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Selected chemistry of cyclophosphazenes and cyclothiaphosphazenes

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CONTENTS

A. INTRODUCTION

The historical development of the cyclophosphazenes and thiazenes has been clearly reflected in Haiduc's comprehensive two-volume *Chemistry of Inorganic Ring Systems* published in 1970 [1]. Whereas $(NPCl_2)_n$ compounds were the earliest compounds to be mentioned, followed by the sulphur analogue $(NSOCl)_3$, the cyclothiaphosphazenes were the latest, only represented by *cis*-$NPCl_2(NSOCl)_2$ [2,3]. Since that time, the study of that mixed system and others has progressed, initiated not only by their interesting chemical properties but also by their possible applications to serve as carriers for (re)active side groups.

Both the cyclophosphazenes $(NP^{V}R^{1}R^{2})_n$ and cyclothiaphosphazenes with general formula $(NP^{V}R^{1}R^{2})_n(NS^{VI}OR^{3})_m$ (R = any inorganic or organic ligand) are cyclic compounds in which nitrogen and phosphorus or sulphur possess alternating

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positions in the ring skeleton. The coordination number at nitrogen is three (including the free electron pair), whereas phosphorus and sulphur are four-coordinated. In combination with the oxidation states of phosphorus(V) and sulphur(VI), this leads to compounds in which the number of π electrons equals the number of atomic centres in the ring, the so-called π-electron precise compounds. Six-membered ring systems with composition $(NPCl_2)_n(NSOCl)_m$ $(n+m=3)$ are given in Fig. 1. Both $NPCl_2(NSOCl)_2$ and $(NSOCl)_3$ appear in two isomeric (*cis*, *trans*) forms.

The structures of these six-membered systems can be described as nearly flat rings with only minor deviations to a chair or boat form [3–6]. The angle between a PCl_2 or SOCl plane and the mean ring plane is about 90°. The local symmetry around phosphorus resembles that of a distorted tetrahedron. For the SOCl centre, the chlorine ligand is in an axial position with respect to the mean ring plane, forcing the oxygen ligand into an equatorial position.

The preparation of two isomers of $NPCl_2(NSOCl)_2$ has been described, a *cis* (oxygen atoms on the same side of the ring plane) [2] and a *trans* form (oxygen atoms on both sides) [7]; $(NPCl_2)_2NSOCl$ could also be obtained from the same reaction mixture [8]. For compounds consisting only of $NPCl_2$ units, higher homologues with $n \geq 4$ were isolated and characterized [9]. For the mixed systems only $(NPCl_2)_3NSOCl$ has been reported [10].

The N–P and N–S bond lengths in the compounds $(NPCl_2)_n(NSOCl)_m$ are significantly shorter than the corresponding "single" bond distance of 1.77 Å [11] and 1.76 Å [12], respectively. Much attention has been paid to the chemical bonding in these benzenoid structures [13]. Recent theoretical calculations for compounds $(NPX_2)_3$ strongly suggest that the phosphorus 3d orbitals contribute considerably to the endocyclic π-bonding [14,15].

This review is concerned mostly with the six-membered rings; only minor attention will be paid to the higher homologues. The purpose of this survey is to describe some chemical and physico-chemical properties of these compounds in combination with their possible application as carrier for (re)active side-groups and as precursors for the preparation of polymeric systems. Relevant literature coverage starts from 1981 up to and including 1990 with a few 1991 references. Literature prior to 1981 with respect to the cyclothiaphosphazenes has been reviewed previously [16].

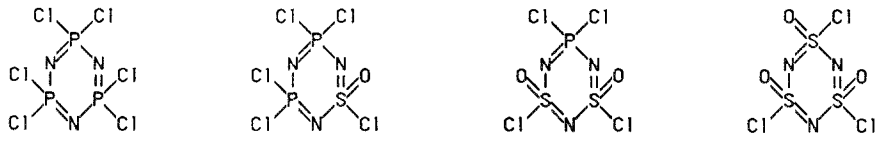


Fig. 1. Cyclic compounds $(NPCl_2)_n(NSOCl)_m$ with $n+m=3$.

B. REACTIVITY

(i) Nucleophilic substitution by dimethylamine

Chlorine replacement reactions in $(NPCl_2)_3$ by amines occupy a special place among the nucleophilic substitution reactions at the four-coordinated phosphorus atom and have been reviewed by many authors. For general reviews on (thia)phosphazenes from 1979 to the present, see ref. 17. Two main pathways can be discerned, a geminal and a non-geminal one, depending on amine, solvent and stage of substitution. Only in the last decades have systematic studies been carried out to elucidate the kinetic parameters governing these reactions. With respect to the dimethylaminolysis of $(NPCl_2)_3$ in tetrahydrofuran or acetonitrile, the first, second and third step of the mainly non-geminal substitution pattern obey a second-order rate law. In both solvents, the free energy of activation is controlled by the entropy of activation [18,19]. Mechanisms involving five-coordinated phosphorus have been suggested to follow the trends in kinetic data in going from mono- to trisubstituted products [18–20]. The stereoselective formation of *trans* isomers ("*trans*-preference") in the disubstitution stage of $(NPCl_2)_3$ has been explained by the larger value (less negative) of $\Delta S^{\ddagger}_{trans}$ compared with $\Delta S^{\ddagger}_{cis}$ caused by the substituent solvating effect (s.s.e.) of the amino group already present [21]. If the fourth chlorine atom is replaced by a dimethylamino group, an S_N1-type mechanism is observed in acetonitrile [19,20].

The dimethylaminolysis of $(NPCl_2)_2NSOCl$ in acetonitrile proceeds along a non-geminal pathway, obeying the reactivity sequence $PCl_2 > SOCl > PClNMe_2$. The nucleophilic attack at the phosphorus centres preferably takes place at the oxygen side of the ring, which leads to *cis*-$NPCl_2NPClNMe_2NSOCl$ and 1α,3α,5α-$(NPClNMe)_2NSOCl$ (for nomenclature see ref. 22) as major reaction products in the first and the second substitution step, respectively [23]. The preference for a reaction at the oxygen side has been explained by the equatorial position of the oxygen ligand with respect to the ring plane [5]. This "steric directive effect" (s.d.e.) obviously overrules the "*trans*-preference" mentioned for $(NPCl_2)_3$. In the third substitution step (at sulphur) nucleophilic attack again occurs at the oxygen side with 1α,3α,5α-$(NPClNMe_2)_2NSONMe_2$ as the main reaction product. Both the substitution at phosphorus and sulphur takes place with inversion of configuration, pointing to an S_N2-type mechanism [23]. A part of the substitution pattern is shown in Fig. 2.

For *cis*-$NPCl_2(NSOCl)_2$, the molecular geometry affects the substitution pathway even more than in the preceding case. Not only are two equatorial oxygen atoms present, but the axial position of the sulphur-bonded chlorine atoms causes short intramolecular distances between the chlorine atoms *trans* to oxygen [3]. This molecular framework hampers the formation of an S_N2 transition state at phosphorus.

