mL, 0.5 M) of benzophenone in ether was added. After 48 h, the reaction was hydrolyzed and all volatile compounds were removed under vacuum at 65 °C and collected in a dry ice–acetone trap. GLC analysis with the use of the two columns and conditions described in the previous reaction gave the following products: 0.40 ± 0.01 mmol of 2,2-dimethyl-5-heptene; 0.29 ± 0.01 mmol of 1,1,3-trimethylcyclopentane; 0.16 ± 0.008 mmol of 3,3-dimethylmethylenecyclopentane; 0.24 ± 0.01 mmol of acetone; 0.15 ± 0.007 mmol of isopropyl alcohol; 0.96 ± 0.02 mmol of 1,1-dimethyl-2-(3,3-dimethylcyclopentyl)ethanol.

The residue left after vacuum stripping was dissolved in ether and washed with water, the ether layer separated and dried, and the ether removed under vacuum. The remaining liquid was shown by IR to have no C=O absorption between 1600–1750 cm^{-1}; NMR analysis indicates 0.38 mmol (88%) of straight-chain 1,2-addition product and 0.12 mmol (12%) of cyclized 1,2-addition product (by difference between mmoles indicated by vinyl protons and mmoles indicated by aromatic protons).

The nonvolatile reaction products were hydrogenated at 40 psig with use of 5% Pd–C in ethanol for 12 h. The resulting hydrocarbon mixture was separated by preparative GLC with use of 8% Apiezon L on Chromosorb W (AW), 60/80 mesh on a 12-ft. column at 220 °C with a flow rate of 70 mL/min of helium. The first compound eluted (retention time 82 min) was identified as 1,1-diphenyl-3,3-dimethylheptane: IR(neat, film) 3030 (aromatic CH), 2950 (aliphatic CH), 1600 cm^{-1} (aromatic CH); NMR($CDCl_3$, Me_4Si) 0.78 (s, 6 H), 0.79–1.8 (m, 9 H), 2.10 (d, 2 H), 4.03 (t, 1 H), 6.90–7.40 ppm (m, 10 H); mass spectrum, *m/e* (relative intensity) 280 (M^+, 6), 22 (4), 168 (3), 167 (100), 166 (7), 165 (14), 152 (9), 91 (4), 71 (8), 57 (18), 43 (8), 41 (5), 28 (15). Anal. Calcd for $C_{21}H_{28}$: C, 90.00; H, 10.00. Found: C, 89.98; H, 10.00.

The second compound eluted (retention time 100 min) was identified as 1,1-diphenyl-2-(3,3-dimethylcyclopentyl)ethane: IR(neat, film) 3030 (aromatic CH), 2945 (aliphatic CH), 1600 cm^{-1} (aromatic C=C); NMR($CDCl_3$, Me_4Si) 0.95 (d, 6 H), 1.10–2.35 (m, 9 H), 3.98 (t, 1 H), 6.9–7.45 ppm (m, 10 H); mass spectrum, *m/e* (relative intensity) 278 (M^+, 4), 168 (19), 167 (100), 166 (4), 165 (9), 152 (8), 91 (4), 69 (5), 57 (8), 55 (5), 28 (20).

Anal. Calcd for $C_{21}H_{26}$: C, 90.51; H, 9.49. Found: C, 90.25; H, 9.67.

The ratio of peak areas for compound 1 to compound 2 were about 90:10 on the preparative GLC chromatogram.

Acknowledgment. We thank the National Science Foundation, Grant No. MPS 7504127, for support of this work.

Supplementary Material Available: All compounds used in this study whose proportion is not reported in the Experimental Section and the results of reactions of all probes with the substrates studied (17 pages). Ordering information is given on any current masthead page.

Synthesis and Hydrolysis of Hexakis(imidazolyl)cyclotriphosphazene

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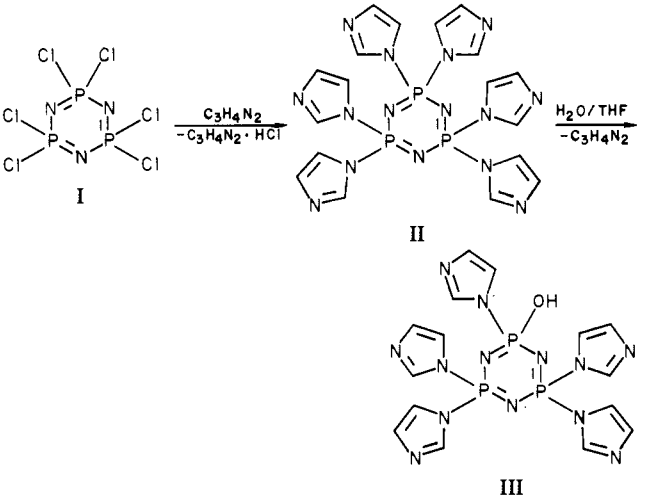
Abstract: The reaction of imidazole with hexachlorocyclotriphosphazene (I) has yielded hexakis(imidazolyl)cyclotriphosphazene (II). Compound II has been studied as a model for the analogous linear high polymer which is a prospective biodegradable carrier macromolecule. Compound II is hydrolytically unstable and decomposes to hydroxyphosphazenes, imidazole, and phosphate in aqueous media. A kinetic analysis of the removal of the first imidazolyl group from II in unbuffered 20% aqueous tetrahydrofuran within the pH range of 6.5–7.8 has shown that the hydrolysis is autocatalyzed by the free imidazole liberated in this step. Initially, the displacement of imidazole is a first-order process with respect to [II], but the release of imidazole gives rise to faster, second-order reaction in which the rate depends on the first powers of [II] and [imidazole]. The evidence favors the influence of free imidazole as a general-base catalyst and not via the formation of hydroxide ion. *N*-Methylimidazole reacts with I to form an unusual series of highly reactive yellow salts of the general formula $[N_3P_3Cl_{6-x}(C_4H_6N_2)_x]^{x+}xCl$ (VII). The chemistry of II and VII is discussed in terms of its relationship to the synthesis and reactions of the analogous linear high polymeric phosphazenes.

