.M. Howell, Chem. Phys. Lett., 1974, *25*, 51.
37. F.H. Westheimer, Acc. Chem. Res., 1968, *1*, 70.
38. G. Baccolini and P.E. Todesco, J. Org. Chem., 1978, *43*, 216.
39. E. Breuer and D.M. Bannett, Tetrahedron Lett., 1977, 1141.
40. E. Vedejs and K.A.J. Snoble, J. Am. Chem. Soc., 1973, *95*, 5778.
41. E. Breuer, S. Zbaida, and E. Segall, Tetrahedron Lett., 1979, 2203.

42. D.W. Allen and H. Ward, Tetrahedron Lett., 1979, 2707.
43. R. Holler and H. Lischka, J. Am. Chem. Soc., 1980, *102*, 4632.
44. H.J. Bestmann, Pure Appl. Chem., 1980, *52*, 771.

CHAPTER V

Importance of orientation in reactions proceeding via five-coordinated phosphorus compounds

V.1 *Introduction*

In many reactions the proximity of two reacting groups within a molecule produces a substantial rate acceleration[1]. This effect can be attributed to the decrease in translational entropy of the reacting groups which facilitates the formation of the transition state[2]. Since the entropy of activation is a major factor in the formation of five-coordinated phosphorus intermediates[3], it is not surprising that orientation effects are important in reactions involving phosphoranes. A classical example is the hydrolysis of ribonucleic acids by RNase A, in which the proximity of the 2'-OH group on the ribose accelerates the reaction (*cf.* Chapter I, Section I.1). In addition, it has been shown in the previous Chapters that the orientation of nitrogen in bicyclic phosphatranes facilitates the formation of stable oxyphosphoranes by P←N bond formation.

The influence of orientation on the formation of phosphoranes can be measured by studying an equilibrium between a four- and a five-coordinated form. Such equilibria can be established directly by treating stable, cyclic oxyphosphoranes with a strong acid[4] (Fig. V.1). It has been shown that rigidity

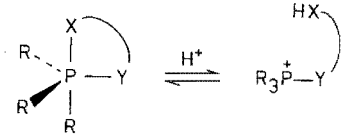


Fig. V.1

in the Y-section results in a faster equilibrium[4]. Another

way to study this equilibrium is to investigate the solvolysis of cyclic, four-coordinated phosphorus esters[5,6]. It seems plausible that reclosure of the ring-opened product more easily occurs if some rigidity exists in the compound. This could result in exocyclic hydrolysis without the need for permutational isomerizations (PI)[5], as shown in Fig. V.2. Thus, exo-

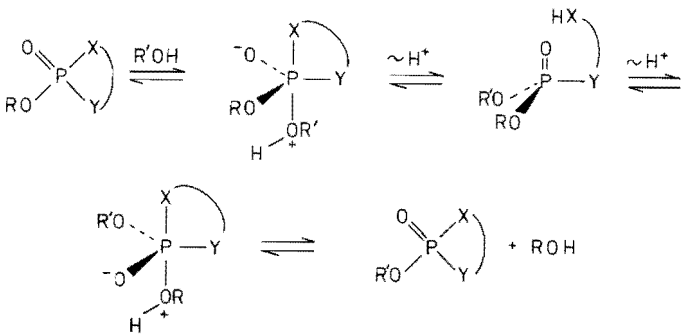


Fig. V.2

cyclic solvolysis which cannot be attributed to PI may be the result of ring opening and reclosure. Cyclic phosph(on)ates having a double bond might show this phenomenon, since the orientation of the double bond might facilitate the reclosure. However, the unsaturated compounds which have been reported yield enols upon ring opening[6], which are rapidly converted to their keto isomers leading to irreversibility of the process (Fig. V.3).

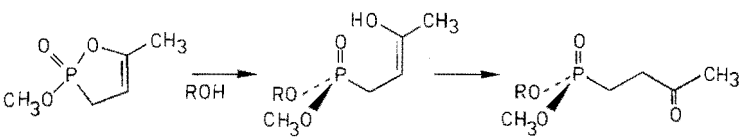
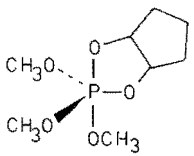
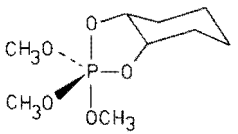


Fig. V.3

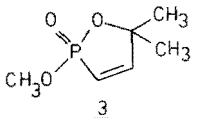
The compounds shown in Fig. V.4 seem more promising models to demonstrate the effect of orientation. According to the arguments outlined above, the equilibria between the phosphoranes 1 and 2 and the corresponding phosphonium ions should



1



2



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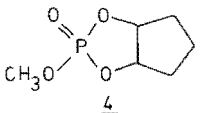
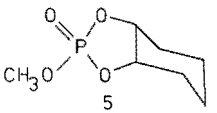


4



5

Fig. V.4

be relatively fast. Similarly, the solvolysis of the cyclic compounds 3-5 is expected to yield a high amount of cyclic product resulting from ring opening and reclosure.

V.2 *Equilibria between phosphoranes and phosphonium ions*

V.2.1 Preparation of the phosphoranes

For the synthesis of a five-membered cyclic, saturated oxyphosphorane a trialkyl phosphite may be reacted with a 1,2-diol in the presence of a hydrogen abstracting reagent, *e.g.* *N*-chlorodiisopropylamine[7] (Fig. V.5). However, since

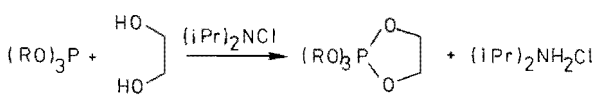


Fig. V.5

acyclic phosphites tend to undergo side-reactions with the chloroamine[8], this method seems to be restricted to spiro-phosphoranes. Another synthetic route, based on work by *Denney et al.*[9,10], uses an activated derivative of the diol. Sulfenate esters are useful for this purpose, since the O-S bond in these compounds is weak (Fig. V.6). The *cis*-1,2-diols required for the prepararion of 1 and 2 were obtained by the selective cis-oxydation of the corresponding cycloalkenes[11,12]

by the routes shown in Fig. V.7.