The dimethylaminolysis has been reported to proceed in a non-geminal mode. In acetonitrile, the sequence of substitution is (S^1)–Cl, (P)–Cl, (S^2)–Cl, (P)–Cl. In diethyl ether, a "normal" pattern is observed, (P)–Cl, (S^1)–Cl (Fig. 3). Reactions in

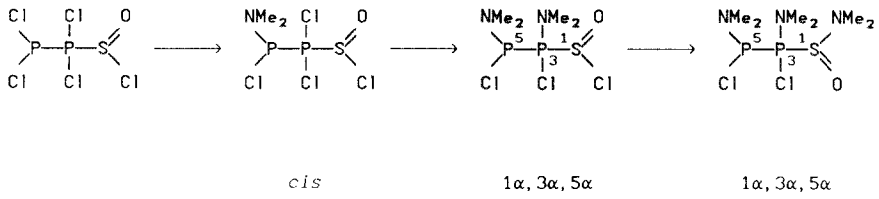


Fig. 2. Major compounds formed in the first, second and third substitution step of the dimethylaminolysis of $(NPCl_2)_2NSOCl$. The ring systems are given in side-view representation. Nitrogen atoms are omitted for the sake of clarity.

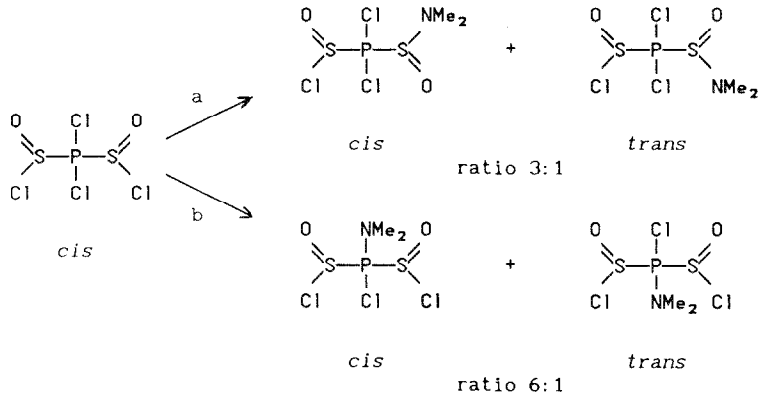


Fig. 3. Mode of monosubstitution of *cis*-$NPCl_2(NSOCl)_2$ by dimethylamine in (a) acetonitrile and (b) diethyl ether.

ether are extremely slow beyond disubstitution. The deviating behaviour in the more polar solvent acetonitrile has been explained to arise from an S_N1-type substitution at sulphur. Obviously, this type of substitution can compete successfully with the sterically hindered S_N2-type attack at phosphorus [22,24]. As these steric effects are absent in compounds $NPCl_2NSOClNSONMe_2$ [25], the subsequent substitution steps follow the usual path. Shielding effects (^1H NMR) have been used to assign structures to the derivatives isolated [24].

Isomerization phenomena at SOCl centres involving chlorine abstraction and induced by dimethylamine hydrochloride or antimony(V)chloride are reported [22].

(ii) Nucleophilic substitution by aziridine

The predominantly non-geminal substitution patterns described in the preceding section can be generalized for all secondary amines with one exception. Aziridine, a cyclic amine with composition $(CH_2)_2NH$, shows a remarkable competition between geminal and non-geminal substitution in reactions with $(NPCl_2)_3$ and $(NPCl_2)_4$ [26,27]. Table 1 (taken partly from ref. 27) compares the ratios of geminal and non-

TABLE 1

Isomer ratios (%) of selected substitution reactions of $(NPCl_2)_3$ with aziridine and dimethylamine[a]

Starting compound	Product	Isomer ratio[b]			Statistical isomer ratio		
		trans	*gem*	*cis*	*trans*	*gem*	*cis*
$N_3P_3Cl_5Az$	bis	20	65	15	40	20	40
$N_3P_3Cl_5NMe_2$	bis	65	≤5	30			
trans-$N_3P_3Cl_4Az_2$	tris	10	90		50	50	
trans-$N_3P_3Cl_4(NMe_2)_2$	tris	55	45				
cis-$N_3P_3Cl_4Az_2$	tris	40	55	≤5	25	50	25
cis-$N_3P_3Cl_4(NMe_2)_2$	tris	80	15	≤5			

[a]Data from ref. 28.
[b]Reactions in Et_2O.

geminal products formed in the second and third substitution step of $(NPCl_2)_3$ with aziridine and dimethylamine.

A similar comparison for $(NPCl_2)_4$ is not possible as data on the dimethylaminolysis of this compound are limited. Millington and Sowerby [29] did report that the dimethylaminolysis of $(NPCl_2)_4$ gives smaller amounts of geminal derivatives than the aziridinolysis. The preferential 2,6-substitution of the tetramer observed for dimethylamine appears to be less pronounced when aziridine is used as nucleophile [27].

Aziridinolysis of compounds $(NPCl_2)_n(NPClAm)_{3-n}$ ($n = 1, 2$; Am = pyrrolidino, piperidino or morpholino) leads to the observation that chlorine substitution takes place at PCl_2 rather than at PClAm centres. The reactivity of the PClAm centres follows the sequence PClAr > PClPip > PClMorph, which is in line with the electron-donating capacity of the amino ligands concerned [30].

(iii) Hydrolysis

As will be pointed out in Sects. C and D, oligomeric and polymeric phosphazene systems can be used as carriers for reactive ligands. For both types of compound, knowledge of their hydrolytic behaviour is of extreme importance. Several authors have reported the hydrolysis of fully substituted compounds $(NPR_2)_3$ (R = amino, alkoxy, or aryloxy) [31]. With respect to the hydrolysis of chlorocyclophosphazenes, only a limited number of papers have appeared prior to 1980 [9,32]. In general, $(NPCl_2)_3$ is relatively stable to water due to its insolubility in this medium. The replacement of a $NPCl_2$ unit by the more electronegative NSOCl enhances the electrophility of the remaining phosphorus centres, making the mixed systems

$(NPCl_2)_m(NSOCl)_n$ more sensitive towards hydrolysis. In polar organic solvents which are not completely dry, hydrolysis takes place rapidly.

In order to gain some insight into the reaction pathways, controlled hydrolysis experiments have been carried out. Reaction of $(NPCl_2)_3$ with one equivalent of water in acetonitrile in the presence of As_4PhCl or $KCl{-}C_{12}H_{24}O_6$ (18-crown-6) afforded salts with composition $[(NPCl_2)_2NPClO]^-A^+$ ($A^+ = AsPh_4^+$ or $KC_{12}H_{24}O_6^+$) [33]. Analogous derivatives with composition $[NPClONPCl_2$-$NSOX]^-A^+$ or $[NPClO(NSOX)_2]^-A^+$ (X = Cl or Ph) have been obtained in the case of the sulphur-containing systems [33,34]. Non-geminal disubstitution has been observed for $(NPCl_2)_3$, when more than two equivalents of water are applied, leading to *cis* and *trans* isomers with composition $[NPCl_2NHPClONPClO]^-A^+$. In the case of $(NPCl_2)_2NSOCl$, the disubstitution follows a geminal pathway, which leads to the formation of $[NPCl_2NSOClNHPO_2]^-A^+$. The different behaviour of the two systems has been elegantly explained from the reaction intermediates $(NPCl_2)_2NHPClO$ (Fig. 4) and $NPCl_2NSOClNHPClO$ (Fig. 5) [35]. Whereas the structure of $(NPCl_2)_2NHPClO$ resembles that of $(NPCl_2)_2NSOCl$, which means that an S_N2-like substitution at phosphorus is still possible, the structure of the most abundant isomer of $NPCl_2NHPClONSOCl$, resembling that of *cis*-$NPCl_2(NSOCl)_2$ [3], only allows for an S_N1-type substitution. The lower electronegativity of the P=O moiety as compared with S=O makes the POCl centre more susceptible to hydrolysis than the SOCl centre. Complete hydrolysis of *cis*-$NPCl_2(NSOCl)_2$ in

