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Hydrolysis Pathways for Aminophosphazenes[1]

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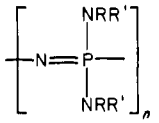
The hydrolysis behavior of the aminocyclotriphosphazenes $(NPR_2)_3$, where R = NH_2, $NHCH_3$, $NHCH_2COOC_2H_5$, $NHCH_2CONHCH_3$, $N_2C_3H_3$ (imidazolyl), $NHCH_2CF_3$, $NHCH_2C_6H_5$, NHC_6H_5, NC_4H_4 (pyrrolyl), NC_4H_8 (pyrrolidino), NC_5H_{10} (piperidino), and NC_4H_8O (morpholino), has been examined in water or aqueous dioxane, acid, and base. The ease of hydrolysis in aqueous dioxane declined with changes in R in the order $N_2C_3H_3$ > $NHCH_2COOC_2H_5$ > $NHCH_2CONHCH_3$ > NH_2 > $NHCH_3$ > NHC_6H_5 > $NHCH_2C_6H_5$ > $NHCH_2CF_3$ > NC_4H_4, NC_4H_8, NC_5H_{10}, and NC_4H_8O. Two different but interconnected mechanistic pathways appear to be followed. In the first, hydrolytic removal of one amino residue from phosphorus occurs to yield species of type $N_3P_3R_5OH$ before cleavage of the phosphazene ring takes place. In the second, cleavage of the phosphazene ring is a fast reaction following protonation of the ring nitrogen atoms. Those compounds which contained amino acid ester or amide side groups hydrolyzed only after prior initial conversion of the ester or amide units to free carboxylic acid groups. Comparisons are made with the behavior of the open-chain high polymers of formula $(NPR_2)_n$, where R = $NHCH_3$, $NHCH_3$ and $N_2C_3H_3$, $NHCH_2COOC_2H_5$, and $NHCH_2CONHCH_3$, and the overall trends are considered in terms of the potential biomedical behavior of these compounds.

High polymeric aminophosphazenes (**1**) are of interest as



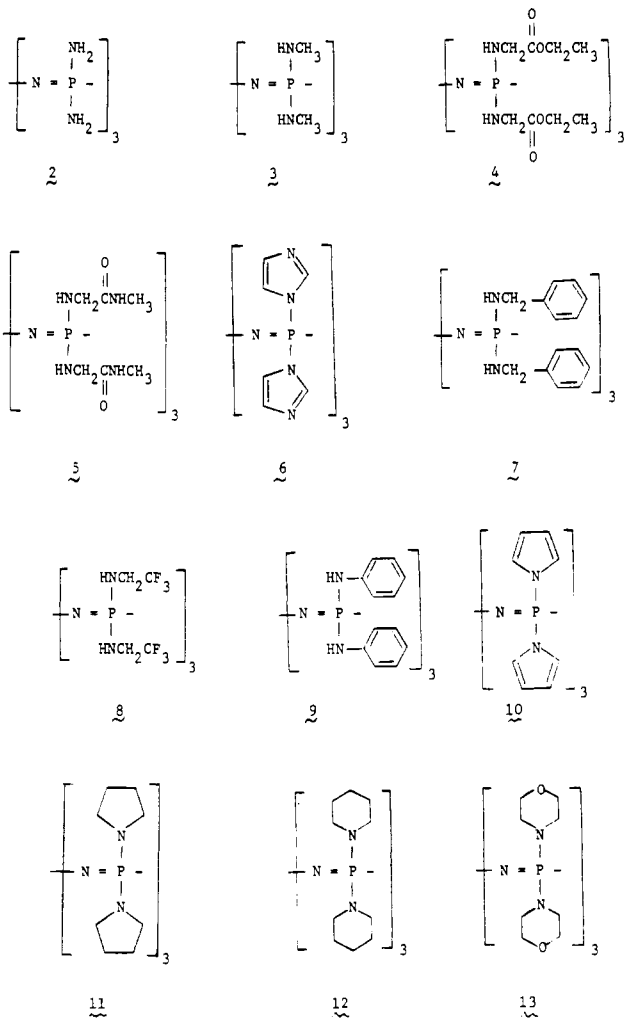
1, $n \simeq 15\,000$

carrier molecules for bioactive agents.[2-13] Inherent in this interest is the need to understand the hydrolytic behavior of such macromolecules. The release of a chemotherapeutic agent from the carrier polymer may requre hydrolytic breakdown of the macromolecular system. Moreover, the use of any polymer in biomedicine requires a prior understanding of the hydrolytic degradation pathways in order to assess the physiological properties of the small-molecule hydrolysis products.

At the present time little is known about the influence of different amino side groups on the hydrolytic behavior of phosphazenes.[6,14] In this study we have examined the general hydrolytic characteristics of several aminophosphazene high polymers and analogous small-molecule cyclic analogues. The latter have been used as models[15] in an attempt to understand the behavior of the high polymers.

Results and Discussion

Synthesis of Cyclic and High Polymeric Phosphazenes. The hexa(amino)cyclotriphosphazenes **2–13** were prepared by the



reactions between hexachlorocyclotriphosphazene (**14**) and ammonia, methylamine, ethyl glycinate, imidazole, benzylamine, trifluoroethylamine, aniline, potassium pyrrolide, pyrrolidine, piperidine, or morpholine. The new compound $[NP(NHCH_2CONHCH_3)_2]_3$ (**5**) was prepared by the reaction between **4** and methylamine. The compounds were characterized by elemental analysis, infrared spectroscopy, mass

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(2) Donaruma, L. G. "Progress in Polymer Science"; Jenkins, A. D., Ed.; Pergamon Press: New York, 1975; Vol. 4, Chapter 1.
(3) Donaruma, L. G., Vogl, O., Eds. "Polymeric Drugs"; Academic Press: New York, 1978.
(4) Renbaum, A., Shen, M., Eds. "Biomedical Polymers"; Marcel Dekker: New York, 1971.
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(6) Allcock, H. R. "Phosphorus-Nitrogen Compounds"; Academic Press: New York, 1972.
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(11) Allcock, H. R.; Fuller, T. J. *Macromolecules* **1980**, *13*, 1338.
(12) O'Brien, J. P.; Allen, R. W.; Allcock, H. R. *Inorg. Chem.* **1979**, *18*, 2230.
(13) Allen, R. W.; O'Brien, J. P.; Allcock, H. R. *J. Am. Chem. Soc.* **1977**, *99*, 3987. Allcock, H. R.; Allen, R. W.; O'Brien, J. P. *Ibid.* **1977**, *99*, 3984.
(14) The hydrolysis of $[NP(NH_2)_2]_3$ (**2**) has been studied in detail: Topelmann, W.; Kroschwitz, H.; Schröter, D.; Patzig, D.; Lehmann, H.-A. *Z. Chem.* **1979**, *19*, 273. Riesel, L.; Hermann, E.; Pätzmann, H.; Somieski, R.; Kroschivitz, H.; Schröter, D.; Lehmann, H.-A. *Ibid.* **1970**, *10*, 466.
(15) Allcock, H. R. *Acc. Chem. Res.* **1979**, *12*, 351

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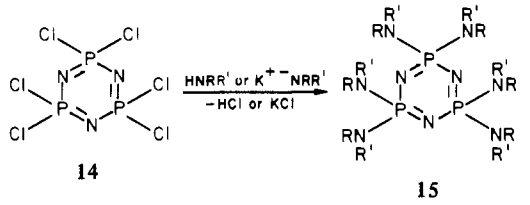


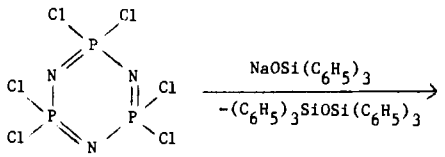
14 15

R or R' = alkyl, aryl, or H

spectrometry, and by ^{31}P and ^{1}H NMR spectroscopy. ^{13}C NMR methods were also used to identify **5**.