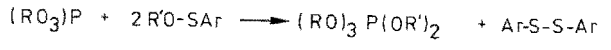


Fig. V.6

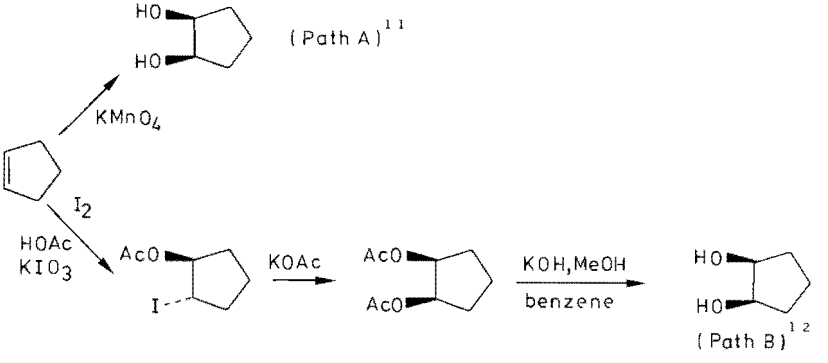
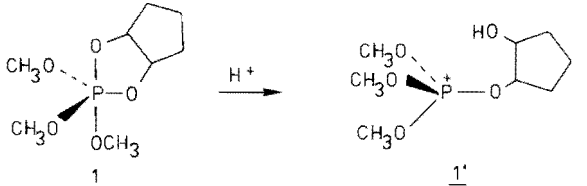


Fig. V.7

V.2.2 Low temperature NMR measurements of oxyphosphoranes in strong acid solution.

Upon cooling a solution of 1 in Freon 21 ($CHFCl_2$) to -120 °C, some line broadening of the NMR signals is observed, but the signal of the three methoxy groups remains one doublet, indicating that pseudorotation of this compound remains fast at low temperature.

The addition of less than one equivalent of fluorosulfonic acid to the Freon solution at about -120 °C causes the appearance of new signals which can be attributed to the ring-opened phosphonium ion 1' (Fig. V.8) because the methoxy



1 1'

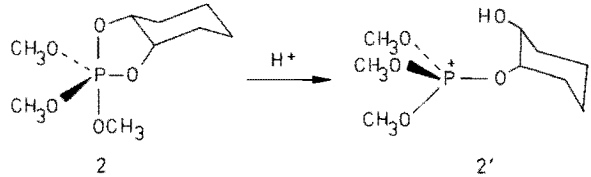
Fig. V.8

doublet of this compound is at lower field than the oxyphosphorane doublet. The ^1H NMR spectrum is temperature dependent: warming of the sample causes broadening of the methoxy doublets of 1 and 1', and coalescence of these signals at -55 ^oC. This behaviour is completely reversible.

In the ^{31}P NMR spectrum of the mixture of 1 and 1', the resonances of the oxyphosphorane (-41.6 ppm) and the phosphonium ion (+4.1 ppm) can be clearly distinguished. At relatively high temperatures (about 0 ^oC) the ^{31}P NMR spectrum reveals the occurrence of an irreversible reaction which produces a phosphate-like compound. Presumably, dealkylation of the phosphonium ion occurs at this temperature.

The line broadening and coalescence phenomena indicate an equilibrium between 1 and 1'. The proton acceptor which is required for the conversion of 1' to 1 is probably a second molecule of 1, since the acid anion FSO_3^- is a very weak base. Consequently, the observed equilibrium is in fact a bimolecular reaction involving a proton transfer: $1 + {}^*1' \rightleftharpoons 1' + {}^*1$. This view is supported by the activation parameters of the equilibrium (*vide infra*).

The behaviour of 2 is completely analogous to that described for 1, but the coalescence temperature of the methoxy doublets is higher (-15 ^oC). Thus, the equilibrium of compounds 2 and 2' is slower than the equilibrium observed for compounds 1 and 1' (Fig. V.9).



2 2'

Fig. V.9

From the line width of the methoxy signals, both of the phosphonium ion and of the phosphorane, the activation parameters for the observed equilibria can be determined. These parameters are listed in Table V.1. The large negative entropy

Table V.1 Activation parameters for equilibria of oxyphosphoranes and phosphonium ions.

Compound	$\Delta H^{\ddagger}$ (kJ/mol)[a]	$\Delta S^{\ddagger}$ (J/deg.mol)[b]	$\Delta G^{\ddagger}$ (kJ/mol)[c]
1	12.5	-169	54.3
2	11.0	-184	56.5

[a] $\Delta H^{\ddagger} = E_A - RT$. E_A was determined from the plot of $\ln\Delta$ *vs.* 1/T (Δ= linewidth of a methoxy peak). See Ref. 13.
[b] Calculated from $\ln(k)=\ln(RT/N_A h)+\Delta S^{\ddagger}/R-\Delta H^{\ddagger}/RT$; k was determined from the plot of $\ln\Delta$ *vs.* 1/T (See Refs. 13 and 14).
[c] $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, calculated at 248 K (-25 °C).

of activation strongly indicates a bimolecular process, in accordance with the assumption of proton transfer from a phosphonium ion to a phosphorane.

V.3 *Solvolysis of cyclic phosph(on)ates with ring retention*

V.3.1 Synthesis of the phosphonate 3 and the phosphates 4 and 5

The starting point for the synthesis of 3 is the cyclic phosphonic acid, 6.(Fig. V.10)[15,16]. The synthesis of 6 is remarkable, since it involves a cyclization of an allenic

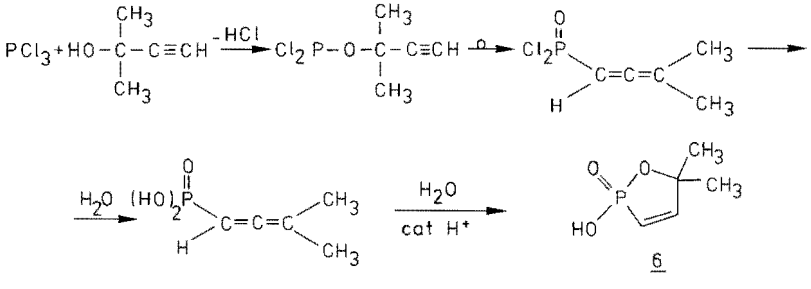
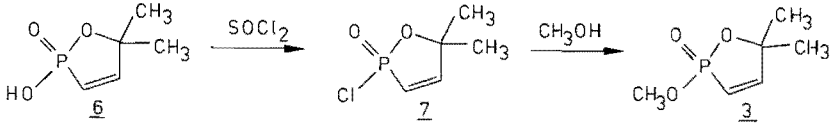


Fig. V.10

phosphonic acid in aqueous acid[15]. This is already an indication of the stability of this ring structure. The preparation of 3, the methyl ester of 6, was accomplished *via* the

acid chloride, 7 (Fig. V.11). Alternative methods for the esterification of phosphonic acids are reaction with trimethyl orthoformate, trimethyl phosphite[17], or diazomethane. However, the former two were not successful in this case while the latter is difficult to use in larger-scale preparations.