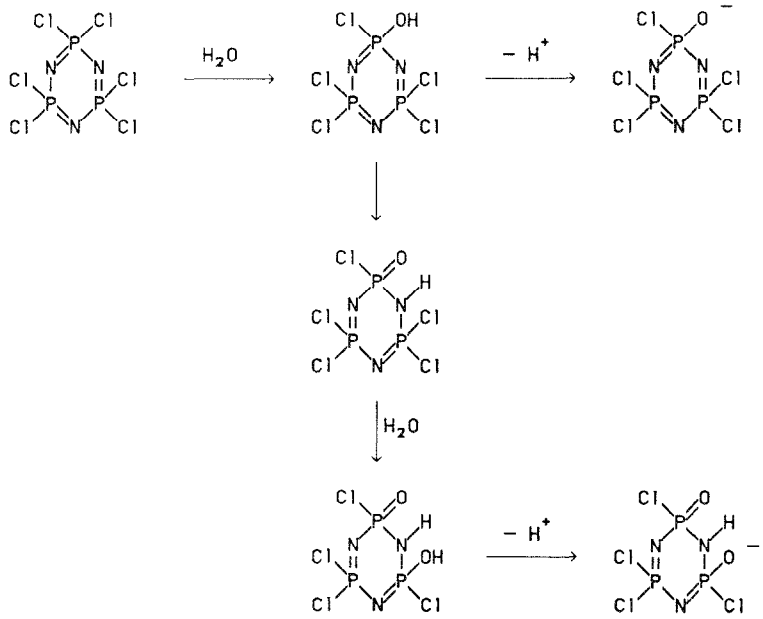


Fig. 4. Reaction pathway for the controlled hydrolysis of $(NPCl_2)_3$.

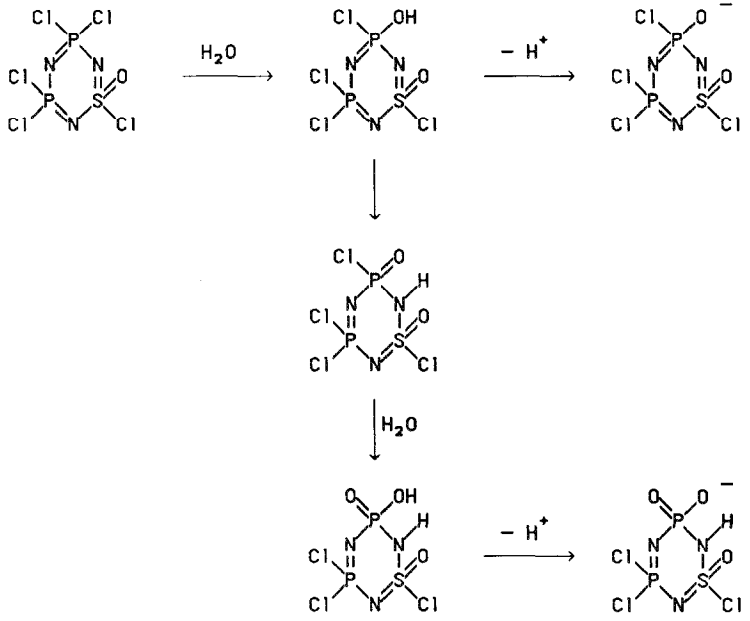


Fig. 5. Reaction pathway for the controlled hydrolysis of $(NPCl_2)_2NSOCl$.

aqueous alkali-metal acetate solution has been reported to yield alkali salts with composition $NHPO_2M(NSO_2M)_2$ (M = Na, K) [36]. The X-ray structure of one of these salts, $NHPO_2Na(NSO_2Na)_2 \cdot 2H_2O$ has been described [37]. The same research group also studied the hydrolysis of $(NPCl_2)_3$ to the corresponding cyclophosphazane $[NHP(O)OH]_3$ by means of semi-empirical MNDO and CNDO/2 methods [38]. Forcing reaction conditions have to be applied to hydrolyze the phenylated ring systems $NPCl_2(NSOPh)_2$ and $(NPCl_2)_2NSOPh$ [33].

It is noteworthy that $POCl^-$ and SOCl moieties are isoelectronic, but this is not the only similarity. Inserted as units in six-membered rings, their spatial orientation is the same, which means that in both cases the oxygen atoms adopt an equatorial position with respect to the mean ring plane and hence the chlorine atoms assume an axial position. This leads to a straightforward conformational relationship between compounds $[(NPCl_2)_a(NSOCl)_bNPClO]^-$ $(a+b=2)$ and $(NPCl_2)_a(NSOCl)_{b+1}$. The correlation between the structures of *cis*-$(NSOCl)_3$ [4] and *cis*-$[(NSOCl)_2NPClO]^-$ [34] or between $(NPCl_2)_2NSOCl$ and $[(NPCl_2)_2NClPO]^-$ [39] may serve as examples. The conformation of the PO_2^- moiety in $[NPCl_2NSOClNHPO_2]^-[KC_{12}H_{24}O_6]^+$ [35] resembles that of a PCl_2 group. It can be deduced from exocyclic and endocyclic bond lengths that in the phosphazene anions the negative charge is not localized at one particular oxygen atom, but is spread over the rings.

The larger the number of $NPCl_2$ units in the compounds $[(NPCl_2)_a(NSOCl)_b(NPClO)]^-$, the more downfield is the ^{31}P NMR signal of

the NPClO group found. Replacement of NSOCl by NSOPh has a similar effect (Table 2).

Recently, it has been shown that hydrolysis manifests itself as a competitive reaction mode, when relatively weak nucleophiles are operative in substitution reactions. For instance, the reaction of $(NPCl_2)_3$ with the monosodium salt of uracil in the presence of not thoroughly dried Bu_4NBr (phase-transfer catalyst) gives appreciable amounts of the hydrolysis products $[(NPCl_2)_2NPClO]^-[Bu_4N]^+$ [39] and $(N_3P_3Cl_5)O(N_3P_3Cl_5)$ (Fig. 6) in addition to the coupling derivative $(N_3P_3Cl_5)OC_4H_2N_2O(N_3P_3Cl_5)$ [40]. The oxygen-bridged compound has also been claimed from an A_2X pattern in $^{31}P\{^1H\}$ NMR spectra of reaction mixtures obtained by hydrolysis of $(NPCl_2)_3$ [41]. This assignment, however, must be rejected because

TABLE 2

Ranges of ^{31}P NMR chemical shifts (solvent $CDCl_3$, external reference $(NPCl_2)_3$, $\delta^{31}P = 19.9$ ppm) of PClO groupings in cyclo(thia)phosphazene anions

Anion	δ(PClO) (ppm)
$[NPClO(NSOCl)_2]^-$	−9 to −13
$[(NPCl_2)NPClONSOCl]^-$	−4 to −7
$[(NPCl_2)_2NPClO]^-$	0 to −2
$[NPClO(NSOPh)_2]^-$	−3 (one example)
$[NPCl_2NPClONSOPh]^-$	−2 to −3