Four water-soluble high polymers of formula $[NP(NHCH_3)_2]_n$, $[NP(NHCH_3)_{1.6}(N_2C_3H_3)_{0.4}]_n$ (imidazolyl), $[NP(NHCH_2COOC_2H_5)_2]_n$, and $[NP(NHCH_2CONHCH_3)_2]_n$ were prepared by the interaction of poly(dichlorophosphazene), $(NPCl_2)_n$, with the appropriate amine with the use of techniques developed previously.[9,10,16]

Preparation of Potential Hydrolysis Intermediates by Alternative Routes. Species of type **17** in which one amino group



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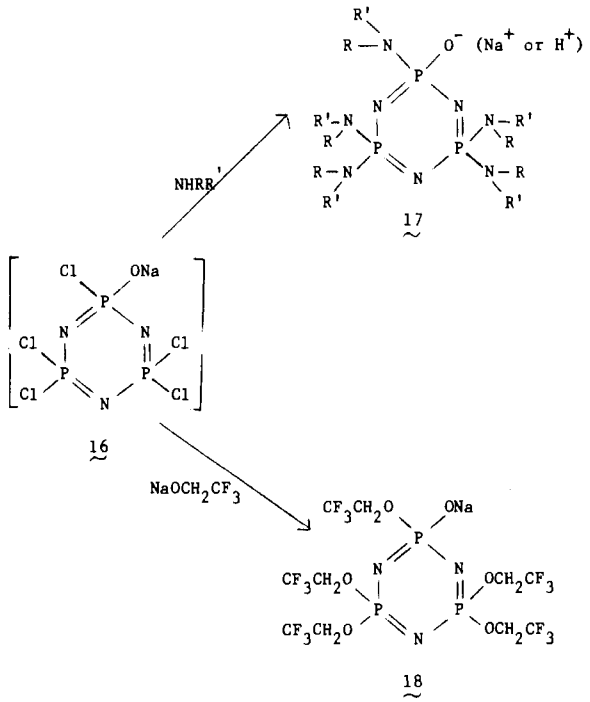

17 16 18

has been replaced by hydroxyl or ONa were postulated as transient hydrolysis intermediates formed from several of the aminocyclotriphosphazenes. These intermediates were prepared independently from **14** by treatment with sodium triphenylsilanolate[17] to form the unstable species $N_3P_3(ONa)Cl_5$ (**16**) and triphenyl silyl ether. Species $N_3P_3(ONa)Cl_5$ reacted with ammonia, methylamine, ethyl glycinate, or imidazole to yield **17**, which were characterized by their ^{31}P NMR spectra and characteristic AB_2 spin systems. The chemical shifts and coupling constants are listed in Table I. Species **17** were too unstable to be isolated. However, **16** reacted with sodium trifluoroethoxide to yield **18**, which was identified by a comparison of its ^{31}P NMR spectrum with that of an authentic sample prepared by an alternative route.[18] Acidification of **18** yielded $N_3P_3(OH)(OCH_2CF_3)_5$, which was purified by sublimation and was identified by ^{31}P NMR spectroscopy and mass spectrometry.

Table I. ^{31}P NMR Data[21]

compd[a]	chem shift, ppm[b] A	B	J,[c] Hz	solvent
2	18.0			H_2O
$N_3P_3(NH_2)_5OH$	5.2	14.5	31.4	H_2O
3	24.6			5 N NaOH
3	21.2			H_2O, C_2H_5OH
$N_3P_3(NHCH_3)_5ONa$	15.5	24.6	36.4	5 N NaOH
$N_3P_3(NHCH_3)_5OH$	7.7	19.2	28.5	H_2O, C_2H_5OH
4	18.9			H_2O
	17.8			C_2H_5OH
20	3.6	15.3	33.0	H_2O
20	2.6	15.0	39.6	C_2H_5OH
$N_3P_3(OCH_2CF_3)_6$	17.7			$C_2H_5OC_2H_5$
$N_3P_3(OCH_2CF_3)_5OH$	11.2	19.2	71.5	$C_2H_5OC_2H_5$
5	20.3			H_2O
21	5.4	16.9	31.4	H_2O
$N_3P_3(NHCH_2CONHCH_3)_5$(ONa)	14.5	22.0	35.0	0.02 N NaOH

[a] Monohydroxy derivatives were prepared from **16**. [b] Where two chemical shifts are given, the spectrum was of the AB_2 type. [c] Coupling constant J_{AB}.

General Comparison of Sensitivity to Hydrolysis. Comparisons were made for compounds **2–13** dissolved in water or aqueous dioxane, in acidic and in basic media. Compounds **2–6** were soluble in water, but **7–13** were not. However, all the compounds were soluble in 30 volume % aqueous dioxane, and the use of this medium provided a broader opportunity for comparisons.

Compound **6** was the only aminocyclophosphazene that hydrolyzed at a detectable rate in water or aqueous dioxane at 25 °C. At 100 °C, compounds **2–6** hydrolyzed (as evidenced by changes in the ^{31}P NMR spectra) but species **7–13** did not. Hydrolysis of **2–6** yielded ammonia, phosphate, and the appropriate side group amine or amino acid. Under these reaction conditions the sensitivity to hydrolysis decreased in the order **6** > **4** > **5** > **2** > **3** > **9** > **7**, **8**, **10–13** on the basis of the speed of changes in ^{31}P NMR spectra and recovered starting materials.

In acidic media at 25 °C, compounds **2–6** degraded to phosphoric acid, ammonium ion, and the appropriate amine salts. The sensitivity to acidic hydrolysis in 1 N or weaker hydrochloric acid decreased in the order **6** > **2** > **4** ≃ **5** > **3**. Hydrolysis was faster in 5 N hydrochloric acid than in 1 N acid. In the stronger acid medium the sensitivity to hydrolysis decreased in the order **6** > **5** > **2** > **3**. The overall speed of hydrolysis in 1 N or stronger acid was higher than in water. The behavior of **7–13** could not be followed because of the insolubility of these species in acidic aqueous dioxane.