6 7 3

Fig. V.11

The cyclic phosphates, 4 and 5, were prepared from the corresponding trimethoxyphosphoranes, 1 and 2, respectively, using the method of dealkylation with acetyl bromide[18]. Both 4 and 5 were obtained as mixtures of diastereomers, as indicated by the presence of two methoxy doublets in ^{1}H NMR and two signals in ^{31}P NMR.

V.3.2 Solvolysis reactions of cyclic compounds

The solvolysis of 3 in CD_3OD at 35 ^{o}C was monitored by ^{1}H NMR. The methoxy doublet of 3 is gradually replaced by a singlet from methanol. No change is observed in the other signals indicating that exocyclic displacement occurs without ring opening (Fig. V.12). The pseudo first-order rate constant

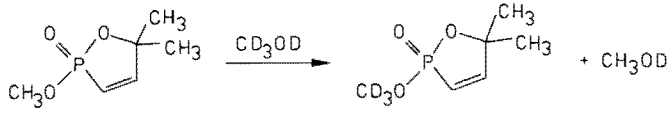


Fig. V.12

for the reaction is 2.9×10^{-6} s^{-1} ($t_{\frac{1}{2}} \approx 61$ h).

The hydrolysis of 3 in D_2O yields methanol and the cyclic phosphonic acid, 6, as indicated by ^{1}H NMR. However, when the reaction is carried out in sodium acetate buffer, an intermediate product is observed which has a methoxy doublet in its NMR spectrum. Probably, this product, 8, is ring-opened (Fig. V.13). The amount of ring-opened product decreases again

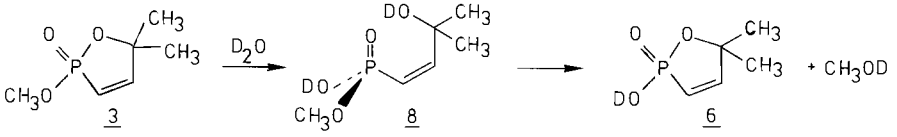


Fig. V.13

as the reaction proceeds, yielding more methanol and the cyclic phosphonic acid, 6. The observed pseudo first-order rate constant for the disappearance of 1 in buffered D_2O solution is 1.5×10^{-6} s^{-1} ($t_{\frac{1}{2}} \simeq$ 128 h). Without buffer, the pH is lowered by the acidic product and the pseudo first-order rate constant is 2.2×10^{-5} s^{-1}, indicating that the reaction is acid-catalyzed.

The methanolysis of 4 in CD_3OD was monitored by ^1H NMR. The methoxy doublets of 4 (two diastereomers) decrease while the methanol peak emerges. A weak new doublet is observed which is attributed to a ring-opened product. In addition, new signals appear from the methine protons (OCH) of the ring which also indicate ring opening. After about 1 day when the spectrum does not change anymore, over 80% of the methoxy groups is present as methanol, while about 50% of the methine protons correspond to ring-opened products. These findings are interpreted by the existence of three products, 9-11 (Fig. V.14),

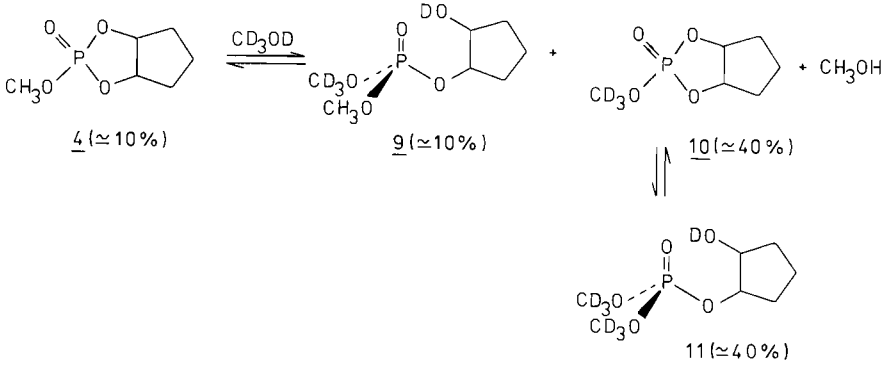
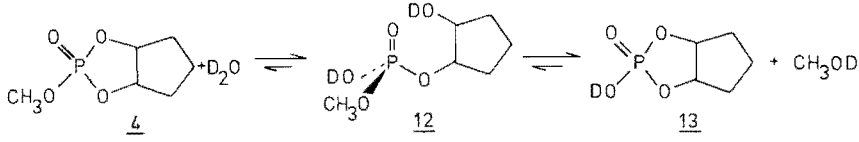


Fig. V.14

which are in equilibrium with the starting compound 4. Since

methanol formation accompanies the formation of 10 or 11, these two products represent 80% of the mixture. In addition, the methoxy doublets of 4 and 9 show that the remaining 20% consists of equal amounts of these compounds. Since the methine signals indicate a 1:1 ratio of ring-opened and cyclic products, it follows that 10 and 11 are also present in equal amounts. The final composition of the mixture is indicated in Fig. V.15.

The hydrolysis of 4 in D_2O with sodium acetate buffer is observed in the ^1H NMR spectrum by the decrease of the methoxy doublets of 4, accompanied by the appearance of a methanol peak and a new doublet. After 1 day when the reaction is ended, the mixture consists of 62% of the compound with the new doublet, 33% of methanol and less than 5% of the starting compound. When the hydrolysis is carried out without the buffer, the original doublets disappear very fast. The new doublet which appeared in the hydrolysis with buffer is again observed, but it decreases again as the reaction proceeds, while the methanol peak increases. At the end of the reaction about 83% of the methoxy groups correspond to methanol. These observations indicate a ring opening followed by reclosure with methanol cleavage (Fig. V.15). Since the hydrolysis pro-



4 12 13

Fig. V.15

ducts 12 and 13 are acidic, the pH of the mixture becomes lower when no buffer is present. The pH is found to influence the product composition: when the solution resulting from the buffered hydrolysis is made more acidic, the new methoxy doublet decreases and the methanol peak grows.

The results for the solvolysis reactions of 5 are very similar to the results described for 4. However, the equilibria for this compound are shifted somewhat to the ring-opened

products.

