Table IV. Atomic Coordinates ($\times 10^4$) and Isotropic Thermal Parameters ($Å^2 \times 10^3$) for Isomer B of $(C_2H_5)(pz)B(\mu\text{-}pz)_2B(C_2H_5)(pz)$

atom	*x*	*y*	*z*	U^a
N1	411 (2)	10495 (1)	1606 (2)	34 (1)
N2	-1171 (2)	10216 (1)	1247 (2)	34 (1)
N5	2824 (2)	9422 (1)	1642 (2)	35 (1)
N6	3930 (2)	9637 (1)	3058 (2)	44 (1)
B	1912 (2)	10199 (1)	564 (3)	33 (1)
C3	-2013 (2)	10494 (1)	2594 (3)	42 (1)
C2	-987 (3)	10949 (1)	3829 (3)	45 (1)
C1	518 (3)	10931 (1)	3173 (3)	45 (1)
C9	4436 (3)	8846 (2)	3762 (3)	49 (1)
C8	3690 (3)	8120 (2)	2831 (3)	48 (1)
C7	2671 (2)	8510 (1)	1505 (3)	42 (1)
C10	3083 (2)	11046 (1)	283 (3)	42 (1)
C11	2268 (3)	11833 (2)	-744 (4)	64 (1)
H1	1506 (24)	11136 (12)	3645 (26)	50
H2	-1218 (23)	11238 (12)	4892 (24)	50
H3	-3103 (23)	10344 (12)	2579 (25)	50
H7	1925 (24)	8270 (14)	535 (28)	50
H8	3837 (23)	7467 (16)	3091 (25)	50
H9	5232 (26)	8835 (12)	4759 (28)	50
H10a	3534 (25)	11275 (14)	1429 (29)	50
H10b	4021 (26)	10853 (14)	-305 (25)	50
H11a	1766 (26)	11655 (15)	-1881 (29)	50
H11b	3016 (24)	12298 (15)	-958 (27)	50
H11c	1351 (27)	12077 (14)	-206 (26)	50

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized U_{ij} tensor.

N_4 plane. The N-B-N plane of the ring forms an angle of 13.6° with the N_4 plane, with which the bridging pz rings are almost coplanar. The structure of isomer B is shown in Figure 2, atomic coordinates are listed in Table IV, and selected bond distances and bond angles are given in Table III.

Corresponding B-N distances of isomers A and B are essentially identical with a surprisingly long bond to the terminal pz groups. Interestingly, the B-N bonds within the central B_2N_4 ring differ by 0.02 Å, perhaps signaling the construction of the pyrazabole skeleton by two monomeric 1-pyrazolylborane units. The B-C distance of 1.593 Å is in excellent agreement with the sum of the covalent radii.

In conjunction with previous X-ray data on pyrazaboles,[21] some structural trends are now quite apparent. Firstly, terminal pz groups have a distinct preference for the axial positions. They are found to be orthogonal to the N_4 plane, and the NN vector includes angles with the BB vector ranging from 100 to 120°. This arrangement seems to impair interaction with the H atoms of the bridging pz groups. Also, the boat conformation of the central B_2N_4 ring is quite predominant. The chair conformation is observed only if the two terminal substituents at each boron atom are different and trans to one another. In addition, the predominance of isomer A suggests that the boat conformation is energetically favored.

Conclusion. The present study illustrates that only the first steps of the interaction of pyrazole with boroxins or borazines, respectively, are comparable by forming adducts such as **4**. Subsequently, different condensations occur to yield either **2** or **3**, respectively, and this difference may be due to the electronic environment of the three-coordinate boron of the heterocycle as illustrated in **4**. Still, the ready conversion of B-O bonds to B-N bonds in the $(-BRO-)_3$/Hpz case is somewhat surprising, as is the lack of a NR'-BR-NR'-bridged analogue of **2**. Also, it must be emphasized that formation of **3** requires a B-N-B bond in the starting material, which may be a borazine or a diborylamine. A substantial difference between **2** and **3** resides in the fact that **2** does not react with refluxing Hpz. In contrast, under these same conditions **3** is readily converted to a pyrazabole of the type $R(pz)B(\mu\text{-}pz)_2BR(pz)$, which may exist in conformational isomers, as was documented for $R = C_2H_5$.