The hydrolysis behavior of cyclo- and polyphosphazenes is of some importance in view of the prospective biomedical use of these compounds.[1,2] In earlier papers we described the kinetics of hydrolysis of aryloxy- and fluoroalkoxycyclophosphazenes in basic media.[3,4] This paper contains an analysis of the hydrolysis reactions of an *amino*-substituted cyclophosphazene. It represents an attempt to deduce the mechanism of hydrolysis in a way that may be relevant to future biomedical studies, and it comprises the use of a small-molecule *cyclo*phosphazene as a model for the reactions of the analogous high polymer.[5]

The cyclophosphazene chosen for this study was hexakis(imidazolyl)cyclotriphosphazene (II). The imidazolyl substituent group was employed for the following reasons. First, the prospect exists that this side group might be used as a coordinative ligand



I II III

for transition metals, especially for the coordination of high polymeric analogues of II to metalloporphyrins.[6] Second, the

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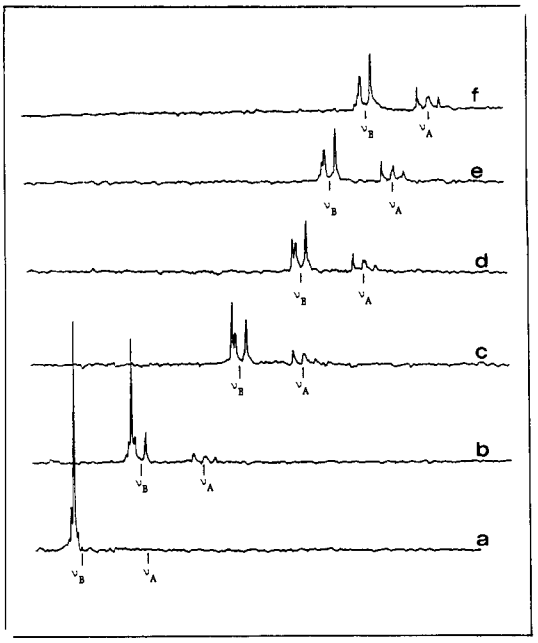


Figure 1. ^{31}P NMR spectra obtained during the transformation of II (spectrum a) to III (spectrum f). The initial concentration of II was 0.0346 M, the pH was 7.1, and free imidazole (1.0 M) was present at the start of the reaction. The spectra are offset for clarity.

Table I. ^{31}P NMR Chemical Shifts[a]

compd	solvent	spin system	A, ppm	B, ppm	J_{AB}, Hz
$N_3P_3(ONa)Cl_5$[b]	THF	AB_2	0.4	19.3	68.7
$N_3P_3(OCH_2CF_3)Cl_5$ (V)	THF	AB_2	16.1	22.4	65.8
$N_3P_3(OH)(Imid)_5$ (III)[c]	THF[c]	AB_2	−9.5	−1.9	52.5
$N_3P_3(OH)(Imid)_5$ (III)[d]	THF	AB_2	−11.4	−3.5	53.5
$N_3P_3(OCH_2CF_3)(Imid)_5$ (VI)	THF	AB_2	5.6	−1.0	61.8
$[NP(Imid)_2]_3$ (II)	THF	A_3	−2.2		
$[NP(OCH_2CF_3)_2]_3$	THF	A_3	17.7		
$[NP(NHC_4H_9)_2]_3$	THF	A_3	18.1		
$[NP(NHCH_3)_2]_3$	H_2O	A_3	23.0		

[a] Relative to aqueous 85% phosphoric acid. In accordance with recent IUPAC recommendations, a positive shift is downfield from H_3PO_4. [b] Prepared by reaction of $NaOSiPh_3$ with $(NPCl_2)_3$. [c] Prepared by hydrolysis of II in 20 vol % aqueous THF (excess imidazole present). [d] A mixture of sample *b*, after treatment with free imidazole, and sample *c*.

biodegradation of the polymeric analogues of II might be expected to yield, imidazole, phosphate, and ammonia. Third, on theoretical grounds it was supposed that the imidazolyl group might be more sensitive to hydrolytic displacement than would other amino groups. Hence, II provided an excellent prototype for mechanistic studies.

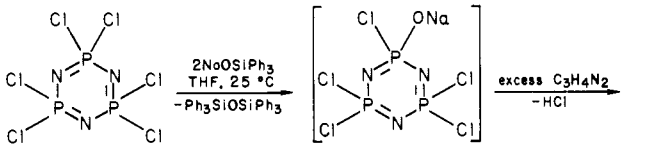
In addition to the synthesis of II and description of its hydrolysis behavior, we also report here the formation of an unusual *N*-methylimidazolyl salt of I, and the utilization of II as a synthetic reagent for the preparation of other organophosphazenes via the nucleophilic displacement of imidazolyl groups.

Results and Discussion

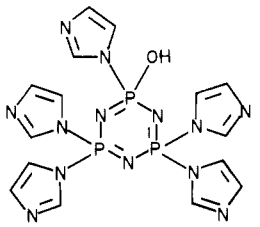
Synthesis of II. Compound II was prepared by the interaction of hexachlorocyclotriphosphazene (I) with more than 12 equiv of imidazole at 25 °C in tetrahydrofuran solvent. A monitoring of the reaction by means of ^{31}P NMR spectroscopy indicated that the replacement of chlorine by imidazolyl groups occurred by both geminal and nongeminal pathways, although the nongeminal route predominated. The identity of II was confirmed by ^1H and ^{31}P NMR spectroscopy, infrared spectroscopy, mass spectrometry, and elemental analysis (see Experimental Section), and a single-crystal X-ray analysis.

Hydrolysis Products from II. The hydrolytic sensitivity of II undoubtedly explains the fact that this compound had not been reported previously in spite of the existence of a great many other aminocyclophosphazenes.[7,8] In contact with water, II is hydrolyzed rapidly to III.

The structure of III was deduced from its ^{31}P NMR spectrum (Figure 1f), which was interpreted as an AB_2 spin system with a coupling constant, J_{AB}, of 52.5 Hz (Table I). Confirmation of the structure of III was obtained by comparison with the NMR spectrum of an authentic sample of III prepared by an alternative route, as shown in the conversion of I to III via the intermediate formation of IV. The intermediate, IV, was not isolated, but its

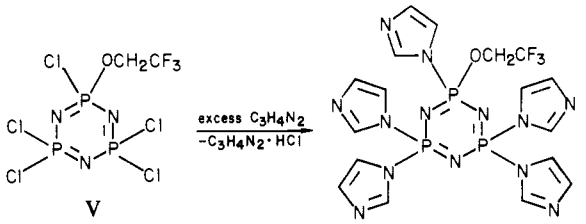


I IV



III

^{31}P NMR spectrum was that of an AB_2 system (Table I). The sample of III prepared from IV showed a ^{31}P NMR spectrum similar to the species formed by hydrolysis of II. Further confirmation of the NMR assignments was obtained from the ^{31}P NMR spectrum of VI, prepared by the reaction of imidazole with V.[9] Species VI also showed an AB_2-type pattern, with a J_{AB} coupling constant of 61.8 Hz.