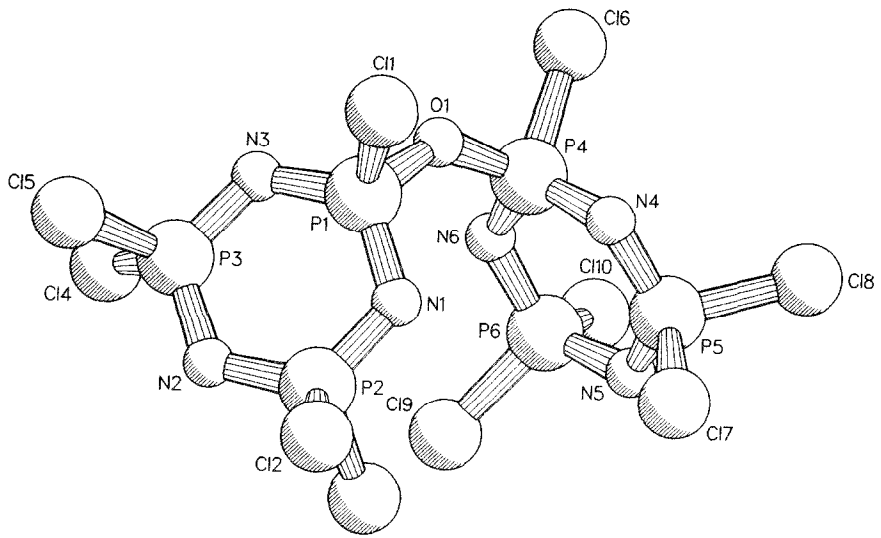


Fig. 6. Molecular structure of $(N_3P_3Cl_5)O(N_3P_3Cl_5)$ (one of the two independent molecules in the unit cell). (Reproduced with permission of *Recueil des Travaux Chimiques des Pays-Bas.*)

P–P coupling between the phosphazene moieties causes an $A_2A'_2XX'$ pattern. A similar phenyl-substituted compound, $N_3P_3Ph_5)O(N_3P_3Ph_5$, obeying an $A_2A'_2BB'$-type ^{31}P NMR pattern, has been reported by Keat et al. [42].

(iv) Metal–halogen exchange and nucleophilic addition

In a recent paper, Allcock et al. have given an excellent review concerning the use of organometallic reagents in phosphazene chemistry [43]. Two main reaction pathways can be discerned, (i) nucleophilic substitution and (ii) initial metal–halogen exchange, followed by nucleophilic substitution and addition. Generally, the perfluorocyclo(thia)phosphazenes give rise to nucleophilic substitution, whereas the chloro-derivatives follow the latter pathway. To illustrate this different kind of behaviour, some examples which were obtained recently in our research group will be discussed.

Fluorination of $(NPCl_2)_2NSOPh$ or *cis*-$NPCl_2(NSOPh)_2$ with KSO_2F leads to very high yields (80–90%) of the corresponding perfluoro systems $(NPF_2)_{3-n}(NSOPh)_n$ ($n = 1, 2$) [35]. Phenyl derivatives are chosen in order to prevent any reaction at sulphur, thus allowing a direct comparison with the corresponding phosphazene derivatives. Nucleophilic substitution of the fluoro ligands in these compounds by means of $(C_5H_4Li)_2Fe \cdot TMEDA$ offers a large variety of metallocene derivatives. For instance, the reaction of $(NPF_2)_2NSOPh$ with $(C_5H_4Li)_2$-$Fe \cdot TMEDA$ yields two isomers of the transannular product $(NPF)_2C_5H_4FeC_5H_4N$-SOPh in a 12:1 ratio, indicating a high degree of stereoselectivity. From a molecular structure determination, the major compound appears to be the $1\alpha,3\beta,5\beta$-isomer [44] (Fig. 7). In addition to these compounds, minor quantities of two other compounds are present, one isomer of the ferrocenyl-bridged derivative $NSOPhNPF_2NPFC_5H_4$-$FeC_5H_4NPFNPF_2NSOPh$ and the monosubstituted product NPF_2NPFC_5-$H_4FeC_5H_5NSOPh$. The formation of this monosubstituted compound can be explained from the presence of small amounts of monolithiated reagent $(C_5H_5)Fe$-$(C_5H_4Li) \cdot TMEDA$.

The presence of only one reactive centre in *cis*-$NPF_2(NSOPh)_2$ excludes the formation of transannular products in the reaction with bislithioferrocene. Spiro derivatives can also be ruled out for steric reasons. Hence, only an intermolecular reaction can lead to product formation. It appears that in this reaction a high stereoselectivity is operative as one side of the phosphazene ring is shielded by the phenyl groups. Only one of the three possible isomers of the bridged compound $(NSOPh)_2NPFC_5H_4FeC_5H_4NPF(NSOPh)_2$ is present in the reaction mixture. This compound crystallizes in two crystal forms, both having monoclinic symmetry. The molecular structure of one of these compounds is given in Fig. 8 [45].

A metal–halogen exchange mechanism has been observed for the reaction of alkyllithium reagents with the chlorine-containing species $(NPCl_2)_{3-n}(NSOPh)_n$ ($n =$ 0, 1, 2). Very reactive intermediates formed during the reaction require a low reaction temperature and the use of quenching agents as propan-2-ol in order to avoid

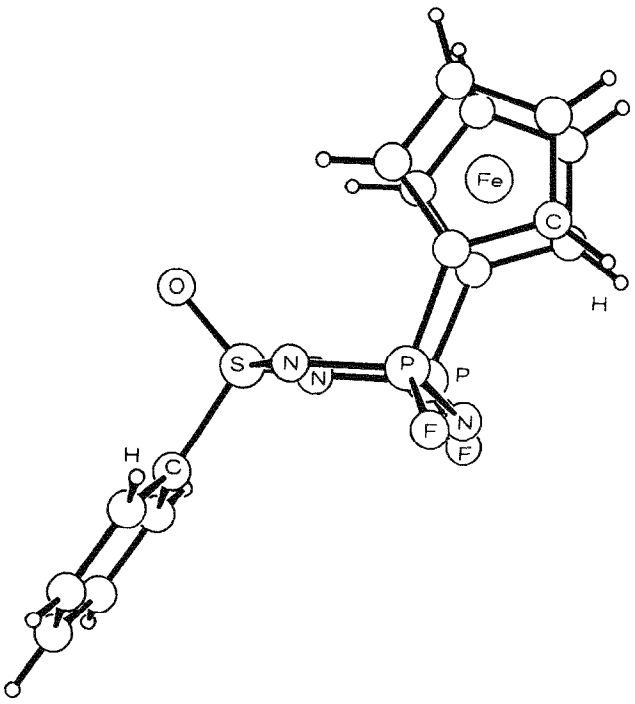


Fig. 7. Molecular structure of 1α, 3β, 5β-$(NPF)_2C_5H_4FeC_5H_4NSOPh$.

uncontrolled decomposition reactions [35,46]. Without these precautions, the yield of cyclic products appears to be less than 10% [47]. In Fig. 9, a possible reaction sequence is given for the formation of two hydrido derivatives in the reaction of $(NPCl_2)_3$ with one equivalent of MeLi and an excess of propan-2-ol. In the presence of two equivalents of MeLi a bicyclic compound with formula $(N_3P_3Cl_4Me)_2$ is also formed, together with small amounts of $(NPCl_2)_2NPMe_2$ and two unidentified products [48]. Product formation in the reactions of RLi (R = Me, ^{t}Bu) with $(NPCl_2)_2NSOPh$, *cis* and *trans*-$NPCl_2(NSOPh)_2$ is also supposed to arise from a metal–halogen exchange process [49].