V.4 *Discussion*

It has been pointed out[4] that the equilibria of oxyphosphoranes and phosphonium ions (*e.g.* Fig. V.1) with simultaneous proton transfer are established *via* a highly symmetrical transition state. Both molecules in this transition state must have a conformation which approximates the oxyphosphorane (Fig. V.16). Therefore, it may be expected that the entropy of activation of this process is strongly dependent on the orientation of the OH group in the phosphonium ion. The ac-

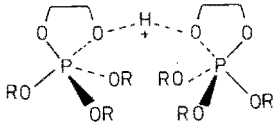
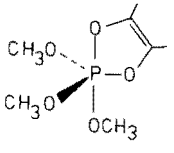


Fig. V.16

tivation parameters listed in Table V.1 support this view. The enthalpies of activation for 1 and 2 are close to the value found for compound 14 (Fig. V.17), while in all three

14



$\Delta G^{\ddagger}$ = 51.2 kJ/mol
$\Delta H^{\ddagger}$ = 11.6 kJ/mol
$\Delta S^{\ddagger}$ = -155 J/deg.mol

Fig. V.17

compounds the $T\Delta S^{\ddagger}$ term is much larger than the $\Delta H^{\ddagger}$ term. The order of $\Delta S^{\ddagger}$ values (14>1>2) indicates that a double bond makes the phosphonium ion slightly more rigid than a five-membered ring whereas a six-membered ring is somewhat less effective.

The solvolysis of the cyclic phosph(on)ates can be discussed conveniently on the basis of the general scheme shown in Fig. V.18. In this scheme, reaction a represents exocyclic solvolysis *via* a pseudorotation mechanism[5], which is not

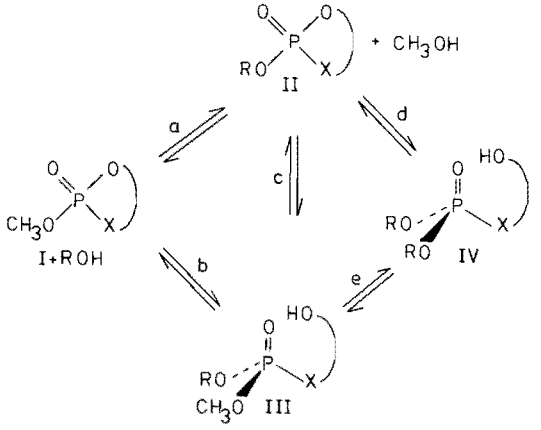


Fig. V.18

possible if X=C. Reaction b is a ring opening reaction whereas c is reclosure of the ring with methanol cleavage. It is important to notice that a second reaction with ROH yields a ring-opened product, IV, with two OR groups. This compound is formed readily from II, whereas the nucleophilic displacement (e) from the acyclic compound III is very slow compared to the other reactions[5]. Based on these considerations it can be concluded that the formation of methanol must be the result of reaction a or c.

For compound 3, a phosphonate, exocyclic solvolysis *via* pseudorotation (a) can be precluded. Therefore, the formation of methanol can only be the result of ring closure. Evidently, in methanol and unbuffered D_2O the ring closure is very fast, since no ring-opened product is observed under these conditions. Probably, the double bond in combination with the two methyl groups force the OH group to remain close to phosphorus, which results in a strained ring-opened product. During the hydrolysis with aqueous buffer, the ring-opened product will be partially ionized (Fig. V.19) which hampers ring closure. Without buffer, the pH of the solution is rapidly lowered by the acidic products. Therefore, the ionization equilibrium of

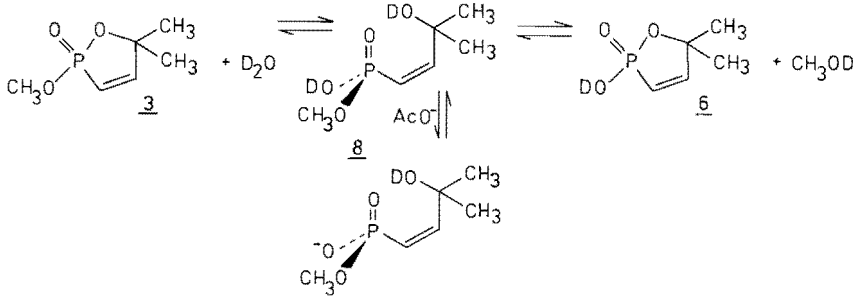


Fig. V.19

8 is shifted to the neutral form which permits ring closure.

According to the scheme of *Westheimer*[5] (*cf.* Chapter I, Fig. I.9), compounds 4 and 5 may undergo exocyclic solvolysis *via* pseudorotation without invoking ring closure. However, in the hydrolysis of methyl ethylene phosphate[5] more than 50% ring opening is observed at every pH, indicating that pseudorotation is somewhat slower than ring opening. By analogy, the solvolysis of 4 is expected to yield at least 50% of the ring-opened products, 9 or 12, if no ring closure occurs. The much smaller amount of the latter products which is actually observed is a strong indication that reclosure of these products takes place, as shown in Fig. V.20 for

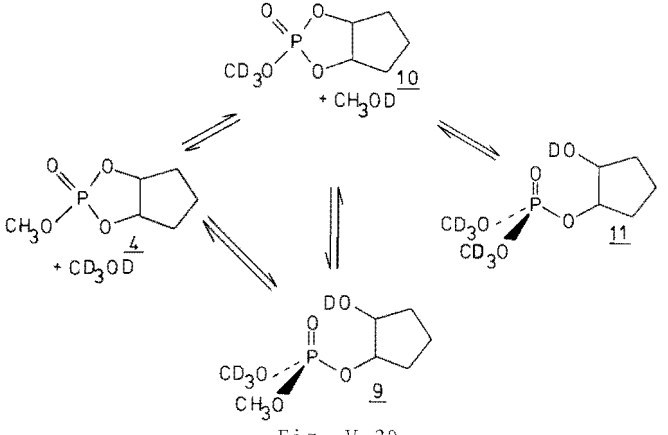


Fig. V.20

the methanolysis reaction. According to the ^1H NMR data the compounds 4 and 9-11 reach an equilibrium in which ring-opened and cyclic products are present in almost equal amounts.