In basic media containing 1 N or stronger sodium hydroxide, the rates of hydrolysis were very slow, with the order of decreasing sensitivity to hydrolysis being **6** > **2**, **5** > **3**, **4**, **7–13**. Species **3**, **4**, and **7–13** were essentially stable to strong base for several weeks. Only slight hydrolysis of **2** and **5** occurred in 1 N sodium hydroxide solution during 24 h. But **6** was unstable during the same treatment. In weaker alkaline solutions (between 0.5 and 1 N, the hydrolysis of **2–5** was still a slow process. However, **4**, **5**, and **6** degraded within 24 h when the concentration of sodium hydroxide was reduced to between 0.03 and 0.5 N.

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(17) Zhivukhim, S. M.; Tolstoguzov, V. P.; Ivanov, A. J. *Russ. J. Inorg. Chem.* (*Engl. Transl.*) **1962**, *7*, 1134.
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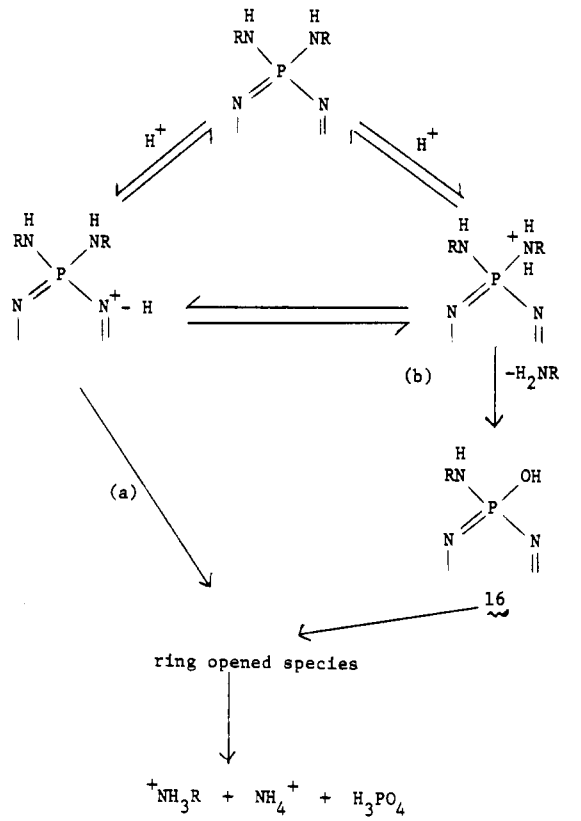
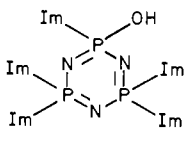
Scheme I



-HNR = $NHCH_3$, $-NHCH_2COHNCH_3$, $-NHCH_2COOCH_2CH_3$, -imidazolyl

Alternative Mechanisms (General Cases). Two mechanisms appear possible in neutral, acidic, or weakly basic media. They involve protonation of atoms in the skeleton or in the side group (Scheme I). Protonation of skeletal nitrogen would lead directly to ring cleavage and, ultimately, to conversion to ammonium ion, phosphoric acid, and the free amine salt (pathway a in Scheme I). Alternatively (pathway b), protonation of a side-group nitrogen, followed by nucelophilic attack by water at phosphorus, would yield a monohydroxycyclophosphazene which, by further hydrolysis, would undergo ring cleavage and eventual degradation. Thus, the detection of a monohydroxycyclophosphazene is the key factor in the identification of this latter pathway. Both mechanisms should be blocked in strongly basic media.

Mechanism of Hydrolysis of 6. The imidazolyl derivative **6** was the most sensitive to hydrolysis of all the compounds studied in water, acid, and strong base. In water, it hydrolyzed exclusively by the loss of one imidazolyl group to yield **19**.[19]



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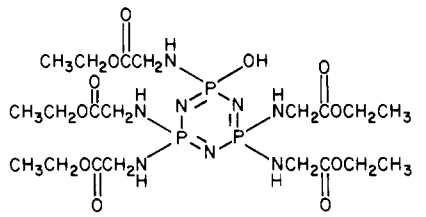
In strong base (1 N or stronger sodium hydroxide solution), compound **6** reacted by the loss of at least two imidazolyl groups but apparently without cleavage of the phosphazene ring. One explanation for the behavior in base is that the pK_a of the hydroxide ion is comparable to that of the imidazolide ion ($\simeq$14.5). Thus, the imidazolide ion becomes a suitable leaving group and can be displaced from phosphorus by hydroxide. In the same way, sodium trifluoroethoxide, which has approximately the same pK_a as hydroxide ion, can displace imidazolyl groups from **6** to yield $[NP(OCH_2CF_3)_2]_3$.[19] Compound **6** was extremely unstable in acidic media; it degraded to phosphoric acid, ammonium ion, and imidazole. At acidities greater than pH 5, compound **6** was decomposed in a few seconds. None of the hydroxycyclophosphazene intermediate **19** was detected in acidic media. The hydrolysis mechanism is complicated because **6** degrades by the loss of more than one imidazolyl group and by ring degradation. Thus, pathways a and b appear to be accessible in acidic media. A detailed study of the hydrolysis of **6** over the pH range 6.8–7.5 has been published.[19]

Mechanisms of Hydrolysis of 4 and 5. Depending on the reaction conditions, hydrolysis of **4** and **5** in water or aqueous dioxane either yields the monohydroxypenta(amino)cyclotriphosphazenes (**20**, **21**) or results in ring degradation to ring-opened species and ultimately to ammonium phosphate, glycine, and ethanol or methylamine. Species **20** and **21** could be isolated when **4** or **5** were heated at 50 °C in water under carefully controlled conditions (see Experimental Section). Compounds **20** and **21** were identified by comparison of their ^{31}P NMR spectra with those of authentic samples prepared by an alternative route. However, at temperatures above 60 °C, hydrolysis yielded ring-cleaved species followed by conversion to the final products mentioned above.

The hydrolysis of **4** or **5** in near neutral media appears to proceed via an initial preliminary hydrolysis of the ester or amide function to the carboxylic acid, followed by hydrolytic cleavage of an *external* P–N bond to yield the mcnohydroxy derivatives **20** and **21**. Evidence for this viewpoint is as follows.

(1) No hydrolytic degradation of **4** or **5** occurred at 25 °C in aqueous media during 30 days. (2) The hydrolysis of **4** or **5** took place rapidly in acidic media. (3) No significant degradation of **4** took place in 100% ethanol, even when the solution was boiled at reflux for 12 h. (4) Ethanol or methylamine were evolved when concentrated aqueous solutions of **4** or **5** were heated. Subsequent ^{31}P NMR analysis of the solutions revealed the presence of **20** or **21**. (5) A solution of $[NP(NHCH_2COONa)_2]_3$, prepared by the ester hydrolysis of **4** in 1 N or stronger sodium hydroxide solution, was stable in the basic medium but was hydrolyzed rapidly to ring-cleaved products when acidified with 6 equiv of hydrochloric acid. (6) Attempts to isolate $[NP(NHCH_2COOH)_2]_3$ by the reaction of **4** with trimethylsilyl iodide[20] were not successful. Apparently once the carboxylic acid group is formed, the phosphazene hydrolyzes rapidly (Scheme II).