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Supplementary Material Available: Complete listings of bond angles and distances and anisotropic thermal parameters for the two isomers of 4,8-diethyl-4,8-bis(1-pyrazolyl)pyrazabole (5 pages); structure factor tables for both isomers (13 pages). Ordering information is given on any current masthead page.

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Reactions of 2-Substituted Ethylamines with Hexachlorocyclotriphosphazene

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The reactions of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, with 2-substituted ethylamines have been investigated. In the case of 2-haloethylamines the following compounds have been prepared: $N_3P_3Cl_5NHCH_2CH_2X$ (X = Cl, Br), 2,2-$N_3P_3Cl_4(NHCH_2CH_2X)_2$ (X = Cl, Br), and 2,2,4,4-$N_3P_3Cl_2(NHCH_2CH_2Cl)_4$. Traces of 2,2,4-$N_3P_3Cl_3(NHCH_2CH_2Cl)_3$ were observed. In acetonitrile nongeminal as well as geminal bis derivatives were obtained. A reaction with 2-chloroethanol led to 2,2-$N_3P_3Cl_4(OCH_2CH_2Cl)_2$ while the use of 2-methoxyethylamine gave 2,4-$N_3P_3Cl_4(NHCH_2CH_2OCH_3)_2$. The mono- and bis((2-chloroethyl)amino) derivatives have been converted to their dimethylamino derivatives, $N_3P_3[N(CH_3)_2]_{6-n}[NHCH_2CH_2N(CH_3)_2]_n$ (n = 1, 2). All compounds were characterized by mass spectrometry and NMR (^{31}P, ^1H) spectroscopy. The regioselectivity observed in these reactions is discussed in terms of substituent and incoming-group effects.

Introduction

The reactions of primary and secondary amines with halocyclophosphazenes are among the most widely studied processes in phosphazene chemistry.[1] The reasons for the intensive study of these reactions are twofold. Kinetic studies and product analysis have allowed for a detailed understanding of the mechanisms by which these reactions occur.[2,3] At the stage of disubstitution in the reaction of primary amines with hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, the relative amount of the geminal (2,2) isomer increases with the steric bulk of the amine. Thus, while the nongeminal (2,4) bis isomers predominate in the reactions of methyl[4,5] and ethylamine,[6] the geminal isomer is produced ex-

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clusively in the reaction of *tert*-butylamine.[7] The formation of the geminal isomer is believed to proceed through a dissociative process in which the rate-determining step is the loss of a chloride ion from the ≡PClNHR center while the nongeminal isomers are formed in a bimolecular process. In addition to these fundamental questions, there is a growing interest in the potential use of certain of the aminophosphazenes as anticancer agents. The aziridinophosphazene derivatives in particular have been examined in detail in this regard.[8,9] The impressive biological activity of the aziridinophosphazenes has led us to consider the examination of other alkylating agents as substituents on the cyclophosphazene ring system. Due to their activity as DNA alkylating agents, 2-haloethylamines are an obvious target series for these studies. This paper describes the synthesis of several 2-substituted (ethylamino)cyclotriphosphazenes, with emphasis on the (2-haloethyl)amino derivatives, for consideration as new antitumor agents and for comparison of the substitution pathway followed in these reactions with available models[2] for primary amines. We have previously reported the biological activity of the (2-haloethyl)amino derivatives.[10] Moderate in vivo and in vitro antitumor activity, accompanied by toxicity at high dose levels, was observed for the nongeminal $N_3P_3Cl_4(NHCH_2CH_2X)_2$ (X = Cl, Br) species.[10]