Just as with 3, the hydrolysis of 4 and 5 is slightly more complicated than the methanolysis by the possibility of ionization. In this case, the ring-opened product 12 does not react further after deprotonation (Fig. V.21), but the addi-

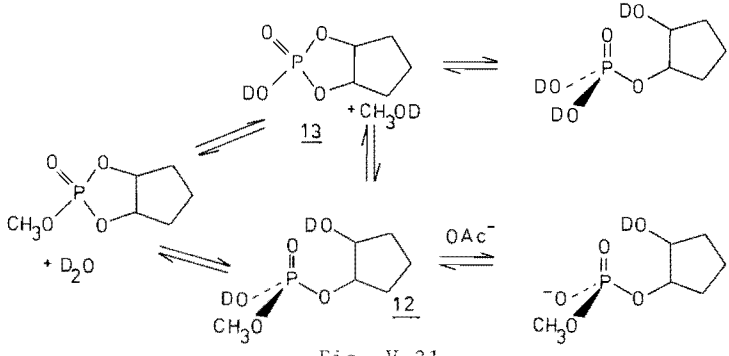


Fig. V.21

tion of acid results in methanol formation, probably *via* ring closure to 13.

V.5 *Experimental*

► *Preparations*

The preparations are described for the compounds containing a cyclopentane ring (1, 4, and their precursors). The synthesis of cyclohexane derivatives is completely analogous.

► *cis-1,2-cyclopentanediol*

Path A[11]: A solution of 40 g $KMnO_4$ (0.25 mol) and 30 g $MgSO_4$ in 800 ml of water was added in 1.5 h to a stirred suspension of 22 g cyclopentene (0.32 mol) in 600 ml ethanol at -15 °C. After filtration, the solution was concentrated, saturated with salt and extracted continuously with chloroform. Evaporation of the chloroform solution yielded 20% of

product (Yield for 1,2-cyclohexanediol: 33%)

Path B[12]: 17 g of cyclopentene (0.25 mol) was dissolved in 100 ml of glacial acetic acid. To this solution, 31.0 g I_2 (0.125 mol) and 13.4 g KIO_3 (0.063 mol) were added carefully, with cooling if necessary. The mixture was stirred for 6 h at room temperature. After standing overnight, 24.6 g of dry potassium acetate (0.25 mol) was added, and the solution was refluxed for 3 h. The 1,2-cyclopentylene diacetate was extracted from the acetic acid with *n*-hexane (continuous extraction). The extract was neutralized with saturated $NaHCO_3$; the iodine was removed with saturated $Na_2S_2O_3$. After evaporation of the solvent, the residue was hydrolysed by refluxing in benzene with a 10% methanolic KOH solution for 1 h. The product was distilled.

^{1}H NMR ($CDCl_3$): δ 1.70 (m, 6 H, CH_2); δ 3.93 (m, 2 H, OCH); δ 4.33 (s, 2 H, OH).

1,2-cyclopentylenebis(p-chlorobenzenesulfenate)

6.5 g of *cis*-1,2-cyclopentanediol (0.064 mol) was dissolved in 400 ml of dry ether containing 18 ml of triethylamine (0.13 mol). The solution was stirred vigorously with cooling in ice/salt, in a dry nitrogen atmosphere. *p*-Chlorobenzenesulfenylchloride (22.9.g) was added dropwise. The salt was removed by filtration, the ethereal solution was dried on $MgSO_4$ and evaporated. A yellowish solid remained which was treated with 100 ml of methanol. The solid was isolated by filtration, dissolved in chloroform and precipitated again by adding pentane. Yield 28% of the theory.

^{1}H NMR ($CDCl_3$): δ 1.8 (m, 6 H, CH_2); δ 3.97 (m, 2 H, OCH); δ 7.13 (s, 8 H, aromatic protons).

Data for the cyclohexane analogue: Yield 49% after crystallization from CCl_4, mp 83-4 °C. Anal. Calcd. for $C_{18}H_{16}O_2S_2Cl_2$: C, 53.87; H, 4.49. Found: C, 53.81; H, 4.45.

► *3,3,3-trimethoxy-2,4-dioxa-3-phosphabicyclo[3.3.0]octane (1)*

To a solution of trimethyl phosphite (0.04 mol) in 25 ml of dry CH_2Cl_2, cooled to -78 °C, was added 1.5 g of 1,2-cyclopentylenebis(*p*-chlorobenzenesulfenate) (0.039 mol) dissolved in a small amount of CH_2Cl_2. The solution was stirred for 4 h, under nitrogen. The precipitate was removed by filtration under N_2 in the cold. The solvent was removed and the phosphorane was purified by distillation, bp 53-4 °C/0.03 mm Hg. Yield 6.2 g (72% of theory). Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.59. Found: C, 43.12; H, 7.51.

^{1}H NMR ($CDCl_3$): δ 1.7 (m, 6 H, CH_2); δ 3.50 (d,122.5 Hz, 9 H, OCH_3); δ 4.30 (dm, 12 Hz, 2 H, OCH).

^{31}P NMR ($CDCl_3$): -45.3 ppm.

► *8,8,8-trimethoxy-7,9-dioxa-8-phosphabicyclo[4.3.0]nonane (2)*

The preparation was analogous to that of 1. Bp 56 °C/0.01 mm Hg, yield 71%. Anal. Calcd. for $C_9H_{19}O_5P$: C, 45.38; H, 7.98. Found: C, 45.60; H, 7.80.

^{1}H NMR ($CDCl_3$): δ 1.6 (m, 8 H, CH_2); δ 3.57 (d, 12.5 Hz, 9 H, OCH_3); δ 4.27 (dm, 13 Hz, 2 H, OCH).

^{31}P NMR ($CDCl_3$): -50.6 ppm.

► *2-methoxy-2-oxo-5,5-dimethyl-1,2-oxaphosphol-3-ene (3)*

The 2-hydroxy derivative (cyclic phosphonic acid, 6) was obtained *via* the procedure of *Macomber and Kennedy*[15]. The acid can be recrystallized from hot water (^{31}P NMR: δ= +43.0 ppm). It was converted to the 2-chloro derivative, 7, as follows: To 1 g of the acid, 10 ml of distilled $SOCl_2$ was added at 0 °C under nitrogen. The resulting clear solution was stirred and refluxed for 1 h. Subsequently, the excess of $SOCl_2$ was removed at low pressure. A small amount of dry chloroform was added to the residue and the solution was filtered. The product was precipitated by slowly adding dry ether. Yield 67%, mp 133-6 °C.