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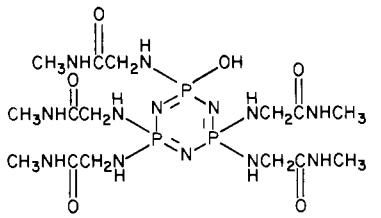

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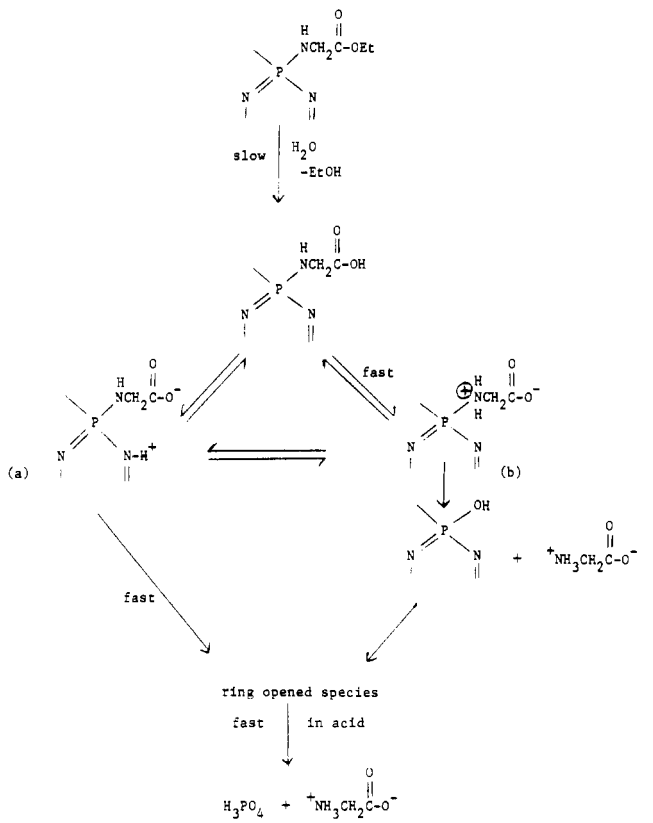
(19) Allcock, H. R.; Fuller, T. J. *J. Am. Chem. Soc.* **1981**, *103*, 2250.

(20) Acyl esters, after treatment with trimethylsilyl iodide, can be hydrolyzed to carboxylic acids: Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968.

Scheme II



The hydrolytic ring-cleavage mechanism appeared to be the principal pathway for the breakdown of **4** and **5** in 1 N or stronger hydrochloric acid. However, intermediate **21** was detected in acidic media. Thus, compound **5** has a slightly more favorable tendency to follow pathway b than does **4**.

In strongly basic media, the ester groups of **4** reacted to yield the stable $[NP(NHCH_2COONa)_2]_3$ and ethanol (Scheme III). No subsequent cleavage of phosphorus–nitrogen bonds could be detected. The ^{31}P NMR spectrum of **4** remained unchanged for several months at a concentration of 0.035 M in 1 N sodium hydroxide solution. In weakly basic media (less than 1 N base) both carboxylate salt and carboxylic acid groups were present, and the latter induced hydrolysis by both pathways a and b in a manner similar to that detected for reactions in neutral media (Scheme II). The hydrolysis of **4** proceeded faster at pH 8.7 than at pH 7 or pH 5, presumably because the rate of phosphazene hydrolysis is critically dependent on the presence of carboxylic acid units.

The hydrolysis of **5** in weakly basic media (0.035 M solutions in <1 N sodium hydroxide solution) proceeded via a mechanism that apparently involved the slow formation of carboxylic acid groups, followed by a ring-cleavage process.

Thus, in neutral, acidic, or weakly basic media, the formation of a carboxylic acid group accelerates the hydrolytic breakdown of **4** or **5**. This provides a valuable method for the introduction of sites of hydrolytic instability into a macromolecular system.

Influence by the Different Side Groups. The extreme sensitivity of imidazolylphosphazenes might be ascribed to three factors. (1) The imidazolyl groups are sufficiently small that the phosphorus atoms of **6** are exposed to nucleophilic attack by water or hydroxide ions. (2) Imidazolyl groups are resonance stabilized in a manner which requires donation of the nitrogen lone pair electrons at the linkage site into the imidazolyl ring rather than into the phosphazene ring. This would weaken the exocyclic P–N bond relative to those in the other compounds studied. (3) Protonation of the dicoordinate imidazolyl nitrogen would favor displacement of the imidazolyl group from phosphorus. The third influence appears to be crucial. Explanation 1 is less convincing when the stability of **10** and **11** is considered. Similarly, explanation 2 is not compatible with the resistance to hydrolysis of **10**.

In general, it appears that the key factor in determining hydrolytic stability and hydrolysis mechanism is the degree to which the exocyclic nitrogen atom can donate its lone-pair electrons into the phosphazene ring. Strong donation favors protonation at ring nitrogen atoms, and this leads to phosphazene ring cleavage. Weak donation to the phosphazene ring or donation into the side-group system favors protonation of the side group and subsequent side-group displacement from phosphorus. This explains why the main hydrolytic pathway for **2**–**6** in acidic media involves phosphazene ring cleavage. It is significant that, in neutral media, compounds **4**–**6** have alternative protonation sites. This influences the hydrolytic stability of the exocyclic P–N bond (Schemes II and III).

Aminophosphazene High Polymers. The order of decreasing sensitivity to hydrolysis in water for the high polymers was $[NP(NHCH_3)_{1.6}(N_2C_3H_3)_{0.4}]_n > [NP(NHCH_2COOC_2H_5)_2]_n > [NP(NH_2CH_2CONHCH_3)_2]_n > [NP(NHCH_3)_2]_n$.

The imidazolyl-mixed substituent polymer $[NP(NHCH_3)_{1.6}(N_2C_3H_3)_{0.4}]_n$ underwent a slow hydrolysis over several months at 25 °C in water, which could be detected by changes in the ^{31}P NMR spectrum. At 100 °C the rate of hydrolysis was accelerated markedly. The hydrolysis involved displacement of imidazole from the polymer.

No changes were detected in the ^{31}P NMR spectra of $[NP(NHCH_2COOC_2H_5)_2]_n$ or $[NP(NHCH_2CONHCH_3)_2]_n$ in water at 25 °C during 30 days. However, at 100 °C glycine was liberated during 24 h and degradation to phosphate occurred. This process was monitored by the appearance of P–O units which could be identified by ^{31}P NMR spectroscopy. By contrast, $[NP(NHCH_3)_2]_n$ underwent no reaction during 24 h at 100 °C in water.

Thus, a parallel exists between the behavior of the polymers and model compounds **3**–**6** in solution in water. If this parallel behavior can be extended to other systems, it can be implied that high polymers based on the repeating units found in **8**–**13** should be stable in aqueous media.