V VI

Although III was formed as an initial hydrolysis product, extended hydrolysis of II for several weeks in an aqueous tetrahydrofuran medium, or in boiling aqueous dioxane, resulted in a total decomposition to imidazole, phosphoric acid, and ammonia. The imidazole was identified by ^1H NMR spectroscopy, and the phosphoric acid was detected by ^{31}P NMR analysis and by the formation of a yellow precipitate of silver phosphate in the presence of silver nitrate.

Kinetics of Hydrolysis of II to III. ^{31}P NMR spectroscopy was used to follow the rate of hydrolysis of II to III in 20 vol % water in tetrahydrofuran (Figure 1). This could be accomplished only within the pH range of 6.5–7.8. In media that contained 0.001 N hydrochloric acid or 0.001 N sodium hydroxide, or in aqueous media buffered to pH 5 or 9, the further hydrolysis of III was faster than its formation from II. Hence, meaningful kinetic analyses could not be obtained for these reaction conditions. However, in the pH range near 7 the conversion of II to III was

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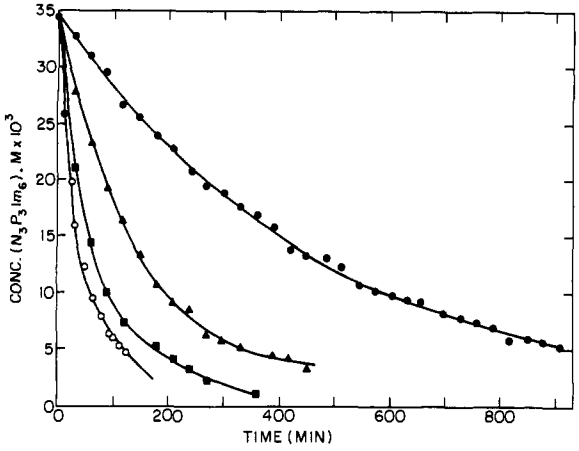


Figure 2. Decrease in the molar concentration of II (0.03457 M) with time as a function of added imidazole: ●, 0.10 M; ▲, 0.25 M; ■, 0.50 M; ○, 1.0 M. The reaction took place in 20 vol % aqueous tetrahydrofuran buffered to pH 7.1 at 28 °C.

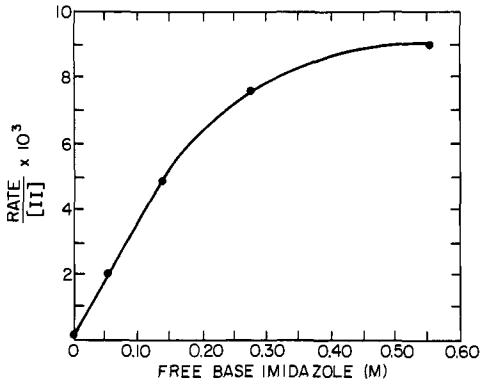


Figure 3. Plot of the hydrolysis (rate)/[II] vs. the molar concentration of free base imidazole in a pH 7.1 buffer. From (rate)/[II] = k_1 + k_2[Im]^n, the initial linearity where [Im] < 0.30 M indicates that n = 1: k_1 = y intercept and k_2 = slope for the linear section of the curve.

faster than the decomposition of III; hence, under these conditions the reaction kinetics could be monitored without interference from the subsequent hydrolyses. The following sections will be devoted to a consideration of (a) the general kinetic features of the reaction and the role played by free imidazole, (b) the effect of pH changes, (c) the influence of temperature, and (d) the role of water.

The rate of hydrolysis of II in unbuffered 20% aqueous tetrahydrofuran was found to be accelerated by the free imidazole liberated during the conversion of II to III. Hence, the reaction has the appearance of an autocatalytic transformation in which the kinetic characteristics change as the reaction proceeds. Initially, the reaction is first order with respect to II. At later stages in the reaction, as free imidazole is liberated, the rate expression becomes complex and can be formulated as rate = k_1[II] + k_{cal}[Imid]^n[II].

The autocatalytic characteristic could be masked by the addition of free imidazole buffer to the system in order to reduce the relative changes in free imidazole and hydrogen ion concentrations as the reaction proceeded (Figure 2). Under these conditions, it was found that the rate changes, at different concentrations of free imidazole, were compatible with a value of 1 for the exponent, n, in the rate equation (Figure 3). In reality, the catalytic effect of free imidazole was so great that, after roughly 40% of the reaction had been completed in unbuffered media or in the presence of added imidazole, the noncatalyzed component, defined by k_1, was insignificant compared to the catalyzed part. Hence, beyond this point the rate expression simplified to: rate = k_{cal}[Imid][II]. Indeed, when high concentrations of imidazole buffer (>0.10 M) were present, a second-order plot of [Imid][II] against time gave a straight line (Figure 4). This indicated that most of the reaction rate could be accounted for by the imidazole-

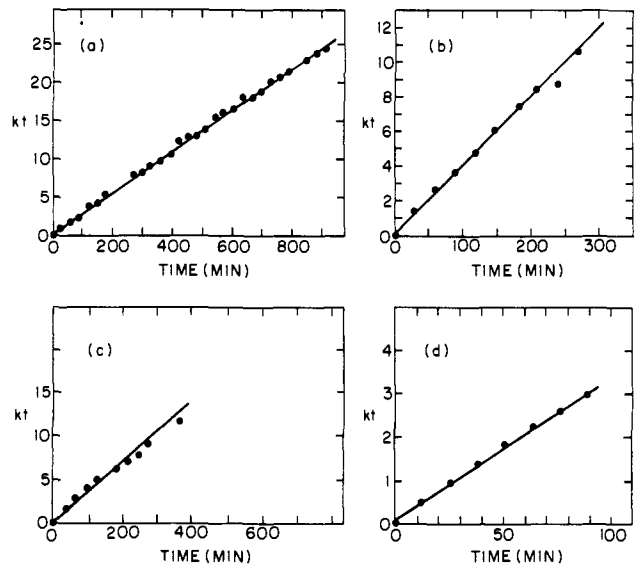


Figure 4. Plots of hydrolysis rate at 28 °C for the conversion of II to III vs. time in 20 vol % aqueous tetrahydrofuran buffered to pH 7.1 with imidazole (a, 0.10 M; b, 0.25 M; c, 0.5 M; d, 1.0 M imidazole). The initial concentration of II was 0.0346 M. The rate expression was kt = $[1/([II]_0 + [Imid]_0)][\ln [([Imid]_0 + x)/([II]_0 - x)] - \ln ([Imid]_0/[II]_0)]$.