^{1}H NMR ($CDCl_3$): δ 1.47 (s, 6 H, CH_3); δ 6.23 (dd, 41 and 8 Hz,

1 H, PCH); δ 6.95 (dd, 59 and 8 Hz, 1 H, PC=CH).

The 2-chloro-oxaphospholene was dissolved in methanol. The methanol solution was refluxed under nitrogen for 0.5 h after which the excess of methanol was removed at low pressure. The residue was crystallized from dry ether. Yield 64%, mp 52.5-53.5 °C. Anal. Calcd. for $C_6H_{11}O_3P$: C, 44.45; H, 6.84. Found: C, 44.66; H, 6.94.

^{1}H NMR ($CDCl_3$): δ 1.44 (s, 3 H, CH_3); δ 1.50 (s, 3 H, CH_3); δ 3.66 (d, 11 Hz, 3 H, CH_3O); δ 5.94 (dd, 31 and 8 Hz, 1 H, PCH); δ 7.01 (dd, 47 and 8 Hz, 1 H, PC=CH).

^{31}P NMR ($CDCl_3$): +40.8 ppm.

► *3-methoxy-3-oxo-2,4-dioxa-3-phosphabicyclo[3.3.0]octane (4)*

To a solution of 1.6 g 1 (7.1 mmol) in 10 ml of dry CH_3CN was added 0.9 g of acetyl bromide. The temperature rose to about 60 °C. The mixture was stirred for 1 h in a nitrogen atmosphere. Evaporation of the reaction mixture yielded 1.3 g of the mixture of diastereomers (100%).

^{1}H NMR ($CDCl_3$): δ 1.87 (m, 6 H, CH_2); δ 3.77 (d, 12 Hz, 3 H, OCH_3, 65%); δ 3.78 (d, 12 Hz, 3 H, OCH_3, 35%); δ 5.10 (dm, 9 Hz, 2 H, OCH).

^{31}P NMR ($CDCl_3$): +18.8 ppm (major isomer)
+19.5 ppm (minor isomer).

► *Spectroscopic study of the reaction of 1 and 2 with FSO_3H*

NMR samples in Freon 21 (bp +9 °C) were prepared by condensing the solvent from a gas cylinder in the NMR tube containing the oxyphosphorane, cooled in an ice/salt bath. The concentration of the samples was about 0.8 mol/l. After immersing the NMR tube in melting pentane (-120 °C) a drop of FSO_3H was added carefully *via* the wall of the tube. The contents were mixed by shaking the sample vigorously. The ^{1}H NMR spectrum was recorded in the temperature range from -120 to -10 °C. At relatively high temperatures, the irreversible

formation of a phosphate was observed.

^{1}H NMR (1+1', -85 °C): δ 1.8 (m); δ 3.6 (d, 13 Hz, OCH_3, phosphorane); δ 4.2 (d, 11 Hz, OCH_3, phosphonium ion); δ 4.5 (dm, OCH).

^{31}P NMR(1+1', -51 °C): δ -41.6 (1); δ +4.1 (1').

^{1}H NMR (2+2', -87 °C): δ 1.6 (m); δ 3.6 (d, 13 Hz, OCH_3, phosphorane); δ 4.2 (d, 11 Hz, OCH_3, phosphonium ion).

Coalescence temperature (T_c) of methoxy doublets: 1, -55 °C
2, -15 °C.

The line width Δ of the methoxy doublets, below T_c, was measured at half height. The line broadening Δν was derived from a plot of lnΔ *vs.* $1/T$[13]. From the plot of lnΔν *vs.* 1/T, the E_A and k (at 248 K) were determined[13,14].

► *Solvolysis reactions of 6-5*

The solvolysis reactions were carried out in NMR sample tubes using a comcentration of 1 mol/l, at a temperature of 35 °C. The reactions were monitored by ^{1}H NMR. The methanol peak appeared at 3.27-3.36 ppm. In case of CD_3OD, the integral of the methanol peak was corrected for the small amount of CHD_2OD (quintet) which is always observed in this solvent.

^{1}H NMR data for the observed products:

3 in CD_3OD: The methoxy doublet of 3 decreases, while concurrently the methanol peak (3.31 ppm) appears.

3 in D_2O/acetate: 3, 1.48 s; 3.64 d, 12 Hz
8, 1.35 s; 3.49 d, 11 Hz
CH_3OD, 3.27 s
| Complex pattern of olefinic protons, 5.2-7.8 ppm.

4 in CD_3OD: 4, 3.81 d, 12 Hz; 3.82 d, 12 Hz
10, 3.73 d, 11 Hz
CH_3OD, 3.36 s

4 in D_2O/acetate: 4, 3.86 d, 12 Hz; 3.87 d, 12 Hz
12, 3.67 d, 11 Hz
CH_3OD, 3.42 s.

References and Notes

1. R.T. Morrison and R.N. Boyd, "Organic Chemistry", Chapter 28, Allyn and Bacon, Boston, 1973.
2. R.D. Gandour, "Transition States of Biochemical Processes", Chapter 14, R.D. Gandour and R.L. Schowen, eds., Plenum Press, New York, 1978, p. 539, and references cited.
3. S.J. Benkovic and K.J. Schray, "Transition States of Biochemical Processes", Chapter 13, R.D. Gandour and R.L. Schowen, eds., Plenum Press, New York, 1978.
4. A.M.C.F. Castelijns, Thesis Eindhoven, 1979.
5. R. Kluger, F. Covitz, E. Dennis, L.D. Williams, and F.H. Westheimer, J. Am. Chem. Soc., 1969, *91*, 6066.
6. W.G. Voncken, Thesis Eindhoven, 1976.
7. S. Singh, M. Swindles, S. Trippett, and R.E.L. Wadding, J. Chem. Soc., Perkin I, 1978, 1438.
8. L.L. Chang and D.B. Denney, J. Org. Chem., 1977, *42*, 782.
9. L.L. Chang, D.B. Denney, D.Z. Denney, and R.J. Kazior, J. Am. Chem. Soc., 1977, *99*, 2293.
10. D.B. Denney, D.Z. Denney, P.J. Hammond, C. Huang, and K.-S. Tseng, J. Am. Chem. Soc., 1980, *102*, 5073.
11. M.F. Clarke and L.N. Owen, J. Chem. Soc., 1949, 315.
12. L. Mangoni, M. Adinolfi, G. Barone, and M. Parrilli, Gazz. Chim. Ital., 1975, 105.
13. R.S. Drago, "Physical Methods in Chemistry", W.B. Saunders, London, 1977, p. 252.
14. T.H. Lowry and K. Schueller Richardson, "Mechanism and Theory in Organic Chemistry", Harper and Row, New York, 1976, p. 100.
15. R.S. Macomber and E.R. Kennedy, J. Org. Chem., 1976, *41*, 3191.
16. R.S. Macomber, J.Am. Chem. Soc., 1977, *99*, 3072.
17. G.M. Kosolapoff and L. Maier, "Organic Phosphorus Compounds", Vol. 6, Wiley, New York, 1973.
18. F. Ramirez, J.F. Marecek, and I. Ugi, J. Am. Chem. Soc., 1975, *97*, 3809.