Experimental Section

Materials. Hexachlorocyclotriphosphazene (**14**) (Ethyl Corp.) was purified by two recrystallizations from hexane and by two sublimations at 50 °C (6.7 Pa; 0.05 torr). Tetrahydrofuran (Fisher) was distilled from sodium/benzophenone. Triethylamine (Eastman) was distilled from sodium hydroxide and then from sodium hydride (Alfa). Aniline (Eastman) was distilled three times from potassium hydroxide under

Scheme III

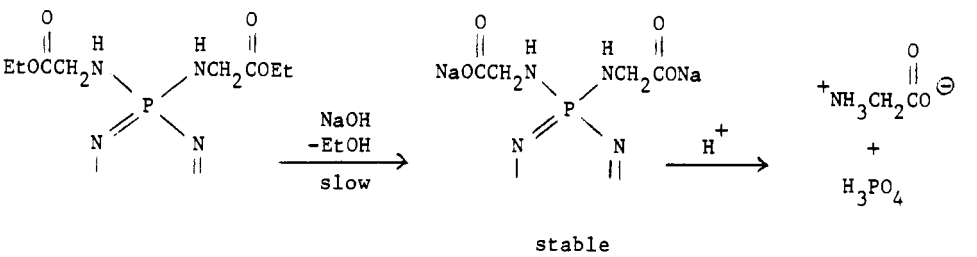


Table II. Characterization Data

compd		anal. % C	% H	% N	% P	% X	mp, °C
2[a]							450
3	found	22.84	7.43	39.78	29.75		258–259
	calcd	22.86	7.62	40.00	29.52		
4	found	38.28	6.31	17.01	12.62	25.78 (X = O)[b]	65–68
	calcd	38.55	6.43	16.87	12.45	25.70	
5	found	31.43	6.92	29.69	13.06	18.90 (X = O)[b]	60–65 dec
	calcd	32.88	6.39	31.96	14.16	14.61	
6	found	40.07	3.46	39.03	17.32		254–258 dec
	calcd	40.23	3.35	39.11	17.32		
7	found	65.09	6.35	16.28	12.15		84–87
	calcd	65.37	6.23	16.34	12.04		
8	found	19.93	2.55	17.63	12.98	47.06 (X = F)	82–83
	calcd	19.92	2.49	17.43	12.86	47.30	
9	found	62.78	5.35	18.38	13.39		272–273
	calcd	62.88	5.24	18.34	13.54		
10	found	53.45	4.67	23.14	17.15	0.80 (X = Cl)	198–200
	calcd	54.23	4.52	23.73	17.51		
11	found	51.96	8.70	22.68	17.73		212–214
	calcd	51.89	8.65	22.70	16.76		
12	found	56.42	9.25	19.65	14.43	0.34 (X = Cl)	262–267
	calcd	56.36	9.39	19.72	14.55		
13	found	44.08	7.40	19.44	14.19		280
	calcd	44.24	7.37	19.35	14.29		

[a] Analytical data reported elsewhere. [b] Percent oxygen determined by difference.

reduced pressure. Benzene (Fisher) was distilled from calcium hydride. The amines, benzylamine (Eastman), morpholine, pyrrole, pyrrolidine, and piperidine (Aldrich), were used as received. Anhydrous ammonia and methylamine (Matheson), trifluoroethanol (Halocarbon Corp.), ethanol (Fisher), trifluoroethylamine hydrochloride (Aldrich), ethyl glycinate hydrochloride (Sigma), imidazole (Eastman), and triphenylsilanol (PCR) were used as received.

Identification of the Hydrolysis Products (General Data). Orthophosphate was identified by ^{31}P NMR spectroscopy[21] by comparison with standard phosphoric acid solutions, by the addition of silver nitrate to neutral, halogen-free solutions to form yellow precipitates of silver phosphates, and by colorimetry with the use of a procedure devised by Martin and Doty[22] and modified by Jencks and Gilchrist.[23] Glycine was identified as the trifluoroacetyl-*n*-butyl ester with the use of mass spectrometry and as free glycine by the ninhydrin test. Aniline was detected by mass spectrometric methods. Imidazole was identified by ^1H NMR techniques. The odor of ammonia was evolved from basic solutions of the hydrolysis residues (with gentle heating sometimes required). Ammonia was also detected by the use of the ninhydrin test. The odor of methylamine or ethanol was detected when neutral solutions of $[NP(NHCH_2COOCH_2CH_3)_2]_3$ (**4**) or $[NP(NHCH_2CONHCH_3)_2]_3$ (**5**) were heated.

Identification of Hydrolysis Intermediates by ^{31}P NMR Techniques. Hydrolysis of **3** in 1 N hydrochloric acid yielded evidence of $N_3P_3(NHCH_3)_5OH$ from peaks at 6.7 and 16.2 ppm (AB_2 with J_{AB} = 14 Hz). After 48 h, approximately 55% of **3** had reacted. The rate of disappearance of **3** (0.0346 M) was 2×10^{-5} M/min (Δt = 1127 min).

Similarly, **20** was detected by the formation of an AB_2 pattern from **4** under a variety of conditions. Thus, after **4** (0.03 M) had been heated at 100 °C in water for 30 min, peaks at 4.5 and 15.4 ppm (J_{AB} = 30.9 Hz) appeared. Indeed, **20** could be isolated from the reactions of **4** in water buffered to pH 7 with tris(hydroxymethyl)aminomethane (0.0526 M). Thus, when **4** was present at a concentration of 0.031 M at 25 °C, no detectable hydrolysis took place in 2.8 days but 20% decomposition to **20** had occurred in 39 days and more than 80% decomposition in 50 days. In acid media (0.061 M potassium hydrogen phthalate buffered at pH 5.3), **4** hydrolyzed more slowly than at pH 7 but showed ^{31}P NMR evidence of phosphazene ring cleavage after 50 days. In basic media, species $N_3P_3R_5ONa$ was detected with peaks at 12.2 and 17.7 ppm (J_{AB} = 37.3 Hz) but only in 2 N or stronger sodium hydroxide solution, but hydrolysis in 0.021 M sodium borate buffered to pH 8.69 yielded the ^{31}P NMR spectrum of **20**. Hydrolysis was faster in this medium than in neutral or acidic media.

The monohydroxy derivative (**21**) was also detected by NMR methods when **5** was hydrolyzed in water or base. For example, the spectrum of **5** in water (Table I) changed to yield an AB_2 pattern with ν_A at 5.4 ppm and ν_B at 16.9 ppm (J_{AB} = 31.4 Hz). In base (0.02–5 N NaOH) the new spectrum contained peaks near 14.5 and 22 ppm ($J_{AB} \simeq$ 35 Hz), which were indicative of the species $N_3P_3(NHCH_2CONHCH_3)_5ONa$. The comparison compound **18** showed an AB_2 spectrum at 11.2 and 19.2 ppm (J_{AB} = 71.5 Hz).