Experimental Section

Hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ (Ethyl Corp.), was recrystallized from petroleum ether to a constant melting point of 113 °C. Solvents were dried and distilled by conventional methods. The 2-haloethylamine hydrohalides[11] and other 2-substituted ethylamines (Aldrich) were used as obtained. Gas chromatography was performed on a Hewlett-Packard 5700A-GC chromatograph using a 5% St-30 on Chromasorb-W column at 180 °C. Medium-pressure liquid chromatography was performed on a locally constructed chromatograph using a pump (Fluid Metering, Inc.) with a maximum capacity of 1–8 L min^{-1} at 110 lb in^{-2} with columns packed with 230–400 mesh silica gel. NMR spectra (in $CDCl_3$) were recorded on a Bruker WM 250 spectrometer operating at 250.1 MHz (^1H) andd 101.2 MHz (^{31}P). Tetramethylsilane (Me_4Si) was used as internal reference for ^1H measurements. For ^{31}P NMR, 85% H_3PO_4 was used as an external standard. Chemical shifts upfield of the reference are assigned a negative sign. Mass spectra were recorded on a Perkin-Elmer RMU-6D spectrometer operating at 80 eV. Elemental analyses were performed by Integral Microanalytical Laboratories.

Preparation of $N_3P_3Cl_5(NHCH_2CH_2Br)$ (1). A solution of $N_3P_3Cl_6$ (6.96 g, 0.02 mol) and 2-bromoethylamine hydrobromide[11] (4.08 g, 0.02 mol) in 50 mL of diethyl ether was stirred at 0 °C. A solution of triethylamine (4.04 g, 0.04 mol) in 50 mL of diethyl ether was added dropwise over a 0.5-h period. The reaction mixture was allowed to stir for 1 h, the system was warmed to room temperature, and the reaction was continued for 24 h. An orange oil was obtained after removal of the triethylamine hydrohalides and the solvent. Additional amine hydrohalides were removed by precipitation with benzene.[12] After removal of the solvent, the mixture was subjected to medium-pressure chromatography and eluted with 25% chloroform/hexane to give 3.1 g (35% of theory) of a colorless oil and 1.1 g of $N_3P_3Cl_6$. The product is very sensitive to heat and moisture and undergoes facile decomposition. Anal.[13] Calcd for $N_3P_3(NCH_2CH_2Br)Cl_5$: C, 5.50; N, 12.0; H, 1.16; mol wt, 432. Found: C, 5.75; N, 12.48; H, 0.94; Mol wt, 432 (mass spectrum).[14] ^1H NMR:[15] δ_{NH} 3.9 (1 H); δ_{CH_2} 3.45 (2 H), $^2J_{HH}$ = 6.0, $^3J_{PH}$ = 13.4; δ_{CH_2Br} = 3.55 (2 H). ^{31}P NMR: $\delta_{=PCl_2}$ 22.5, $^3J_{PP}$ = 48; $\delta_{=PCl(NHCH_2CH_2Br)}$ 19.2.

Preparation of 2,2-$N_3P_3Cl_4(NHCH_2CH_2Br)_2$ (2). This preparation was allowed to proceed as above except that the following quantities of reagents were used: 3.48 g (0.01 mol) of $N_3P_3Cl_6$, 4.08 g (0.02 mol) of 2-bromoethylamine hydrobromide, and 4.04 g (0.04 mol) of triethylamine. After medium-pressure chromatography, 1.3 g (25% of theory) of a white crystalline material, mp 75 °C, was obtained along with traces of **1** and unidentified materials. Anal.[12] Calcd for $N_3P_3Cl_4(NHCH_2CH_2Br)_2$: C, 9.17; H, 1.91; mol wt, 519. Found: C, 9.34; H, 2.11; mol wt, 519 (mass spectrometry).[14] ^1H NMR:[15] δ_{NH} 4.0 (1 H); δ_{CH_2} 3.36 (2 H), $^1J_{HH}$ = 6.1, $^3J_{PH}$ = 10.4; δ_{CHBr} 3.51 (2 H). ^{31}P NMR: $\delta_{=PCl_2}$ 22.3, $^3J_{PP}$ = 47; $\delta_{=P(NHCH_2CH_2Br)_2}$ 10.4.