Summary

This thesis describes investigations concerning the role of five-coordinated phosphorus compounds (phosphoranes) as intermediates in phosphorylation and group transfer reactions. In phosphatranes, which have the general formula $XP(OCH_2CH_2)_3N$, an intramolecular phosphorylation can be accomplished by the formation of a P←N bond, yielding a tricyclic phosphorane. Semiempirical MO calculations predict that phosphorylation in these compounds is induced by protonation of the exocyclic phosphorus ligand X (X=O or S). This is confirmed by NMR studies of the phosphatranes in strong acid solution. These observations provide a rationalization of acid catalysis in phosphorylation reactions and stress the role of protons in, *e.g.*, oxidative phosphorylation.

Stable phosphatranes containing a five-coordinated phosphorus atom can be obtained by alkylation of the bicyclic phosphatranes $XP(OCH_2CH_2)_3N$ (X=O or S) at the exocyclic phosphorus ligand. The trigonal bipyramidal (TBP) configuration around the phosphorus atom in the tricyclic phosphatranes is demonstrated by an X-ray structure determination. This configuration is also inferred from the NMR data in solution.

The apical and basal ligands in tricyclic phosphatranes cannot be interconverted by pseudorotations, since the cage structure precludes these isomerisations. As a consequence of this property, the reactivity of apical and basal ligands of a TBP can be compared. Evidence is offered that nucleophilic attack preferentially occurs on the carbon atoms bound to basal oxygen atoms, *i.e.*, group transfer *via* five-coordinated phosphorus intermediates occurs selectively at the pseudo-

basal sites of the TBP configuration.

The tricyclic phosphatranes demonstrate that a phosphorane intermediate is readily formed by intramolecular phosphorylation when a nucleophile is oriented in a suitable position. Other model compounds, which resemble the cyclic intermediate postulated in the RNase catalysed hydrolysis of ribonucleic acids, support this view. Five-membered cyclic phosphoranes are found to be in rapid equilibrium with phosphonium ions in strong acid solution, provided the ring of the phosphorane contains an element of rigidity, *e.g.*, a double bond or a fused ring. The activation parameters of this process demonstrate that the $T\Delta S^{\ddagger}$ term of the free enthalpy of activation is dominant. In addition, five-membered cyclic phosphates with a second ring fused to the 1,3,2-dioxaphospholane ring undergo solvolysis predominantly with exocyclic ester cleavage, whereas a pseudorotation mechanism predicts more ring opening. Furthermore, a cyclic phosphonate containing a double bond in the ring also undergoes exocyclic solvolysis, which cannot be explained by pseudorotation. These results strongly indicate that orientation is more important than pseudorotation in determining the mechanism of solvolysis of these compounds.

Samenvatting

In dit proefschrift wordt een onderzoek beschreven naar de rol van vijfgecoördineerde fosforverbindingen (fosforanen) als intermediairen bij fosforylerings- en groepsoverdrachtsreakties. In fosfatranen, waarvan de algemene formule $XP(OCH_2CH_2)_3N$ is, kan intramolekulaire fosforylering plaatsvinden door vorming van een P←N-binding, waardoor een tricyclisch fosforaan ontstaat. Semi-empirische MO-berekeningen voorspellen dat fosforylering in deze verbindingen plaatsvindt wanneer het exocyclische fosforligand X (X=O of S) geprotoneerd wordt. Dit wordt bevestigd door NMR-metingen aan fosfatranen opgelost in sterk zuur. Zuurkatalyse bij fosforyleringsreakties kan met behulp van deze resultaten verklaard worden, terwijl tevens de belangrijke rol van protonen bij b.v. oxidatieve fosforylering duidelijker wordt.

Stabiele fosfatranen met een vijfgecoördineerd fosforatoom kunnen verkregen worden door alkylering van bicyclische fosfatranen (X=O of S) op het exocyclische fosforligand. Met behulp van een Röntgenanalyse is aangetoond dat het fosforatoom in de tricyclische fosfatranen een trigonaal bipiramidale (TBP) omringing heeft. De NMR-gegevens zijn hiermee in overeenstemming.

De apikale en basale liganden in tricyclische fosfatranen kunnen niet verwisseld worden door pseudorotaties, aangezien de kooistruktuur deze isomerisaties onmogelijk maakt. Dankzij deze eigenschap kan de reaktiviteit van de apikale en basale liganden van een TBP vergeleken worden. Het blijkt dat nucleofiele aanval bij voorkeur plaatsvindt op de koolstofatomen die gebonden zijn aan de basale zuurstofatomen, d.w.z. dat groeps-

overdracht *via* intermediairen met vijfgecoördineerde fosfor selektief plaatsvindt vanuit de pseudo-basale posities van de TBP-configuratie.

Uit de experimenten met fosfatranen blijkt dat een fosforaan-intermediair gemakkelijk gevormd wordt door intramolekulaire fosforylering, wanneer een nucleofiel aanwezig is met een goede orientatie. Andere modelverbindingen, die overeenkomst vetonen met het cyclische intermediair dat verondersteld wordt bij de hydrolyse van ribonucleinezuren o.i.v. RNase A, steunen deze opvatting. Fosforanen met het fosforatoom in een vijfring blijken in snel evenwicht te zijn met fosfoniumionen in een oplossing met sterk zuur, mits de ring van het fosforaan enigszins star is, bijvoorbeeld door een dubbele binding of een tweede ring. De aktiveringsparameters voor dit proces tonen aan, dat de $T\Delta S^{\ddagger}$-bijdrage aan de vrije enthalpie van aktivering domineert. Ook blijkt,dat bij de overeenkomstige cyclische fosfaten in solvolysereakties voornamelijk de exocyclische esterbinding verbroken wordt, terwijl bij een pseudorotatiemechanisme meer ringopening verwacht wordt. Bovendien vindt bij een cyclisch fosfonaat met een dubbele binding in de ring ook exocyclische solvolyse plaats, wat niet verklaard kan worden met pseudorotatie. Deze resultaten wijzen erop dat de exocyclische solvolyse van deze verbindingen eerder toe te schrijven is aan oriëntatie-effekten dan aan pseudorotatie.