Ring-opened products, when formed, were detected by the appearance of broad, complex spectra.

The high polymer $[NP(NHCH_3)_2]_n$ underwent no change in the ^{31}P NMR spectrum at 7.8 ppm in water at 25 °C although some decomposition was evident after 2 weeks at 100 °C. Species $[NP(NHCH_3)_{1.6}(N_2C_3H_3)_{0.4}]_n$ yielded ^{31}P NMR spectra after 1 h at 100 °C in water that showed the appearance of a peak at 3.5 ppm in addition to the one at 9.5 ppm in the starting material. The new peak was ascribed to $P(OH)NHCH_3$ units, which now constituted about 10% of the total side groups. Polymer $[NP(NHCH_2COOC_2H_5)_2]_n$ underwent a spectral change from a peak at 1.0 ppm to peaks at −0.2 ppm (P(OH)NHR) (12% conversion after 0.5 h in water at 100 °C) and to −0.65 ppm ($P(OH)_2$) after 24 h at 100 °C. Phosphate and glycine were detected by standard analytical tests. The polymeric amide $[NP(NHCH_2CONHCH_3)_2]_n$ underwent a spectral shift from 3.0 to 0.7 ppm (P(OH)NHR) (9% conversion) after 0.5 h in water at 100 °C.

All these shift positions are relative to 85% H_3PO_4 with a D_2O lock and with polymer concentrations $\simeq$0.3 M. Positive shifts are downfield.

Preparation of the Hexa(amino)cyclotriphosphazenes. Compounds **2**, **3**, **6**,[19] **9**, and **12** were prepared by standard methods.[6] The detailed experimental procedures used for the preparation of **4**, **5**, **7**, **8**, **10**, **11**, and **13** are described in the following sections. Elemental analysis for the compounds **3**–**13** are listed in Table II.[24]

Preparation of Hexakis(ethyl glycinato)cyclotriphosphazene, $[NP(NHCH_2COOC_2H_5)_2]_3$ (4). Glycine ethyl ester hydrochloride (48.7 g, 0.349 mol) was suspended in benzene (500 mL) and triethylamine (153 g, 152 mol). The stirred mixture was boiled at reflux for 3 h and was then cooled to 0 °C by means of an ice bath. The solution was filtered under nitrogen, and the filtrate was transferred to a reaction vessel (1 L) equipped with a stirrer, an addition funnel, and

(21) The ^{31}P and ^{13}C NMR spectra were obtained with the use of a JEOL PS 100 NMR spectrometer operated in a ^1H-decoupled Fourier transform mode at 40.5 and 23 MHz, respectively. The spectral data were transformed by the use of a Nicolet 1080 data processor. ^1H NMR spectra were obtained at 100 MHz with the same instrumentation.

(22) Martin, J. B.; Doty, D. M. *Anal. Chem.* **1949**, *21*, 965.

(23) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1964**, *86*, 1410.

(24) Microanalytical data were determined by Galbraith Laboratories, Knoxville, Tenn.

a nitrogen inlet. To a stirred filtrate (cooled to 0 °C) was added dropwise $(NPCl_2)_3$ (10.2 g, 0.019 mol), dissolved in benzene (100 mL). The reaction mixture was allowed to warm to 25 °C and was stirred for an additional 24 h. It was then filtered under nitrogen to remove amine hydrochloride salts, and the filtrate was stirred for an additional 24 h. The solution was filtered again under nitrogen. The solvent was removed with the use of a rotary evaporator until approximately 75 mL remained. The concentrated solution was then added to petroleum ether (1 L). After 6 h the petroleum ether was decanted off and the oily residue was purified by chromatography, first on silica with methylene chloride as eluent and later with the use of ethanol. Crystals were recovered from the ethanol fractions and were purified by chromatography on neutral alumina with elution by benzene. A white, waxy solid, **4**, was obtained in 70% yield; mp 65–68 °C. The product could be recrystallized from a solution in methylene chloride and pentane.

Preparation of Hexakis(methylglycinamido)cyclotriphosphazene, $[NP(NHCH_2CONHCH_3)_2]_3$ (5). Methylamine (150 mL) was added rapidly to a stirred solution of $[NP(NHCH_2COOCH_2CH_3)_2]_3$ (1.0 g, 0.001 mol) dissolved in tetrahydrofuran (50 mL) with the use of a dry ice condenser. After a 3-h reaction, methylamine (150 mL) was permitted to escape during a 16-h period under nitrogen. The solvent was removed with the use of a rotary evaporator, and a white solid remained (32.8% yield). The solid was purified by reprecipitation from 2-propanol into petroleum ether, followed by filtration under nitrogen. The hygroscopic product was collected and dried under vacuum. It decomposed at >60 °C with gas evolution. The product dissolved readily in water or alcohols but was insoluble in most organic solvents. A ^1H NMR spectrum of the material in deuterium oxide had two absorbances at 3.55 ppm (br, CH_2) and 1.75 ppm (s, CH_3). A ^{13}C NMR spectrum of the product had resonances at 28.4 (CH_3), 25.9 (CH_2), and 177 ppm (CO) in deuterium oxide.[21] No ethyl groups were detected by either method. The infrared spectrum of the sample showed a carbonyl stretch at 1680 cm^{-1}. This was consistent with that expected for an acyl amide. These results indicate that the conversion of the ester groups to the amide groups to yield **5** was complete. The product was stable to water for several weeks at 25 °C.

Preparation of Hexakis(trifluoroethylamino)cyclotriphosphazene, $[NP(NHCH_2CF_3)_2]_3$ (8). Trifluoroethylamine hydrochloride (50 g, 0.369 mol), suspended in tetrahydrofuran (200 mL), triethylamine (197 g, 0.369 mol), and a solution of $(NPCl_2)_3$ (10 g, 0.027 mol) dissolved in tetrahydrofuran (50 mL), were combined in an airless-ware flask (500 mL) equipped with a magnetic stirrer, reflux condenser, and a nitrogen inlet. The reaction mixture was boiled at reflux for 96 h. It was then filtered under nitrogen. The solvent was removed from the filtrate with the use of a rotary evaporator to yield a red wax. This was purified by chromatography on silica, with chloroform used as eluent. Alternatively, chloroform (100 mL) was added to the residue, and the solution was filtered and concentrated. Water (100 mL) was then added to the chloroform concentrate. Vigorous shaking of the mixture yielded an emulsion, and the slow addition of hexane yielded a white, semicrystalline solid suspended at the interface between the organic and aqueous phases. The solid was isolated by filtration and was dried to yield **8** (<20% yield; mp 82–83 °C). The product could be recrystallized from a suspension of the solid in a mixture of chloroform and hexane. Incomplete replacement of chloride by trifluoroethylamino groups took place when the reactions between $(NPCl_2)_3$, trifluoroethylamine hydrochloride, and triethylamine were carried out at 25 °C.