Attempted Preparation of $N_3P_3(NHCH_2CH_2Br)_XCl_{6-X}$ ($X > 2$). All attempts to achieve higher degrees of substitution resulted in formation of **2** and/or ill-defined oils.

Preparation of $N_3P_3Cl_5(NHCH_2CH_2Cl)$ (3). This preparation was allowed to proceed as above except that the following reagents were used: 3.48 g (0.01 mol) of $N_3P_3Cl_6$, 1.16 g (0.01 mol) of 2-chloroethylamine hydrochloride,[11] and 2.02 g (0.02 mol) of triethylamine. The crude product was separated by flash chromatography[16] using 25% chloroform/hexane to yield 1.5 g (38% of theory) of a colorless oil. Anal.[13] Calcd for $N_3P_3Cl_5(NHCH_2CH_2Cl)$: C, 6.10; H, 1.27; mol wt, 388. Found: C, 640; H, 1.31; mol wt, 388 (mass spectrum).[14] ^1H NMR:[15] δ_{NH} 3.7 (1 H); δ_{CH_2} 3.42 (2 H), $^2J_{HH}$ = 5.8, $^3J_{PH}$ = 15.3; δ_{CH_2Cl} 3.67 (2 H). ^{31}P NMR: $\delta_{=PCl_2}$ 21.9, $^3J_{PP}$ = 47; $\delta_{=PCl(NHCH_2CH_2Cl)}$ 19.2.

GC Study of Solvent Dependence in the Reactions of 2-Chloroethylamine with $N_3P_3Cl_6$. The reaction of excess 2-chloroethylamine with $N_3P_3Cl_6$ in various solvents was examined by removing aliquots at 1, 6 and 24 h and subjecting them to analysis by gas chromatography. The results are summarized in Table S1 (supplementary material).

Preparation of 2,2-$N_3P_3Cl_4(NHCH_2CH_2Cl)_2$ (4). The reaction was allowed to proceed as above with use of 3.48 g (0.01 mol) of $N_3P_3Cl_6$ and 2.30 g (0.02 mol) of 2-chloroethylamine hydrochloride in 75 mL of chloroform and 4.08 g (0.04 mol) of triethylamine in 75 mL of chloroform. The resulting orange oil was a mixture of the mono- and bis((2-chloroethyl)amino)phosphazenes and a large amount of resinous material. Separation with flash chromatography using a 20% chloroform/hexane eluant gave 200 mg of $N_3P_3Cl_5(NHCH_2CH_2Cl)$ and 1.3 g (30% of theory) of a very heat- and moisture-sensitive white solid. Anal.[13] Calcd for $N_3P_3Cl_4(NHCH_2CH_2Cl)_2$: C, 11.07; H, 2.30; mol wt, 435. Found: C, 10.65; H, 1.74; mol wt, 435 (mass spectrum).[14] ^1H NMR:[15] δ_{NH} 4.16 (1 H); δ_{CH_2} 3.31 (2 H), $^2J_{HH}$ = 5.5, $^3J_{PH}$ = 13.7; δ_{CH_2Cl} 3.71. ^{31}P NMR: $\delta_{=PCl_2}$ 21.2, $^3J_{PP}$ = 46.6; $\delta_{=P(NHCH_2CH_2Cl)_2}$ 11.3.