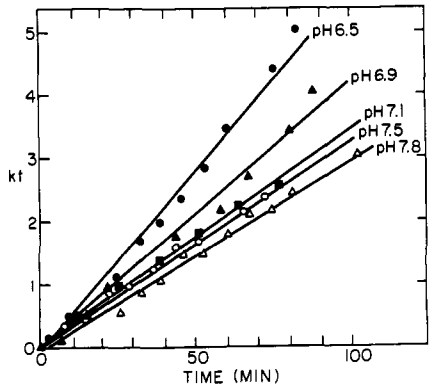


Figure 5. Second-order plots for the rates of hydrolysis of II to III as a function of pH. The solvent was 20 vol % aqueous tetrahydrofuran buffered with imidazole (1.0 M). The initial concentration of II was in the range between 33.21 and 42.33 mM. The rate expression used is the same as that shown for Figure 4.

catalyzed pathway. At pH 7.1 the maximum catalytic effect occurred when the concentration of free-base imidazole was approximately 0.4 M (Figure 3). Under these conditions the reaction can be considered as a pseudo-first-order reaction in [II]. At low imidazole concentrations (<0.25 M), a plot of rate vs. added imidazole concentration approached a straight line (Figure 3), and this suggests that, in this concentration region, the basicity of imidazole is not counteracted noticeably by the acidity of the POH groups.

The kinetic data for the variation of hydrolysis rate with changes in added imidazole concentration are summarized in Table II and in Figure 3. The initial linearity of the line in Figure 3 is an indication that the rate of the reaction is dependent on the first-order concentration of imidazole (present in the free-base form). The catalytic effect in imidazole is substantial. This is reflected in the value of k_{cal} = 3.48 × 10^{-2} (28 °C) compared to the uncatalyzed rate, k_1 = 1.32 × 10^{-4} (determined from an extrapolation of the line in Figure 2 to an imidazole concentration of 0). Because the catalytic influence by imidazole is a direct one when the concentration is less than 0.25 M, only one imidazole molecule is involved in the rate-controlling step.

The rate of hydrolysis of II is only slightly dependent on pH changes within the pH range of 6.5–7.8. This is illustrated by the plots of the second-order equation (see the Experimental Section) in Figures 5 and 6. These rates are for pseudo-first-order

Table II. Reaction Rates for the Hydrolysis of II and III

[II],[a] M	[Imid], M	[Imid],[b] M	k_{2nd}, 1/(M min)[c]	rate, M/min	k_{2nd}, 1/(M min)[d]	k_{obsd}, min^{-1}[e]	pH	temp, °C	k_{1st}, min^{-1}[f]
0.034 57[g]	0.10	0.05499	0.025	7.1×10^{-5}[h]	0.037	2.1×10^{-3}	7.1	28.0	0.002
0.034 57[g]	0.25	0.1375	0.036	1.7×10^{-4}[h]	0.036	4.9×10^{-3}	7.1	28.0	0.006
0.034 57[g]	0.50	0.2750	0.031	2.6×10^{-4}[h]	0.028	7.6×10^{-3}	7.1	28.0	0.012
0.034 57[g]	1.00	0.5500	0.032	3.2×10^{-4}[h]	0.017	9.1×10^{-3}	7.1	28.0	0.019
0.034 57[g]	1.00	0.4014	0.060	4.8×10^{-4}[i]	0.035	1.4×10^{-2}	6.5	28.0	0.026
0.033 21[g]	1.00	0.5000	0.046	6.9×10^{-4}[i]	0.042	2.1×10^{-2}	6.9	28.0	0.024
0.034 57[g]	1.00	0.5500	0.032	3.2×10^{-4}[i]	0.017	9.1×10^{-3}	7.1	28.00	0.019
0.042 33[g]	1.00	0.6342	0.033	5.7×10^{-4}[i]	0.021	1.3×10^{-2}	7.5	28.00	0.022
0.034 57[g]	1.00	0.7100	0.033	4.5×10^{-4}[i]	0.018	1.3×10^{-2}	7.8	28.00	0.024
0.034 57[g]	1.00	0.5500	0.060	8.9×10^{-4}[j]	0.093	2.6×10^{-2}	7.1	38.00	0.035
0.034 57[k]	1.00	0.4775	0.011	1.6×10^{-4}[j]	0.009	4.5×10^{-3}	7.1[l]	28.00	0.005

[II],[m] M	[Tris],[n] M	[Tris],[n,b] M	rate, M/min	k_{2nd}, 1/(M min)	k_{obsd}, min^{-1}[e]	pH	temp, °C	k_{1st}, min^{-1}
0.031 04[g]	0.054	0.019	1.2×10^{-5}[o]	0.020[p]	3.8×10^{-4}	7.4	22.5	5.6×10^{-4}
0.015 52[g]	0.054	0.019	4.2×10^{-6}[o]	0.014[p]	2.7×10^{-4}	7.4	22.5	3.4×10^{-4}
0.007 759[g]	0.054	0.019	2.0×10^{-6}[o]	0.013[p]	2.6×10^{-4}	7.4	22.5	2.7×10^{-4}
0.031 04[g]	0.054	0.019	1.2×10^{-5}[o]	0.020[p]	3.8×10^{-4}	7.4	22.5	5.6×10^{-4}
0.031 04[k]	0.054		5.8×10^{-6}[o]		1.9×10^{-4}	7.4[l]	22.5	2.6×10^{-4}
0.031 04[g]	0.054	0.019	4.1×10^{-5}[q]	0.025[p]	1.3×10^{-3}	7.4	35.6	2.1×10^{-3}
0.031 04[g]	0.054		1.9×10^{-5}[q]		6.0×10^{-4}	7.4[l]	35.6	1.1×10^{-3}

[a] The Nicolet program NTCFT was used. [b] Free-base form. [c] Calculated by using the equation shown in the text of the Experimental Section.[20] [d] Calculated from the equation rate = k_{2nd}[Imid][II]. Rate = Δ[II]/Δt. [e] k_{obsd} = rate/[II]. [f] $-\ln$ [II] = $k_{1st}t$. [g] The solvent was 20 vol % aqueous THF. [h] After 90 min. [i] After 50 min. [j] After 25 min. [k] The solvent was 20 vol % D_2O–THF. [l] Adjusted according to the equation pH = pD(meter reading) + 0.41.[19] [m] The Nicolet program NFTNMR was used. [n] Media buffered with tris(hydroxymethyl)-aminomethane, [Tris]. [o] After 1400 min. [p] Rate = k_{2nd}[Tris][b][II]. Rate = Δ[II]/Δt. [q] After 480 min.