Preparation of Hexakis(benzylamino)cyclotriphosphazene, $[NP(NHCH_2C_6H_5)_2]_3$ (7). Hexachlorocyclotriphosphazene, $(NPCl_2)_3$ (10 g, 2.87×10^{-2} mol) was added to benzylamine (100 mL), and the mixture was stirred with the use of a magnetic stirrer. An exothermic reaction occurred. The mixture was heated at 100 °C and was stirred for 5 h. The reaction mixture was cooled to 25 °C, and a white precipitate of benzylamine hydrochloride formed. This was removed by filtration. The filtrate was added to petroleum ether (300 mL), and the white precipitate formed was removed by filtration. It was washed with petroleum ether (100 mL) and was dried under vacuum (0.03 torr) for 16 h. The white product (**7**) was obtained in 72.4% yield (16.0 g; mp = 78–79 °C). A mass spectrum of the compound had a parent peak at 772 au (calc 772).

Preparation of Hexapyrrolylcyclotriphosphazene, $[N_3P_3(NC_4H_4)_6]$ (10). Fresh metallic potassium (2.3 g, 0.06 mol) was added to dry toluene (200 mL) and the mixture was boiled at reflux to disperse the potassium. To this mixture at 25 °C was added dropwise freshly distilled pyrrole (20 mL). A white turbid mixture formed. No unreacted potassium was detected. A solution of hexachlorocyclotriphosphazene (1.7 g, 4.88×10^{-3} mol) in toluene (50 mL) was added dropwise at 25 °C. After 16 h of reaction, the mixture was filtered and the volume of the light-yellow filtrate was reduced by half with the use of a rotary evaporator. Benzene (50 mL) was added to the concentrated filtrate, and the solution was cooled to 0 °C by means of an ice bath. The crystals that formed were isolated, washed with diethyl ether, and dried. The product (**10**) was recrystallized from benzene to yield white crystals (1.34 g, 51.3%; mp = 200 °C). The mass spectrum contained a parent peak at 532 au (calcd, for **10**, 532).

Preparation of Hexapyrrolidinocyclotriphosphazene, $[N_3P_3(NC_4H_8)_6]$ (11). Pyrrolidine (50 mL) was added dropwise to a stirred solution of hexachlorocyclotriphosphazene (10 g, 0.029 mol) in dry diethyl ether (100 mL). An exothermic reaction took place. The stirred mixture was boiled at reflux for 16 h. The mixture was then filtered, and the precipitate was washed with water. The white residue was dried in vacuo and was recrystallized from acetone. The yield of **11** was 89% (13.9 g; mp = 228 °C). A mass spectrum of the material showed a parent peak at 555 au (calcd, for **11**, 555).

Preparation of Hexamorpholinocyclotriphosphazene, $[N_3P_3(NC_4H_8O_6)_6]$ (13). A mixture of $(NPCl_2)_3$ (10 g, 0.029 mol) and morpholine (150 mL) was stirred initially at 25 °C. The onset of the reaction resulted in a 65 °C exotherm. The reaction mixture was boiled at reflux for 16 h. The mixture was then cooled to 25 °C, and the precipitate was removed by filtration. The solid material was extracted with benzene for 48 h. The benzene was removed, and the white residue was washed with water until a negative chloride test was observed with silver nitrate solution (0.01 M). The precipitate was dried in vacuo, washed with petroleum ether, and dried in vacuo (0.03 torr) for 16 h. A white powder (**13**) was obtained in 85.8% yield (16.2 g; mp = 267 °C). A parent peak was found in the mass spectrum at 652 au (calcd, for **13**, 652).

Hydrolysis of Hexa(amino)cyclotriphosphazenes. A solution of hexa(amino)cyclotriphosphazene (0.3 g) in water (75 mL) and dioxane (225 mL) was boiled at reflux for at least 160 h. The solvent was removed, and the products were characterized by melting points, and by ^1H and ^{31}P NMR spectrometry in solution with deuterium oxide as solvent. Compounds **3** and **7–13** were stable. The others (**2** and **4–6**) were unstable under these reaction conditions.

Hydrolysis of $[NP(NHCH_3)_2]_3$ (3) in Water. A solution of $[NP(NHCH_3)_2]_3$ (3.0 g, 9.6×10^{-3} mol) in water was boiled at reflux for 336 h. The white precipitate which formed was isolated by filtration, was washed with water and then ethanol, and was then dried. This material could not be identified by microanalysis and appeared to be a polyphosphate or polyphosphoramidate.

Reaction of $NaOSiPh_3$ with $[NPCl_2]_3$. Triphenylsilanol (0.794 g, 0.00287 mol) dissolved in tetrahydrofuran (THF) (100 mL) was added to a stirred suspension of excess sodium hydride in THF (100 mL). The reaction mixture was filtered under nitrogen, and the filtrate was added dropwise to a stirred solution of $[NPCl_2]_3$ (1.00 g, 0.00287 mol) dissolved in THF (100 mL). After a 2-h reaction, the mixture contained the unstable intermediate $[N_3P_3(ONa)Cl_5]$ (**16**), formed in 20–30% yield on the basis of ^{31}P NMR methods, and triphenylsilyl ether, identified by melting point (225–227 °C) and mass spectrometry (*m/e* 534 au, calcd 534). Intermediate **16** was characterized further by a subsequent reaction with sodium trifluoroethoxide to yield $[N_3P_3(ONa)(OCH_2CF_3)_5]$.

Preparation of $[N_3P_3(ONa)(OCH_2CF_3)_5]$ from the Reaction between $[N_3P_3(ONa)Cl_5]$ (16) and $NaOCH_2CF_3$. A filtered solution of sodium trifluoroethoxide, prepared by the cautious addition of trifluoroethanol (10 mL) dissolved in THF (50 mL) to an excess of sodium hydride suspended in THF (100 mL), was added rapidly to the reaction mixture that contained **16**. After 16 h, the solvent was removed with the use of a rotary evaporator, and an oily white solid remained. After centrifugation, an oily layer that contained $[NP(OCH_2CF_3)_2]_3$ was removed. Diethyl ether was added to the residue and the mixture was filtered. A ^{31}P NMR spectrum of the filtrate was identical with that of an authentic sample of $[N_3P_3(ONa)(OCH_2CF_3)_5]$ prepared by an alternative route.[25] Another sample of $[N_3P_3(ONa)(OCH_2CF_3)_5]$, prepared in the same way, was acidified (with concentrated

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hydrochloric acid) in pentane, and the solvent was removed. The residue was fractionally sublimed at 100 °C (0.05 torr), and a portion of the sublimate was found to contain $[N_3P_3(OH)(OCH_2CF_3)_5]$,[18] identified by ^{31}P NMR methods and by mass spectrometry. A parent ion was found at 647 au (calcd, for $[N_3P_3(O_6C_{10}H_{11}F_{15})]$, 647).