Analogous reactions with $(NPCl_2)_4$ resulted in the formation of compounds $(NPCl_2)_3NPH(O^iPr)$, $(NPCl_2)_3NPHMe$ and $(NPCl_2)_3NPClMe$ [50]. The last compound is assumed to be formed by a direct nucleophilic attack at phosphorus. Interesting results are obtained when alkyliodides are used as quenching agents. In the presence of MeI, a bicyclic compound is formed with formula $(N_4P_4Cl_6Me)_2$, whereas addition of EtI leads to the formation of $(N_4P_4Cl_6Me)(N_4P_4Cl_6Et)$ [50]. Recrystallization of $(N_4P_4Cl_6Me)_2$ from petroleum ether results in two crystal modifications, $P\bar{1}$ and $Fdd2$, respectively. The molecular structure, belonging to the triclinic crystal phase, is given in Fig. 10 [51].

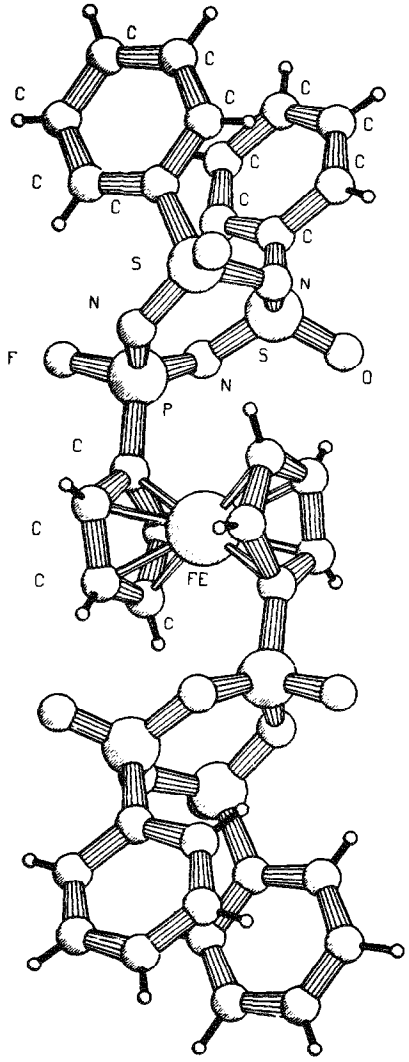


Fig. 8. Molecular structure of an isomer of $(NSOPh)_2NPFC_5H_4FeC_5H_4NPF(NSOPh)_2$. (Reproduced with permission of *Acta Crystallographica*.)

As described by Allcock et al., reactions of $(NPCl_2)_3$ with RMgCl in tetrahydrofuran also proceed via a metal–halogen exchange mechanism with $(NPCl_2)_2N(MgCl)PCl$ as reactive intermediate [43,52]. For secondary and tertiary alkyl Grignards, a nucleophilic substitution process cannot be fully excluded. Two kinds of product can be isolated, viz. a monosubstituted cyclophosphazene $N_3P_3Cl_5R$ and a bicyclic product $(N_3P_3Cl_4R)_2$, the ratio of two products depending on the nature of R (Me, ^{t}Bu, Ph, etc.) and the reaction temperature [52]. Reaction of the sulphur-containing ring system *trans*-$NPCl_2(NSOPh)_2$ with MeMgCl in THF and

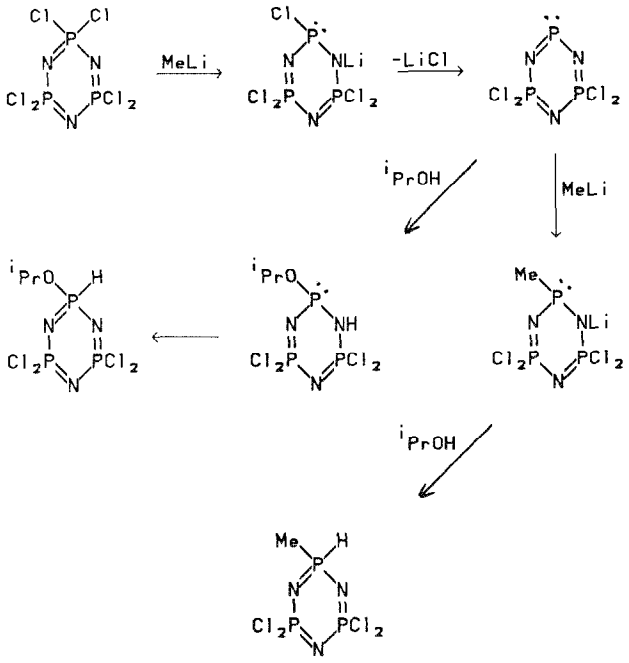


Fig. 9. Pathway for the formation of cyclic compounds in the reaction of $(NPCl_2)_3$ and one equivalent of MeLi in THF. Compound $(NPCl_2)_2NP$ is the reactive intermediate.

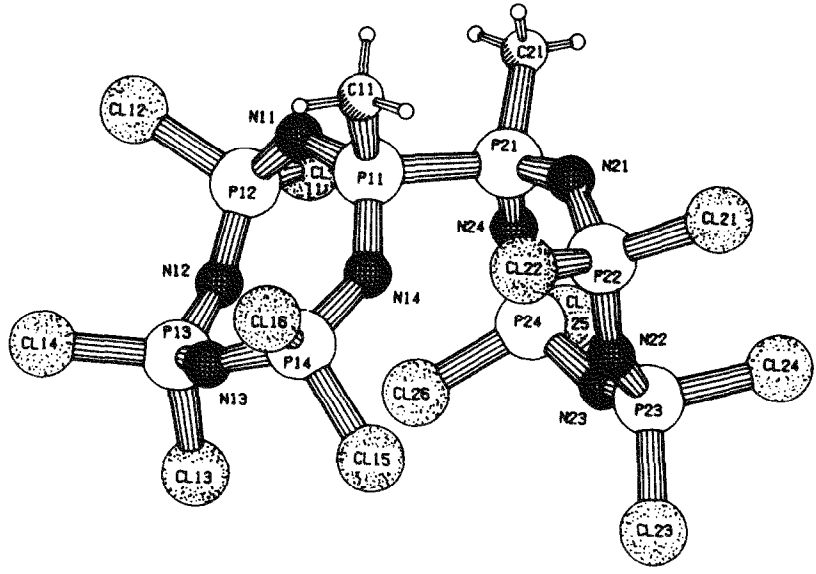


Fig. 10. Molecular structure of the triclinic modification of $(N_4P_4Cl_6Me)_2$. (Reproduced with permission of *Acta Crystallographica.*)

an excess of propan-2-ol shows that chlorine substitution occurs both along a nucleophilic pathway and a metal–halogen exchange process. For ^{t}BuMgCl as reagent, nucleophilic substitution is predominant [53].

Reactions between $(NPCl_2)_3$ and Grignard reagents in the presence of $[(C_4H_9)_3PCuI]_4$ leads to the formation of a phosphazenocuprate intermediate (Fig. 11) [54,55]. This intermediate can react with propan-2-ol or alkylhalides to give *gem*-hydridoalkyl [56] and *gem*-bisalkyl derivatives [43], respectively. The scope of the latter synthesis is somewhat limited as no reaction takes place with branched alkyl iodides. Comparable results have been obtained for reactions of the sulphur-containing ring system *trans*-$NPCl_2(NSOPh)_2$ with copper-assisted Grignard reagents and subsequent quenching with propan-2-ol or alkylhalides [53].