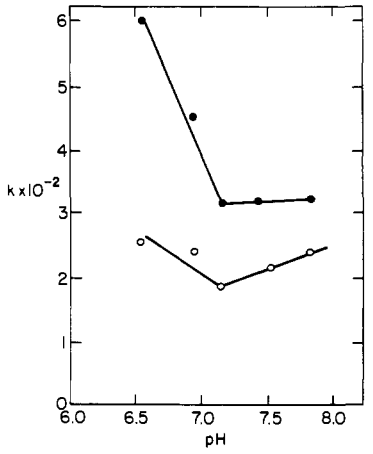


Figure 6. pH–(rate) profile for the hydrolysis of II at 28 °C in a 1.0 M imidazole buffer. The concentration of free-base imidazole exceeded 0.4 M, while the initial concentration of II was between 33.21 and 42.33 mM: ●, second-order plot; ○, pseudo-first-order plot.

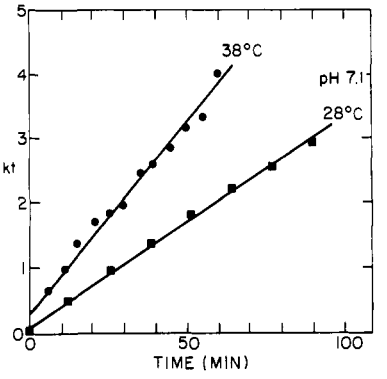


Figure 7. Second-order plot (from expression shown for Figure 4) for the hydrolysis of II (34.57 mM) to III at two temperatures, in 20 vol % aqueous tetrahydrofuran buffered to pH 7.1 with imidazole (1.0 M).

conditions, with an appreciable excess of imidazole present in the buffered systems. However, outside this pH range in acidic or basic media, the rate of hydrolysis is accelerated markedly.

The second-order rate constants for the hydrolysis of II at 28 and 38 °C (at a concentration of [II] of 0.03457 M in 1.0 M imidazole buffer at pH 7.1) were 0.0324 and 0.0603, respectively (Figure 7). The calculated activation energy was 11.5 kcal/mol, $\Delta G^{\ddagger}$ was 22.1 kcal/mol, $\Delta H^{\ddagger}$ was 10.9 kcal/mol, and $-\Delta S^{\ddagger}$ was 37.2 eu, cal/K mol. The activation energy was lower than the values found previously for the basic hydrolysis of fluoroalkoxycyclophosphazenes, $[NP(OCH_2(CF_2)_xCF_3)_2]_{3 \text{ or } 4}$.[4] It was higher than the values reported for spiroarylenedioxyphosphazenes[3] and was in the same range as those measured for (*m*-nitrophenoxy)- or (*p*-nitrophenoxy)cyclophosphazenes.[3]

The role of water in this reaction was investigated by the study of a deuterium isotope effect. The experiments were performed by a comparison of the hydrolysis rates of II in 20 vol % water in tetrahydrofuran (Figure 4d) and in 20% D_2O in tetrahydrofuran, buffered either to pH 7.4 with 0.054 M tris(hydroxymethyl)aminomethane or to pH 7.1 with 1.0 M imidazole. The different fractions of imidazole present in the free-base form in the two different media were taken into account. The hydrolysis rate was 3.06 times faster in the water–THF medium than in D_2O–THF at pH 7.1. This suggests that a proton is involved in the rate-determining step, and this, in turn, implies that the catalytic effect of imidazole can be traced to its influence as a *general* basic catalyst rather than to a specific nucleophilic effect. This viewpoint is supported by the observation that *N*-methylimidazole or tris(hydroxymethyl)aminomethane catalyzes the hydrolysis at approximately the same rate as does imidazole (Table III). Thus, the hydrolysis of II appears to resemble the general-base-catalyzed hydrolysis proposed for acetylimidazole.[10-14]

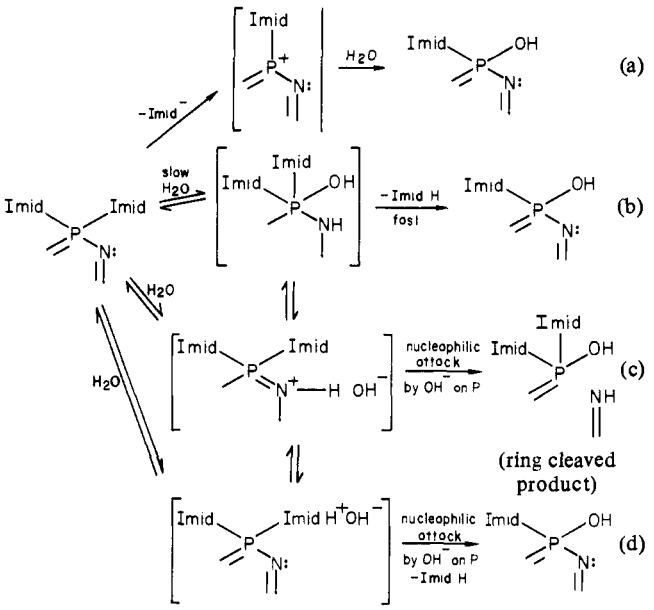
Table III. Hydrolysis Rates in the Presence of Different Added Bases[a,b]

[II], M	10^6(rate) (Δt, min)[c]	10^4(rate)/ [II][d]	base (0.054 M)
0.017 97	6.6 (2563)	3.6	*N*-methylimidazole
0.017 97	7.2 (2563)	4.0	imidazole
0.015 52	3.5 (2563)	2.2	tris(hydroxymethyl)-aminomethane

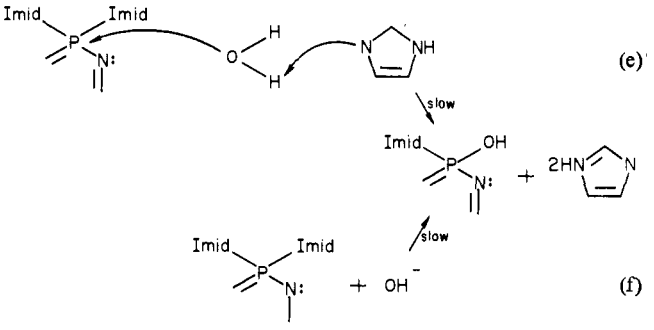
[a] pH 7.4. Solvent was 20 vol % aqueous tetrahydrofuran. [b] Temperature 22.5 °C. [c] Rate = Δ[II]/Δt, M/min. [d] Rate/[II], 1/min.

(10) D. G. Oakenfull and W. P. Jencks, *J. Am. Chem. Soc.*, **93**, 178 (1971).