Reactions of $[N_3P_3(ONa)Cl_5]$ (16) with Amines. Under nitrogen, a stirred solution of the intermediate $[N_3P_3(ONa)Cl_5]$ (prepared as described above) at 0 °C was treated with an excess of methylamine (>100 mL), added by means of a dry ice condenser. After 48 h, the solvent was removed with the use of a rotary evaporator. Water was added to the residue, and the mixture was centrifuged. The oil layer was removed. A ^{31}P NMR spectrum of the aqueous layer was compatible with an A_3 spin system plus an AB_2 spin system. These were consistent with the structures $[NP(NHCH_3)_2]_3$ and $[N_3P_3(ONa)(NHCH_3)_5]$, respectively.

Similarly, ammonia (>100 mL) or a filtered solution of ethyl glycinate at 0 °C (prepared from a boiling mixture of glycine ethyl ester hydrochloride (12 equiv, 4.81 g, 0.0138 mol) in triethylamine (30 g, 0.297 mol) after 4 h at reflux followed by cooling by means of an ice bath) was added to a stirred solution of the intermediate **16** under nitrogen at 0 °C. After a 48-h reaction, the solvent was removed. Water was added, and, after centrifugation, the oil was removed from the mixture. Part of the ^{31}P NMR spectrum of the aqueous layer was interpreted as an AB_2 spin system assigned to the structures $[N_3P_3(ONa)(NH_2)_5]$ or $[N_3P_3(ONa)(NHCH_2COOCH_2CH_3)_5]$, respectively. When treated with methylamine at 0 °C, the latter compound in tetrahydrofuran (50 mL) was converted to $[N_3P_3(ONa)(NHCH_2CONHCH_3)_5]$, as identified by ^{31}P NMR spectroscopy (see Table I). The preparation of the hydrolysis intermediate $[N_3P_3(OH)(N_2C_3H_3)_5]$ (imidazolyl), from the reaction between **16** and imidazole, is described elsewhere.[19]

Preparation of Poly[bis(methylglycinamido)phosphazene], $[NP(NHCH_2CONHCH_3)_2]_n$. The polymer $[NP(NHCH_2COOCH_2CH_3)_2]_n$[10] (2.50 g, 0.001 mol) was dissolved in tetrahydrofuran (150 mL) and was cooled to 0 °C by means of an ice bath. To this solution was added methylamine (150 mL) by means of a dry ice condenser. The methylamine was retained in the reaction vessel for 4 h. It was then allowed to volatilize and escape in a stream of nitrogen over a period of 16 h. The solvent was removed with the use of a rotary evaporator. The solid residue was washed with petroleum ether and was reprecipitated twice from 2-propanol into petroleum ether. The resultant white polymer (>30% yield) had a glass transition temperature (by thermomechanical analysis) of 36 °C. A ^{31}P NMR spectrum and the microanalytical data were compatible with the structure $[NP(NHCH_2CONHCH_3)_2]_n$. A ^{13}C NMR spectrum of the material was similar to that of $[NP(NHCH_2CONHCH_3)_2]_3$ (**5**). Anal.[24] Calcd for $[NP(NHCH_2CONHCH_3)_2]_n$: C, 32.88; H, 6.39; N, 31.96; P, 14.16; Cl, 0.0. Found: C, 32.90; H, 6.43; N, 31.86; P, 14.09; Cl, 0.15.

Hydrolysis of Poly[(amino)phosphazenes]. An aqueous solution of polymers $[NP(NHR)_2]_n$ (where $n \simeq 10000$) (0.03 M) was treated as described previously. The resultant polymers were then characterized by ^{31}P NMR spectrometry.

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Registry No. **2**, 13597-92-7; **3**, 1635-63-8; **4**, 79839-15-9; **5**, 79839-16-0; **6**, 74868-58-9; **7**, 58419-88-8; **8**, 79839-17-1; **9**, 13264-13-6; **10**, 79839-18-2; **11**, 4864-72-6; **12**, 2277-98-7; **13**, 53521-33-8; **14**, 940-71-6; **16**, 75283-92-0; **18**, 24524-93-4; **20**, 79839-19-3; **21**, 79839-20-6; $N_3P_3(NH_2)_5OH$, 79839-21-7; $N_3P_3(NHCH_3)_5ONa$, 75267-53-7; $N_3P_3(NHCH_3)_5OH$, 75267-52-6; $N_3P_3(OCH_2CF_3)_6$, 1065-05-0; $N_3P_3(OCH_2CF_3)_5OH$, 35825-49-1; $N_3P_3(NHCH_2CONHCH_3)_5(ONa)$, 79839-22-8; $[NP(NHCH_3)_2]_n$, 40101-94-8; $[NP(NHCH_2COOCH_2CH_3)_2]_n$, 79839-05-7; $[NP(NHCH_2CONHCH_3)_2]_n$, 79839-06-8; $(NPCl_2)_n$, 26085-02-9; imidazole, 288-32-4; glycine ethyl ester HCl, 623-33-6; methylamine, 74-89-5; trifluoroethylamine HCl, 373-88-6; benzylamine, 100-46-9; pyrrole, 109-97-7; pyrrolidine, 123-75-1; morpholine, 110-91-8; triphenylsilanol, 791-31-1; sodium trifluoroethoxide, 420-87-1.

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Cyclic Azide as an Aqueous Solution Intermediate: Evidence Pro and Con[1]

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Isotope tracer experiments on the reaction between $H^{15}NO_2$ and $N_2H_5^+$ corroborate the existence of separate high- and low-acidity pathways. Experiments at 0.60 M H^+, with $([HNO_2]/[N_2H_5^+])_0 = 2.0$, yield N_2O and N_2 of the isotopic composition predicted for N-atom scrambling caused by a cyclic azide intermediate, but these data and others at different stoichiometric ratios can also be interpreted as mixtures of reaction products resulting from double nitrosation and linear azide pathways. No evidence of photochemical cyclization of linear azide in solution was found in irradiation experiments, although it has been reported to occur in alkali-metal azide crystals.

The products of the hydrazine–nitrous acid reaction have long been known to include NH_3, HN_3, N_2, and N_2O. In acid solution, it has been established that HN_3 is the virtually exclusive product, with N_2 and N_2O resulting from a rapidly sequential HN_3–HNO_2 reaction:[2,3]

$$N_2H_5^+ + HNO_2 = HN_3 + 2H_2O + H^+ \quad (1)$$

$$HN_3 + HNO_2 = N_2O + N_2 + H_2O \quad (2)$$

Perrott, Stedman, and Uysal[3] established that reactions 1 and 2 constitute a limiting (high-acidity) pathway and postulated that NH_3 and directly formed N_2O arise from a competing pathway whose importance increases with decreasing acidity:

$$N_2H_5^+ + HNO_2 \longrightarrow NH_2NHNO \xrightarrow{[H^+]} \begin{matrix} NH_3 + N_2O \\ HN_3 + H_2O \end{matrix} \quad (3)$$

An isotopic tracer study of the reaction between ^{15}N-labeled hydrazine ($^{15}N_2H_5^+$) and excess nitrous acid, presenting evidence for a cyclic azide intermediate species, has recently been reported from the University College of Swansea.[4] An in-

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