Curriculum vitae

De schrijver van dit proefschrift werd geboren op 29 augustus 1953 te Terneuzen. Na het behalen van het diploma gymnasium ß aan de Rijksscholengemeenschap "Petrus Hondius" te Terneuzen in 1971, werd in hetzelfde jaar begonnen met de studie op de afdeling der Scheikundige Technologie aan de Technische Hogeschool te Eindhoven. Het afstudeerwerk werd verricht bij de vakgroep Organische Chemie o.l.v. prof. dr. H.M. Buck en dr. ir. A.M.C.F. Castelijns. In december 1976 werd het ingenieursexamen met lof afgelegd.

Vanaf 1 januari 1977 tot 1 januari 1981 was hij als wetenschappelijk ambtenaar in dienst van de Nederlandse Stichting voor Zuiver Wetenschappelijk Onderzoek. In deze periode werd het onderzoek, beschreven in dit proefschrift, uitgevoerd onder leiding van prof. dr. H.M. Buck.

Dankwoord

Gedurende het onderzoek dat geleid heeft tot dit proefschrift heb ik van velen steun ondervonden op synthetisch en spectroscopisch gebied, alsmede de interpretatie van resultaten, zowel binnen als buiten de vakgroep Organische Chemie. Voor deze hulp wil ik een ieder van harte bedanken.

Verder wil ik mijn dank uitspreken tegenover diegenen die een bijdrage hebben geleverd aan de uiteindelijke vormgeving van dit proefschrift.

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Stellingen

1. Het introduceren van twee mechanismen, met tegengestelde stereochemische konsekwenties, voor de oxidatie van acyclische fosfieten, respectievelijk fosfieten met het fosforatoom in een zesring, wordt onvoldoende gerechtvaardigd door het verschil in reaktiviteit tussen acyclische en cyclische fosforverbindingen.

   M. Mikołajczyk en J. Łuczak, J. Org. Chem., 1978, *43*, 2132.

2. De toekenning van radikaalstrukturen op basis van gesuperponeerde anisotrope ESR-spektra is minder eenduidig dan door *Mishra en Symons* gesuggereerd wordt.

   S P. Mishra en M.C.R. Symons, J. Chem. Soc., Dalton, 1976, 139.

3. Het feit, dat *Pilar* fosforescentie noemt als voorbeeld van stralingsloze overgangen, maakt zijn boek niet tot een lichtend voorbeeld op dit gebied.

   F.L. Pilar, "Elementary Quantum Chemistry", McGraw-Hill, New York, 1968, p. 447.

4. Ten onrechte wordt aan fosforanylradikalen vaak een tetraedrische struktuur toegekend met het ongepaarde elektron in een σ^*-orbital van een P-X-binding, terwijl de mogelijkheid van een trigonaal bipiramidale struktuur met het elektron in een apikale positie buiten beschouwing gelaten wordt.

   T. Berclaz, M. Geoffroy en E.A. Lucken, Chem. Phys. Lett., 1975, *36*, 667.
   T. Gillbro en F. Williams, J. Am. Chem. Soc., 1974, *96*, 5032.

M.C.R. Symons, Chem. Phys. Lett., 1976, *40*, 226.
J.W. Cooper, M.J. Parrott en B.P. Roberts,
J. Chem. Soc., Perkin II, 1977, 730.

5. Aangezien de konfiguratie van het stikstofatoom in 1,4-dihydropyridines nagenoeg vlak is, is het weinig realistisch de selektiviteit van de hydride-overdracht van NADH te verklaren aan de hand van "model"systemen zoals tricyclische orthoamines, waarin de stikstofatomen piramidaal zijn.

J.M. Erhardt, E.R. Grover en J.D. Wuest,
J. Am. Chem. Soc., 1980, *102*, 6365.

6. De mededeling van *Houalla et al.*, dat de vorming van drie hydrolyseprodukten van een tricyclisch fosfiet "logique" is, wekt ten onrechte een gevoel van domheid bij de lezer, aangezien het voorgestelde intermediair beslist niet de verhouding verklaart waarin deze produkten gevormd worden.

D. Houalla, M. Sanchez, R. Wolf en F.H. Osman,
Tetrahedron Lett., 1978, 4675.

7. Indien men in het ESR-spektrum van fosforanylradikalen hyperfijninterakties waarneemt ten gevolge van vier liganden, is er veel verbeeldingskracht nodig om de aanwezigheid van een vijfde ligand zonder hyperfijninteraktie te veronderstellen.

S.P. Mishra en M.C.R. Symons, J. Chem. Soc.,
Chem. Commun., 1974, 279.
A. Hasegawa, K. Ohnishi, K. Sogabe en M. Miura,
Mol. Phys., 1975, *30*, 1367.

8. Bij de Perkow-reaktie en de Wittig-reaktie wordt een intermediair verondersteld met vijfgecoördineerde fosfor. Helaas wordt soms weinig aandacht besteed aan het feit dat de eigenschappen van fosforanen ook voor deze intermediairen gelden.

T.-L. Ho, "Hard and Soft Acids and Bases Principle in Organic Chemistry", Academic Press, New York, 1977, p. 105.
E. Breuer, S. Zbaida en E. Segall, Tetrahedron Lett., 1979, 2203.

9. Aangezien recentelijk aangetoond is dat DNA zowel links- als rechtsdraaiende schroefstrukturen kan vormen, kan beter gesproken worden van een "touwladder"-model dan van een "wenteltrap"-model.
A.H.-J. Wang, G.J. Quigley, F.J. Kolpak, J.L. Crowford, J.H. van Boom, G. van der Marel en A. Rich, Nature, 1979, *282*, 680.
R. Wing, H. Drew, T. Takano, C. Broka, S. Tanaka, K. Itakura en R.E. Dickerson, Nature, 1980, *287*, 755.

10. Het feit, dat bij het in dit proefschrift beschreven onderzoek Freon is gebruikt, betekent niet dat de schrijver het gebruik van aerosols toejuicht.

11. De opdracht "knop met de klok mee draaien" in de gebruiksaanwijzing van een digitaal horloge wijst op een gering vertrouwen bij de fabrikant in de verkoop van zijn produkt.

12. Bergbeklimmen is tot op zekere hoogte een veilige sport.

D. van Aken Eindhoven, 6 januari 1981.