Scheme I



Scheme II



Reaction Mechanism for the Hydrolysis of II. Consider first the initial uncatalyzed hydrolysis of II by a first-order process before the liberation of free imidazole. Four plausible mechanistic possibilities exist. (a) A slow ionization of imidazole could occur from phosphorus, followed by a fast reaction of the cyclophosphazenium cation and the imidazolyl anion with water (Scheme I). This is the least appealing mechanism because of the high activation energy anticipated for the ionization step. (b) A molecule of II might react with a water molecule to form a pentacoordinate transition state from which an imidazole molecule could be lost. Mechanisms c and d require the interaction of II with water with coordination of a proton and generation of hydroxide ion. These latter mechanisms would require displacement of imidazole by hydroxide ion in a manner reminiscent of the hydrolysis of alkoxy- and aryloxyphosphazenes.[3,4] pK_a Data are not available for the skeletal nitrogen atoms of this phosphazene, and it is not yet possible to predict whether mechanism c or d would be preferred. Hence, the absence of any detectable ring cleavage in this reaction constitues marginal evidence against pathway c. Mechanisms b and d are kinetically indistinguishable.

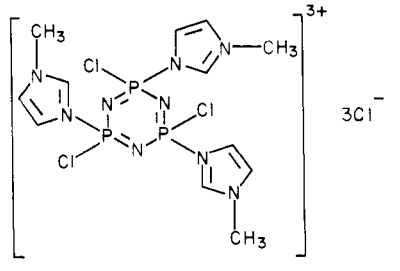
Second, in the presence of free imidazole, the rate acceleration can be ascribed either to the role of imidazole as an expeditor of an attack by a water molecule on II (mechanism e of Scheme II) or to its ability to liberate free hydroxide ion (mechanism f of Scheme II). Mechanism e represents a general-base-catalyzed process, while mechanism f is a *specific*-base-catalyzed reaction. Both mechanisms e and f could account for the rate accelerations observed for the hydrolysis of II in *unbuffered* media. However, three facts favor mechanism e in *buffered* media. First, rate accelerations are observed with increased concentrations of imidazole, even when the concentration of hydroxide ions is fixed at pH 7.1 (see Figures 2 and 3). Second, the rates for the hydrolysis of II in the buffered media are relatively independent of pH within the pH range of 6.5–7.8 (see Figures 5 and 6). Thus, small increases in the concentrations of hydroxide ions should not dramatically enhance the rates of the hydrolysis reactions. Mechanism f does not account for these two facts. Finally, the rates of hydrolysis of II depend on the amounts of free-base imidazole present. As discussed, this effect can be attributed to the role of imidazole as a *general* base. A rate-limiting proton transfer assisted by imidazole, as shown in mechanism e, accounts for all three observations. Mechanism e resembles the process proposed by others[10–14] for the hydrolysis of acetylimidazole.

The second-order mechanism e can be used satisfactorily to describe the hydrolysis reactions only within the pH range of 7.1–7.8. A dramatic increase occurs in the *second-order* rate constants when the pH is changed from pH 7.1 to 6.5 (Figure 6), and changes in the mechanism and the characteristic kinetics seem probable under these new reaction conditions. Clearly, additional studies are required to determine the roles played by imidazole and acids within that pH range.

Reactions of Sodium Trifluoroethoxide with II. The ease of displacement of imidazole from II by hydroxide ion or water is reminiscent of the displacement of chlorine from I by wide variety of nucleophiles.[7,8] Hence, the prospect exists that II (or its polymeric analogue) might be used as an intermediate for the synthesis of a range of organophosphazenes that are not readily accessible through the use of I. Therefore, exploratory studies were undertaken to examine the behavior of II in the presence of a variety of potential nucleophiles. The results were monitored by ^{31}P NMR spectroscopy.

Sodium trifluoroethoxide reacted with II at 25 °C to yield hexakis(trifluoroethoxy)cyclotriphosphazene, $[NP(OCH_2CF_3)_2]_3$. However, no reaction was detected between ethanol or trifluoroethanol and II under the same conditions. *N*-Methylimidazole did not react with II at room temperature. This reagent is probably not a strong enough base to displace the imidazole anion from II.

Reaction of *N*-Methylimidazole with $(NPCl_2)_3$ (I). Although imidazole interacts with I to yield II, *N*-methylimidazole was found to react with I to yield a yellow salt. This species was *not* the product of a cleavage of the nitrogen–methyl bond (as might perhaps have been supposed by comparison with the reported reaction of trimethylamine with I).[15] Instead, elemental analyses were consistent with the formation of species that possessed the composition of I *plus* two to four *N*-methylimidazole units. The proposed structure of one of these products is shown in VII. The



VII

retention of the cyclotriphosphazene ring in VII was demonstrated by the reaction of VII with sodium trifluoroethoxide to yield hexakis(trifluoroethoxy)cyclotriphosphazene, $[NP(OCH_2CF_3)_2]_3$. Compound VII reacted vigorously and exothermically with water, trifluoroethanol, methylamine, *n*-butylamine, or imidazole, with

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(12) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).
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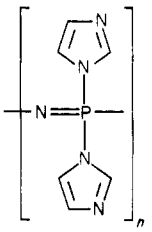
(14) M. L. Bender and L. J. Brubacher, "Catalysis and Enzyme Action", McGraw-Hill, New York, 1973.
(15) A. B. Burg and A. P. Caron, *J. Am. Chem. Soc.*, **81**, 836 (1959).

the liberation of *N*-methylimidazole or its hydrochloride. *n*-Butylamine reacted with VII to give hexakis(*n*-butylamino)cyclotriphosphazene, $[NP(NHC_4H_9)_2]_3$, methylamine yielded $[NP(NHCH_3)_2]_3$, and imidazole gave II. These products were identified unambiguously by ^{31}P NMR comparisons with authentic samples. It is of interest that imidazole is sufficiently basic to displace the *N*-methylimidazolium ion.

Relationship to Macromolecular Synthesis. The reactions discussed in this paper are model studies for those of the analogous linear high polymers.[16] The long-range objective of the high polymeric studies is the synthesis of macromolecules that can function as carrier molecules for coordinated species such as transition metals,[1] metalloporphyrins,[6] or for covalently-bound chemotherapeutic agents[17] and which can undergo degradation in a biological environment to harmless small molecules.

Synthesis and mechanistic work with macromolecules is nearly always more demanding than the analogous studies carried out with small molecules. Hence, the model studies reported here have a special significance. First, it seems clear from the model studies that a high polymer of formula VIII would be hydrolytically



VIII

unstable at biological pH conditions and would decompose eventually to imidazole, phosphate, and ammonia. Second, the prospect exists that the salt formation demonstrated with *N*-methylimidazole could occur with imidazole in a macromolecular system to cross-link the chains. Preliminary evidence has been obtained that both of these suppositions are correct.