Preparation of a $N_3P_3Cl_4(NHCH_2CH_2Cl)_2$ Mixture. This preparation was allowed to proceed above using 1.74 g (0.005 mol) of $N_3P_3Cl_6$ and 1.16 g (0.01 mol) of 2-chloroethylamine hydrochloride in 50 mL of acetonitrile and 2.02 g (0.02 mol) of triethylamine in 50 mL of acetonitrile. After flash chromatography, a trace of $N_3P_3Cl_5(NHCH_2CH_2Cl)$ and 0.9 g (25% of theory) of a 2:1 (by ^{31}P NMR) mixture of geminal:nongeminal $N_3P_3Cl_4(NHCH_2CH_2Cl)_2$ were obtained. Further separation by preparative-layer chromatography using 10% hexane/benzene[11] resulted in enrichment to a 1:1 mixture. However, most of the material adhered irreversibly to the plate. ^{31}P NMR (of nongeminal components): $\delta_{=PCl_2}$ 23.5, $^3J_{PP}$ = 40.2; $\delta_{=PCl(NHCH_2CH_2Cl)}$ 22.5.

Preparation of 2,2,4,4-$N_3P_3Cl_2(NHCH_2CH_2Cl)_4$ (5). This preparation was allowed to proceed as above with use of 6.00 g (0.017 mol) of $P_3N_3Cl_6$ and 11.6 g (0.1 mol) of 2-chloroethylamine hydrochloride in 150 mL of diethyl ether and 20.4 g (0.2 mol) of triethylamine in 150 mL of diethyl ether. The reaction was allowed to stir for 48 h and then continued at reflux for 12 h. An orange oil and a large amount of resinous material were obtained. Flash chromatography of the oil using 20% chloroform/hexane gave 0.25 g of 2,2-$N_3P_3Cl_4(NHCH_2CH_2Cl)_2$ and 0.90 g (10.1% of theory) of a white solid, mp 105 °C. Anal.[13] Calcd for $N_3P_3Cl_2(NHCH_2CH_2Cl)_4$: C, 18.47; H, 4.14; mol wt, 523. Found: C, 19.08; H, 4.83; mol wt, 523 (mass spectrum).[14] ^1H NMR:[15] δ_{NH} 4.5 (1 H); δ_{CH_2} 3.30 (2 H), $^2J_{HH}$ = 5.8, $^3J_{PH}$ = 13.2; δ_{CH_2Cl} 3.68. ^{31}P NMR: $\delta_{=PCl_2}$ 24.5, $^3J_{PP}$ = 50.5; $\delta_{=P(NHCH_2CH_2Cl)_2}$ 13.3.

The ^{31}P NMR spectrum of the crude reaction mixture shows the presence of a small amount of 2,2,4-$N_3P_3Cl_3(NHCH_2CH_2Cl)_3$ (**6**). Specific attempts at synthesis of this material did not lead to any isolable material. ^{31}P NMR: $\delta_{=PCl_2}$ 25, $^3J_{PP}$ = 50.7; $\delta_{=PCl(NHCH_2CH_2Cl)}$ 14.8; $\delta_{=PCl(NHCH_2CH_2Cl)_2}$ 14.1.

Attempted Preparation of $N_3P_3Cl_{6-n}(NHCH_2CH_2Cl)_n$ ($n = 5, 6$). All attempts to achieve higher degrees of substitution produced ill-defined resinous materials.

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(11) Extreme care should be exercised in handling these toxic materials.
(12) Benzene is a known carcinogen and hence should only be used in a well-ventilated area while appropriate protective gloves are worn.
(13) The facile decomposition, especially when neat, of all of the ((2-haloethyl)amino)phosphazenes resulted in deviations in the elemental analyses beyond the level that is normally expected.
(14) Mass spectrometry data are available as supplementary material.
(15) All NMR (^1H, ^{31}P) coupling constants are in Hz.
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Attempted Cyclization of $N_3P_3Cl_5(NHCH_2CH_2X)$ (X = Cl, Br) to $N_3P_3Cl_5(NCH_2CH_2)$. Various reactions were attempted in order to convert the (2-haloethyl)amino derivatives to the corresponding aziridinophosphazenes. Reagents employed included triethylamine, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBu), lithium diisopropylamide, (2,2,6,6-tetramethylpiperidino)lithium, and 1,8-bis(dimethylamino)naphthalene (Proton Sponge). In all cases, the formation of a large number of trace products was observed.