Nucleophilic addition of the phosphazeno-cuprate derived from $(NPCl_2)_3$ (Fig. 11) to aldehydes and ketones has been proven to provide a facile entry (one-pot reaction, high yields) to geminal alkyl(hydroxyalkyl) derivatives of $(NPCl_2)_3$ [55], an example of which is given in Fig. 12 [57]. These hydroxy compounds may serve as reactive precursors in further reactions (see also Sect. D).

C. BIOLOGICAL ACTIVITY OF AZIRIDINYL-SUBSTITUTED CYCLOPHOSPHAZENES AND CYCLOTHIAPHOSPHAZENES

(i) In vitro and in vivo experiments

Aziridinyl-substituted cyclophosphazenes have been recognized as cytostatic agents for more than 30 years. They can be described as combinations of a biologically active group (1-aziridinyl) and an electron-directing (depending on other substituents) phosphazene ring as carrier material. The first examples were reported by Chernov et al. in 1959, who mentioned among other things the cytostatic activity of $N_3P_3Az_6$ (Az = 1-aziridinyl) or "Apholate" (Fig. 13) against rat- and mouse sarcomas [58]. The same compound, now called Myko 63, was described to be active in murine tumour models, P388, L1210 and B16 [59]. Another derivative, $N_3P_3Az_5Morph$ (Morph = morpholino), known as "Fotrin" (Fig. 13), entered clinical trials in the USSR [60].

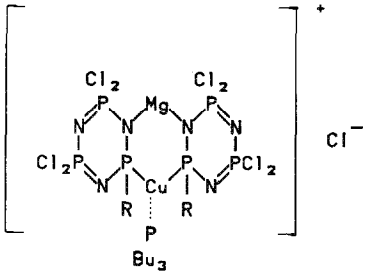


Fig. 11. Proposed structure of the phosphazenocuprate.

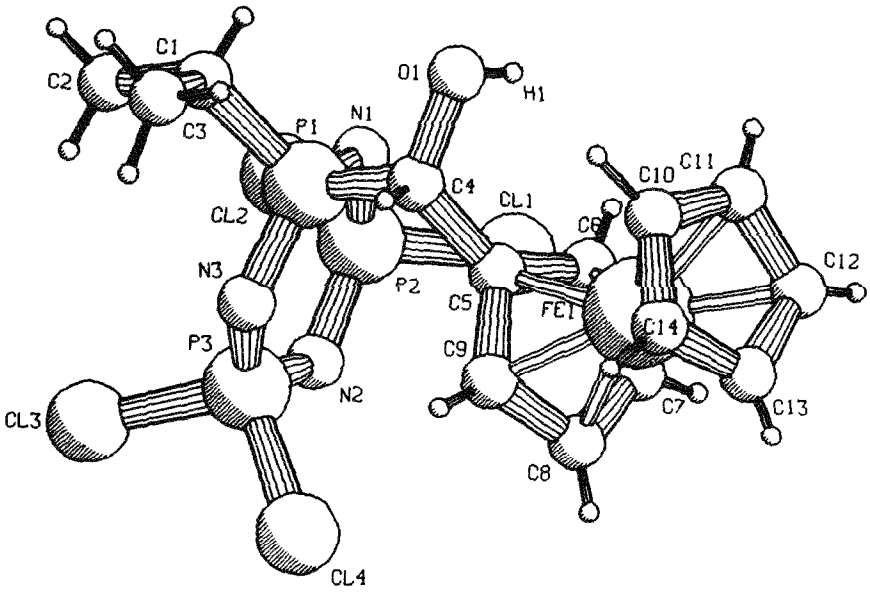
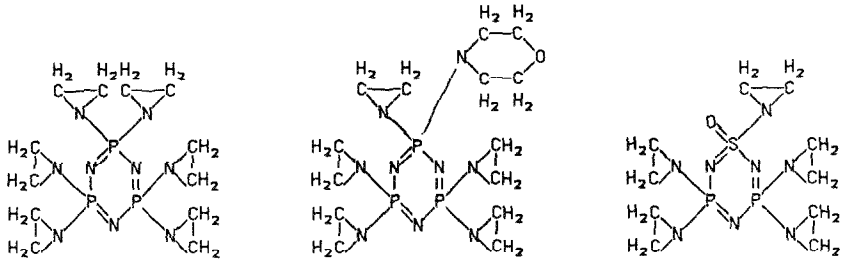


Fig. 12. Molecular structure of $(NPCl_2)_2NP^iPrCH(OH)$-η^5-C_5H_4-Fe-η^5-C_5H_5. (Reproduced with permission of *Acta Crystallographica*.)



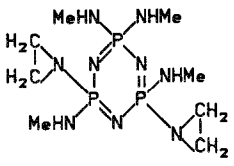
APHOLATE FOTRIN SOAz

Fig. 13. Cytostatic cyclo(thia)phosphazenes.

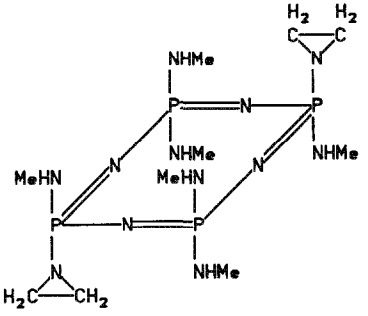
Much attention has been paid to the pentakis(1-aziridinyl) derivative of $(NPCl_2)_2NSOCl$ (code name SOAz, Fig. 13). Numerous publications on its preparation [61], structure [62] and in vitro and in vivo biological activity [63–73] have appeared. Although its cytostatic activity was demonstrated in mice models, SOAz cannot be applied as an anticancer drug on the human level [73] (see also Sect. C.(ii)).

A systematic study of the cytostatic activity in vitro of a large number of aziridinyl derivatives $N_3P_3Az_{6-n}R_n$ ($n = 1, 2$) has shown a direct relationship between the electron-releasing capacity of R (defined by substituent constants $\alpha_R(\gamma_R)$ [9]) and the biological activity. Higher $\alpha_R(\gamma_R)$ values lead to a higher activity [65,74]. Moreover, it has been found that the hydrolytic instability of R results in a loss of activity. From the series of compounds $N_3P_3AzR_5$ and *gem*-, *trans*- and *cis*-$N_3P_3Az_2R_4$, a general sequence of activity can be derived: mono $\ll$ *gem* $\ll$ *trans* $\cong$ *cis*. It has been argued that at least two active centres (i.e. P atoms linked to one or two aziridinyl groups) are required for effective tumour growth inhibition [75]. Mono- and bis(aziridinyl) derivatives from the tetrameric system $(NPCl_2)_4$ show the same pattern, although their activity is smaller than the trimeric analogues.

In addition to their in vitro activity, the compounds mentioned above also display an in vivo activity in mice tumour models. It has to be emphasized, however, that the predictive value of in vitro data with respect to the therapeutic effect in vivo is rather limited. No clear evidence is available with regard to the biological mode of action of the aziridinyl derivatives. Attempts to demonstrate incorporation of Apholate and SOAz in DNA gave no conclusive results [76,77]; another study reported conformational changes in double-stranded DNA when exposed to SOAz [78]. DNA damage brought on by SOAz, *trans*-$N_3P_3Az_2(NHMe)_4$ (AZP, Fig. 14) and a *trans*-bis(1-aziridinyl)-tetrakis(methylamino) derivative of $(NPCl_2)_4$ (AZM, Fig. 14) has been investigated in two tumour cell lines. For each of the compounds, a different effect has been observed. In addition, it has been shown that for AZP and AZM the concentrations required for cytotoxicity in the clonogenic assay are of the same order as those leading to DNA damage [79].