Experimental Section

Materials. Hexachlorocyclotriphosphazene (I) (Ethyl Corp.) was purified by two recrystallizations from hexane and by two sublimations at 50 °C (0.05 torr). Imidazole (Eastman) was recrystallized from benzene and then sublimed at 50 °C (0.05 torr). *N*-Methylimidazole was distilled under vacuum before use, and triethylamine was distilled from barium oxide. Tetrahydrofuran (Fisher) was distilled from sodium–benzophenone ketyl. Anhydrous methylamine (Matheson), trifluoroethanol (Fluorocarbon Chem), ethanol (Fisher), tris(hydroxymethyl)aminomethane (Fisher), and deuterium oxide (Bio-Rad) were used as received.

NMR Spectra and Kinetic Technique. The ^{31}P NMR spectra of II and III were followed as a function of time with the use of a Jeol PS 100 NMR spectrometer operated at 40.5 Hz in a ^1H-decoupled Fourier transform mode, with pulsing at 10–15-s intervals and with a 40–45° nuclear flip angle. The spectra were transformed by the use of a Nicolet 1080 data processor employing the programs NFTNMR and, after revision, NTCFT. When the program NFTNMR was employed, 500 scans were required to give well-resolved spectra. Program NTCFT required only five scans to give a well-resolved spectrum. The ^{31}P spectra consisted of a singlet from unreacted II plus an AB_2 peak pattern from III. Thus, the actual concentrations of II and III were calculated from the peak area integrations and the known initial concentration of II. This was accomplished automatically when program NTCFT was used. The peak integrations were accurate to less than ±3%.

pH measurements were made with a Perkin-Elmer C-28 pH meter. The buffer systems were prepared from weighed amounts (Table II) of imidazole or tris(hydroxymethyl)aminomethane in 20% water in tetrahydrofuran, followed by an adjustment of the medium to the desired pH by the addition of concentrated hydrochloric acid. The buffer solutions that contained D_2O were corrected to the pH equivalent of the H_2O-containing systems by the use of the equation, pH = pD + 0.41.[18]

Seven types of reaction conditions were used for the kinetic analyses: (1) reaction in media buffered to pH 7.4 with 0.054 M tris(hydroxymethyl)aminomethane; (2) five sets of reactions buffered with 1 M imidazole to pH 6.5, 6.9, 7.1, 7.5, and 7.8; (3) four sets of hydrolyses buffered to pH 7.1 with 0.10, 0.25, 0.50, and 1.0 M imidazole; (4) reactions buffered to pH 7.4 in the presence of added imidazole or *N*-methylimidazole (Table III). Product analysis and preliminary kinetic studies were carried out at 22.5 °C (room temperature) or 35.6 °C (thermally-regulated water bath), and the kinetic analyses performed entirely within the NMR spectrometer were at either 28.0 or 38.0 °C.

The overall equation used for the analysis of the kinetic data was

$$kt = \left(\frac{1}{[II]_0 + [Imid]_0}\right)\left[\ln\left(\frac{[Imid]_0 + x}{[II]_0 - x}\right) - \ln\left(\frac{[Imid]_0}{[II]_0}\right)\right]$$

where x is the molar concentration of II reacted at time t and $[II]_0$ and $[Imid]_0$ are the concentrations of II and imidazole, respectively, at $t = 0$. An exponential method was employed to establish the order of the reactions for various concentrations of imidazole at a fixed concentration of II. The concentration of imidazole in the free-base form in the buffered media was calculated from the Henderson–Hasselbach equation by defining the pK_a of imidazole as 6.9 (or 7.2 in D_2O) and from a knowledge of the pH of this medium (pH 7.1).

Preparation of Hexakis(imidazolyl)cyclotriphosphazene (II). To a stirred solution of imidazole (2.345 g, 0.0345 mol) in tetrahdydrofuran (150 mL) was added dropwise, under nitrogen, hexachlorocyclotriphosphazene (I) (1.00 g, 2.874×10^{-3} mol) dissolved in tetrahydrofuran (50 mL). The reaction mixture was stirred vigorously for 1 h and was then filtered under nitrogen. The solvent was removed from the filtrate with the use of a rotary evaporator, and the solid residue was either washed with tetrahydrofuran (≃20 mL) to remove unreacted imidazole and leave II in about an 80% yield or recrystallized directly from hot tetrahydrofuran (≃50 mL) to give II as white crystals (≃20% yield). A parent ion was found for II in the mass spectrum at *m/e* 537 amu (calculated for II 537), with successive fragments being observed that corresponded to the loss of from one to three imidazole residues. Three broad resonances were found in the ^1H NMR spectrum at 8.27, 7.22, and 7.08 ppm (relative to an external Me_4Si reference in D_2O solvent) with relative peak integrations of 1:1:1. A single peak was found in D_2O solvent for the ^{31}P NMR spectrum at 2.35 ppm relative to an external 85% phosphoric acid reference. Compound II was soluble in chloroform, slightly soluble in tetrahydrofuran and water, and insoluble in benzene, ether, petroleum ether, and acetonitrile. Compound II, after recrystallization from tetrahydrofuran, decomposed between 254 and 258 °C. Anal.[19] Calcd for $C_{18}H_{18}N_{15}P_3$: C, 40.07; H, 3.46; N, 39.03; P, 17.32. Found: C, 40.23; H, 3.35; N, 35.11; P, 17.32. A single-crystal X-ray analysis of II has been completed and has been used to confirm the structure.[20]

Hydroxypentakis(imidazolyl)cyclotriphosphazene (III). Compound III was prepared by the hydrolysis of II in 20% aqueous tetrahydrofuran solvent and was isolated as a colorless or light yellow colored oil by the removal of the solvent with the use of a rotary evaporator. It was soluble in water, tetrahydrofuran, and alcohols but was insoluble in hydrocarbons and toluene. The characterization of III is described in an earlier section of the paper.

Reaction of $NaOSi(C_6H_5)_3$ with $(NPCl_2)_3$ (I). Triphenylsilanol (1.59 g, 0.00575 mol) was dissolved in tetrahydrofuran (100 mL) and was added cautiously to a stirred suspension of excess sodium hydride in tetrahydrofuran (75 mL). The reaction mixture was filtered under nitrogen and was added dropwise in tetrahydrofuran (100 mL). After the mixture had been stirred for 4 h, the reaction mixture was concentrated and examined by ^{31}P NMR spectroscopy. The spectrum was an AB_2 spin system as reported in Table I. A portion of the concentrate was evaporated to dryness to yield a solid that was washed successively with hexane and toluene. The insoluble white residue melted at 225–227 °C and showed a parent ion in the mass spectrum at 534 amu which was consistent with the presence of $(C_6H_5)_3SiOSi(C_6H_5)_3$. Imidazole (5 g, 0.0735 mol) was added to the remainder of the concentrate, and the mixture was agitated vigorously. After centrifugation to remove the imidazole hydrochloride, the supernatant liquid was subjected to ^{31}P NMR analysis. The spectrum was identical with that of III formed directly by hydrolysis of II (see Table I).

Synthesis of (Trifluoroethoxy)pentakis(imidazolyl)cyclotriphosphazene (VI). (Trifluoroethoxy)pentachlorocyclotriphosphazene (V)[9] (0.5 mL) was allowed to react with excess imidazole (5 g, 0.0735 mol) in tetrahydrofuran (100 mL). The mixture was filtered, and the solution was

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(17) H. R. Allcock, T. J. Fuller, and K. Matsumura, unpublished work.
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(19) Elemental analyses by Galbraith Laboratories, Knoxville, TN.
(20) R. J. Ritchie, T. J. Fuller, and H. R. Allcock, *Inorg. Chem.*, **19**, 3842 (1980).

evaporated to dryness. The white, crystalline residue, after recrystallization from diethyl ether, gave a mass spectrum with a parent ion at 569 amu. It melted at 82–83 °C and had a ^{31}P NMR spectrum that was interpreted as an AB_2 spin system, as reported in Table I.

Displacement of Imidazole from II by $NaOCH_2CF_3$ To Form $[NP(OCH_2CF_3)_2]_3$. Compound II (0.961 g, 1.79×10^{-3} mol) in tetrahydrofuran (100 mL) was placed in a round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, and an addition funnel. To this solution was added sodium trifluoroethoxide in tetrahydrofuran, prepared from sodium (1.25 g, 0.054 mol) and excess trifluoroethanol (a fivefold excess of $NaOCH_2CF_3$ over that required for total imidazole replacement). The reaction mixture was stirred overnight at 23 °C, and the excess sodium trifluoroethoxide was deactivated with a small amount of aqueous hydrochloric acid. The solvent was then removed, and the resultant oil was dissolved in benzene and washed with water. The benzene layer was separated, and the solvent was removed. Sublimation yielded a white solid (0.2922 g, 23%), mp 44–49 °C (lit. 49–50 °C). A mass spectrum showed a parent ion at 729 amu that indicated the presence of $[NP(OCH_2CF_3)_2]_3$. No partly substituted phosphazene species were detected from the mass spectrum, and no evidence of peaks from imidazolyl residues were seen.

Reaction between *N*-Methylimidazole and $(NPCl_2)_3$. All of the following manipulations were carried out under a nitrogen atmosphere. *N*-Methylimidazole (1.5 g, 0.03 mol) was vacuum-distilled from potassium hydroxide and was added to a solution prepared by dissolving $(NPCl_2)_3$ (1 g, 0.003 mol) in tetrahydrofuran (70 mL). A yellow precipitate developed immediately following addition of the *N*-methylimidazole. The reaction mixture was stirred for 20 min, and the yellow precipitate was collected by filtration in a Schlenk filter funnel. It was washed with tetrahydrofuran and dried under vacuum. The product was insoluble in tetrahydrofurn, benzene, acetonitrile, and diethyl ether. It reacted with water or ethanol with decomposition. This salt proved difficult to purify because of its insolubility and sensitivity to hydrolysis. Microanalysis of the crude product suggested a composition close to that of VII, but accurate correspondence between theory and the analysis results could not be obtained.

Reactions of Species of Type VII. A stirred suspension of VII (prepared as described above) (0.5 g) in tetrahydrofuran (100 mL) was treated under dry nitrogen with excess *n*-butylamine (6.3 g, 0.0862 mol). The yellow solid dissolved slowly, with bleaching of the color. A ^{31}P NMR spectrum of the concentrated reaction mixture showed a clean spectrum identical with that of an authentic sample of $[NP(NHC_4H_9)_2]_3$ (see Table I). Similarly, VII (0.5 g) was allowed to react with imidazole (5.8 g, 0.862 mol) in tetrahydrofuran (100 mL). A ^{31}P NMR spectrum showed the presence of II only (Table I). Methylamine (100 mL) reacted with a stirred suspension of VII (0.5 g) in tetrahydrofuran (100 mL) at 0 °C during 2 days under dry nitrogen to yield $[NP(NHCH_3)_2]_3$, identified by its ^{31}P NMR spectrum (Table I).

A solution of sodium trifluoroethoxide, prepared from trifluoroethanol (8.62 g, 0.0862 mol) and sodium hydride in tetrahydrofuran (175 mL), was filtered and added to a stirred solution of VII (0.5 g) in tetrahydrofuran (100 mL). After reaction for 2 days at 25 °C the mixture was concentrated. A ^{31}P NMR spectrum gave unambiguous evidence for the presence of $[NP(OCH_2CF_3)_2]_3$ as the only phosphorus-containing species present (see Table I).

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Organometallic Phosphazenes: Synthesis and Rearrangement of Propynyl- and Propadienylcyclotriphosphazenes

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Abstract: A new series of 1,1-dialkyltetrachlorocyclotriphosphazenes with prop-2-ynyl (VI), prop-1,2-dienyl (V), and prop-1-ynyl (XII) substituents have been prepared. These syntheses involve the reactions of cuprio- or lithiophosphazene anions (II or IX) with prop-2-ynyl bromide which lead initially to the formation of the prop-2-ynyl complexes (VI). The prop-2-ynyl side group was found to undergo an alumina-initiated rearrangement to the prop-1,2-dienyl group (V), and both compounds VI and V underwent a methyllithium-initiated rearrangement to the prop-1-ynyl derivatives (XII). These organometallic-initiated rearrangements were monitored by ^{31}P NMR spectroscopy. The structural characterization of all the new compounds is described, and the NMR results, together with the various rearrangements, are discussed in terms of electronic interactions between the C_3H_3 group and the phosphazene ring. The formation of the lithiophosphazene anion (IX, R = CH_3) was studied by low-temperature ^{31}P NMR spectroscopy, and the results are discussed in terms of the electron distribution within the phosphazene ring.

The synthesis of phosphazene compounds with organic substituents bound to the skeleton through direct phosphorus–carbon bonds has received considerable attention in recent years.[2-6] Phosphazene compounds that contain unsaturated organic substituents are of particular interest.[5-8] Olefinic or acetylenic side groups can serve as sites for many different types of organic transformations or as building blocks for polymerization or oligomerization reactions.[7] Acetylenic phosphazenes can be used as ligands for transition metals.[8,9]

The general route employed for the synthesis of this class of compounds has, until now, involved the reactions of organometallic reagents with halophosphazenes.[2-4,7,8] a procedure that is often accompanied by side reactions such as ring coupling or skeletal cleavage.[2-4,7,8]

In this paper we describe a new route for the synthesis of organo-substituted phosphazenes with acetylenic side groups. The

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