AZP



AZM

Fig. 14. Water-soluble cytostatic cyclosphazenes with two active centres. For the preparation of these compounds, see refs. 75 and 80.

(ii) Clinical trials

As mentioned earlier, Fotrin was the first aziridinylcyclophosphazene to be used in a clinical trial. Although the patent [60] claims a broad spectrum of antitumour properties, evaluation of clinical results is not available in the literature.

Based on the results of extended preclinical studies [63–71], SOAz was selected for clinical trials both in The Netherlands and in France. The drug, administered intravenously, is remarkably well tolerated by patients and about 50% is excreted unreacted in the urine within 24 h of administration [81,82]. At high dose levels, SOAZ has a strong tendency for cumulation of bone marrow toxicity, which for some patients appears to be irreversible [83, 84]. This phenomenon appears to be independent of the administration schedule [85]. The cumulative tendency of the myelosuppression did not allow for further clinical studies.

Another member of the series of aziridinyl-substituted cyclophosphazenes that entered clinical trials was AZP (Fig. 14). This compound has been tailor-made, based on the structure–activity relationships as described in the preceding paragraph (two active centres, MeNH groups as electron-donating substituents). From an in vivo study on mice it was expected that AZP should only display a small cumulative bone marrow toxicity [86]. Although the results of a phase I clinical trial have been described to be promising [87], a phase II study again points to a tendency for cumulative bone marrow toxicity [88]. This result did not warrant further clinical research.

Attempts have been made to overcome toxicity effects and/or to enhance the antitumour action, e.g. by preparation of aziridinylcyclophoshazenes linked to polyamines [89,90]. With respect to further research it has to be emphasized that the aziridinyl group is still the biologically active site in the drug, unfortunately possessing a detrimental bone marrow toxicity as an intrinsic property. Other medical applications will also encounter this limitation on a clinical level.

D. USE OF ORGANO-SUBSTITUTED CYCLOPHOSPHAZENES AND CYCLO(THIA)PHOSPHAZENES IN POLYMER CHEMISTRY

(i) Introduction

It is well-known that ring opening polymerization of $(NPCl_2)_3$ under controlled conditions can lead to the formation of a linear polymer $-[NPCl_2]_n-$, which is soluble in common organic solvents and can undergo a large variety of chlorine substitution reactions [9,91,92]. Also, partially organo-substituted cyclophosphazenes can be induced to polymerize [91]. The P–N backbone exhibits an intrinsic flexibility which can be enhanced by irregularities in the distribution of the side groups. In general, the physico-chemical properties, e.g. water solubility, liquid crystallinity, flame retardancy, and so on, are determined by the substituents, which can

be varied widely as a consequence of the versatile reactivity of the PCl_2 centres combined with the stability of the phosphazene chain. Eypel F, $-[NP(OR)_2]_n-$ (Ethyl Corporation), in which R stands for different fluoroalkyl groups may serve as a commercially available example. This polymer is characterized by its flexibility, even at very low temperatures, its resistance to solvents, hydrocarbon fuels and lubricants, its outstanding fatigue resistance and flame retardancy [93]. The presence of hydrolytically unstable substituents, e.g. glyceryl or ethylglycinato units, renders the polymeric chain sensitive to hydrolysis and thus suitable as a bioerodible device for controlled drug release [94–96].

As it is beyond the scope of this survey to cover all papers on polyphosphazenes, only some examples from the 1990 literature (Table 3) are given to illustrate the diversity of research in this field.

In addition to ring-opening polymerization, two other methods for preparing polymers with a P–N backbone may be mentioned. The first method concerns condensation polymerization of *N*-silylphosphoranimines at about 160–200 °C, leading to the formation of organo-substituted polyphosphazenes [104,105]. For example:

$$Me_3SiN=\underset{\displaystyle Ph}{\overset{\displaystyle Me}{\overset{|}{\underset{|}{P}}}}-OCH_2CF_3 \rightarrow Me_3SiOCH_2CF_3 + -[N=\underset{\displaystyle Ph}{\overset{\displaystyle Me}{\overset{|}{\underset{|}{P}}}}]_n-$$

TABLE 3

Examples of research in 1990 on polyphosphazenes $-[NP(OR)_2]_n-$ and $-[NP(NR_2)_2]_n-$

Subject	Authors	Ref.
Structure of extruded $-[NP(OCH_2CF_3)_2]_n-$	Antipov, Kulichikhin, Borisenkova, Barancheeva, Tur and Plate	97
Diffusion of Ag^+ ions in MEEP/CF_3SO_3Li	Cammarata, Talham, Crooks and Wrighton	98
Crystallization kinetics of $-[NP(OCH_2CF_3)_2]_n-$	Ciora and Magill	99
Second-order non-linear optics in a phosphazene copolymer	Dembek, Kim, Allcock, Devine, Steier and Spangler	100
Sensitized photochemistry of $-[NP(OC_6H_4{}^iPr\text{-}p)_2]_n$	Gleria, Minto, Bortolus, Porzio and Meille	101
Electrolytic behaviour of $-[NP(NHC_6H_5)_{2-x}(NHC_6H_4SO_3H\text{-}p)_x]_n-$	Kurachi, Shiomoto and Kajiwara	102
Excimer fluorescence of $[NP(OPh)_2]_n$ and $-[NP(OC_6H_4CH_3)_2]_n-$	Yeung, Frank and Singler	103

The polymers thus obtained are characterized by the presence of direct P–C bonds. The same procedure, but now using a combination of precursors, can also be applied for the preparation of copolymers. Polymers with more complex side groups become available by derivatization of the organic groups prior to or after the polymerization process [104,105].

Another method for the preparation of polyphosphazenes proceeds along thermal decomposition of trichlorophosphazophosphorylchloride [106].

$$Cl_3P{=}NPOCl_2 \rightarrow Cl{-}[NPCl_2]_n{-}POCl_2 + POCl_3$$

The polymerization reaction appears to be reproducible. Molecular weights between 2×10^2 and 10^4 can be obtained.

Recently, the ring-opening polymerization of the cyclic system $(NPCl_2)_2NSCl$ has been reported to give the novel polymeric system $-[NSCl(NPCl_2)_2]_n-$ [107]. As the chlorine atoms can undergo substitution reactions, this polymer may provide another entrance to a large variety of new inorganic polymers.

(ii) Radical polymerization of organofunctional cyclo(thia)phosphazenes

A special class of phosphazene polymers with flame-retardant properties is formed by those consisting of a carbon–carbon main chain with pendant inorganic cyclophosphazene side groups. Preparation of these hybrid inorganic–organic polymers can be achieved by radical polymerization of olefin-substituted cyclophosphazenes [108]. The first reported polymers were derived from $N_3P_3F_5[C(CH_3){=}CH_2]$. Copolymerization with styrene or vinylbenzylchloride led to a broad range of copolymers with 6–38% phosphazene content, depending on the feed ratio. Attempts at radical homopolymerization failed [109]. A second series of copolymers has been prepared from $N_3P_3F_5[C(OC_2H_5){=}CH_2]$ and styrene or methyl methacrylate as precursors. For the copolymerization with styrene a phosphazene content up to 44% could be obtained [110]. For both series of copolymers the molecular weights decrease with an increasing phosphazene content. This has been explained from the strong σ-electron-withdrawing capacity of the fluorophosphazene unit, which induces a high polarity in the olefin moiety, thus favouring termination reactions. Therefore, to enhance the reactivity of alkenylfluorocyclophosphazenes in radical polymerization the olefin has to be separated from the phosphazene moiety by an insulating spacer and/or to be connected with an electron-donating group. Indeed, a higher content of the phosphazene part can be obtained, when $N_3P_3F_5[C_6H_4C(CH_3){=}CH_2]$ is used as a precursor [111,112].

A broad range of homo- and copolymers has been synthesized from vinyloxypentachlorocyclophosphazenes [113–116]. In these precursors the oxygen atom acts as the insulating moiety between the double bond and the inorganic ring, whereas the chlorophosphazene entity exhibits a lower electron-withdrawing capacity than the fluoro analogue. Analogous results were obtained in the case of

$NPCl_2NPCl(OCH{=}CH_2)NSOPh$ [117] as a precursor. Copolymerization of the latter with $N_3P_3Cl_5(OCH{=}CH_2)$ led to a copolymer with a 50–50% distribution of phosphazene and thiaphosphazene rings at the main chain (Fig. 15) [118]. The homopolymers $-[CH_2CH(ON_3P_3Cl_5)]_n-$ and its sulphur analogue are thermally labile and show elimination of HCl around 110 °C, the number of equivalents corresponding with the number of PCl_2 groupings, followed by a complex pattern of decomposition reactions at higher temperatures [116,118].

Although the "vinyloxy" polymers and copolymers exhibit many interesting properties, such as flame retardancy and susceptibility for chlorine substitution reactions, two points make them less attractive for industrial applications, viz. laborious synthetic procedures combined with relatively low yields and the instability of the P—O bond, even under mild reaction conditions. With respect to the last point it has been demonstrated that treatment of $-[CH_2CH(ON_3P_2SOPhCl_3)]_n-$ with CF_3CH_2ONa and an excess of CF_3CH_2OH in THF leads to cleavage of P—O bonds and consequently to degradation of the polymeric structure [119].

To circumvent the instability of the P—O bond, polymer precursors with direct P—C bonds must be used. Suitable polymer precursors, e.g. styrene-, acrylate- and methacrylate-substituted cyclophosphazenes (Fig. 16), can be obtained by application of the "nucleophilic addition method" described previously [54,55]. Radical polymerization of the styryl precursor leads to an unstable polymer which becomes insoluble by gradual cross-linking. In copolymerization with styrene a stable polymer has been obtained with 25% phosphazene incorporation. Homopolymerization of the meth-

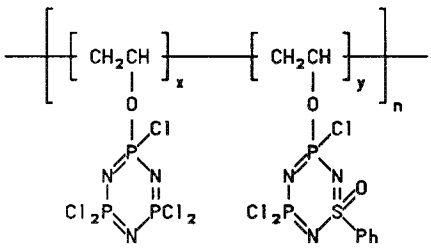


Fig. 15. Hybrid inorganic–organic polymer having two different cyclophosphazene entities.

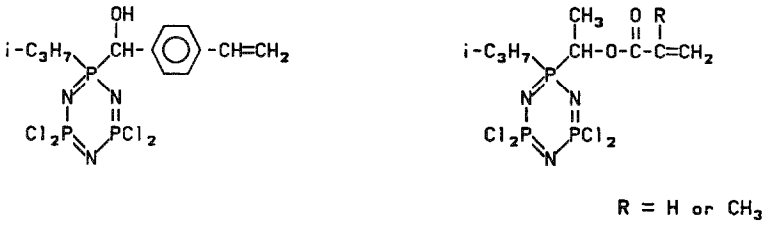


Fig. 16. Precursors for radical polymerization, bearing a styryl, acrylate or methacrylate moiety as organofunctional groups.

acrylate precursor results in the formation of a stable polymer, poly(cyclophosphazene)methacrylate (PCPhMA), which appears to possess excellent flame retardant properties [120].

Thermally stable homo- and copolymers can be obtained starting from vinylbiphenylyloxypentachloro (or pentafluoro) cyclophosphazenes as precursors. The aryloxy moiety in these compounds acts as an insulating unit between the phosphazene ring and the organo-reactive site [121,122]. Preliminary data are reported for the preparation and polymerization of a methacryloyloxymethylphenoxy cyclophosphazene derivative [123].

(iii) Hydrosilylation

Hydrosilylation (coupling between an SiH site and a C=C bond in the presence of a platinum catalyst) has proven to be a very useful tool in preparing organo-substituted polysiloxanes and many publications on this subject have appeared. Applications in the phosphazene area, however, are limited. Network formation in polyfluoroalkoxyallylphenoxyphosphazenes by hydrosiloxanes has been described [124]. Low-molecular weight polyorganophosphazenes can be cross-linked by hydrosiloxanes provided olefinic groups are present in the phosphazene. Although many of these groups can undergo hydrosilylation, 2-allylphenoxy appears to be the preferred substituent [125].

Very recently we reported the synthesis of phosphazene-substituted polysiloxanes (Fig. 17) by hydrosilylation of allyl derivatives of cyclophosphazenes with polymethylhydrosiloxanes in the presence of a divinyltetramethyldisiloxane platinum complex as a catalyst [126]. Again, the spacer between the double bond and the cyclophosphazene plays a decisive role in the course of the coupling reaction. As found for the preparation of hybrid inorganic–organic polymers (see preceding paragraph) the olefin moiety must be sufficiently insulated from the electron-with-

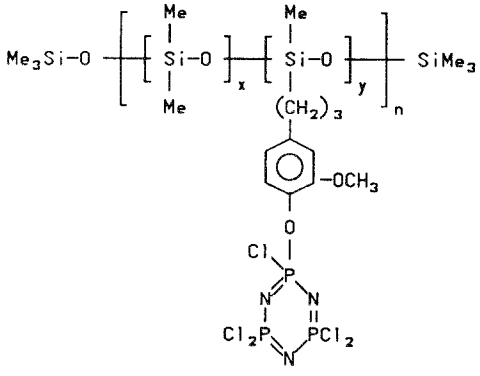


Fig. 17. Phosphazene-substituted polysiloxane.

drawing phosphazene group, because, otherwise incomplete or no hydrosilylation takes place. For example, efforts to induce a reaction with $(NPCl_2)_2NPClOCH_2CH=CH_2$ (spacer OCH_2) were not successful, whereas hydrosilylation with $(NPCl_2)_2NPClOC_6H_3(OCH_3)CH_2CH=CH_2$ (see Fig. 17) proceeded almost quantitatively. Besides these electronic effects, the steric hindrance exerted by the phosphazene group also influences the course of the reaction.

E. GENERAL REMARKS AND CONCLUSIONS

The stability of the cyclic framework of phosphazenes and thiaphosphazenes combined with their multifunctionality renders these compounds very useful in a large variety of reactions. It is possible to direct the physico-chemical and biological properties by means of the substituents attached to the ring. It is expected that the application of these rings as pendant groups in polymeric systems will grow continuously. In this context, the preparation on an industrial scale of hybrid polymers with a high-temperature stability and excellent flame retardant capacities represents an interesting challenge for further research.

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