Preparation of $N_3P_3[N(CH_3)_2]_5[NHCH_2CH_2N(CH_3)_2]$ (7). A three-necked, round-bottomed flask fitted with a nitrogen inlet, a Dewar condensor exiting through a mercury bubbler, a magnetic stirring bar, and a rubber septum was charged with 2.0 g (0.005 mol) of **3** in 150 mL of chloroform. The system was flushed with nitrogen and cooled to −78 °C. Dimethylamine, 6.0 g (0.13 mol), was added directly by syringe. The solution was stirred for 1 h at −78 °C, allowed to warm to room temperature, and stirred for an additional 3 h. The solvent was removed, and the oil-salt mixture was taken up in benzene.[12] After removal of the salt, the solution was passed through a short silica gel column. The solvent was removed, and then the residual oil was removed and taken up in hexane and a minimum of methylene chloride. Storage at 0 °C resulted in the formation of 1.9 g (84% of theory) of a white crystalline solid. Anal. Calcd: mol wt, 441. Found: mol wt, 441 (mass spectrum).[14] ^{1}H NMR:[15,17] δ_{CH_2} 3.30 (2 H), $^2J_{HH}$ = 6; $\delta_{CH_2N(CH_3)_2}$ 3.66 (2 H); $\delta_{CH_2N(CH_3)_2}$ 2.34 (6 H); $\delta_{P(NHR)N(CH_3)_2}$ 2.84 (6 H), $^3J_{PH}$ = 14; $\delta_{P[N(CH_3)_2]_2}$ (12 H) 3.80, $^3J_{PH}$ = 12. ^{31}P NMR: $\delta_{\equiv P(NHR)[N(CH_3)_2]}$ 23.6, $^3J_{PP}$ = 41.5; $\delta_{\equiv P[N(CH_3)_2]_2}$ 27.2.

Preparation of 2,2′-$N_3P_3[N(CH_3)_2]_4[NHCH_2CH_2N(CH_3)_2]$ (8). The reaction was allowed to proceed as the other dimethylaminolyses with use of 6.02 g (0.134 mol) of dimethylamine and 2.9 g (0.007 mol) of **4**. A yield of 1.6 g (42% of theory) of a white crystalline solid was obtained; mp 57 °C. Anal. Calcd: mol wt, 485. Found: mol wt, 485 (mass spectrum).[14] ^{1}H NMR:[15,17] δ_{CH_2} 3.28 (4 H); $\delta_{CH_2N(CH_3)_2}$ 2.18 (12 H); $\delta_{P[N(CH_3)_2]}$ 2.59, $^3J_{PH}$ = 10.5. ^{31}P NMR: $\delta_{\equiv P(NHR)_2}$ 19.7, $^3J_{PP}$ = 41.5; $\delta_{\equiv P[N(CH_3)_2]_2}$ 27.5.

Preparation of a $N_3P_3[N(CH_3)_2]_4[NHCH_2CH_2N(CH_3)_2]_2$ Mixture. This reaction was allowed to proceed as the other dimethylaminolyses with use of 6.0 g (0.134 mol) of dimethylamine and 2.0 g (0.005 mol) of the geminal/nongeminal $N_3P_3Cl_4(NHCH_2CH_2Cl)_2$ mixture. A yield of 1.5 g (68% of theory) of an oil that resisted crystallization was obtained. Anal. Calcd: mol wt, 485. Found: mol wt, 485 (mass spectrum). The ^{31}P NMR spectrum of the nongeminal isomer(s) (**9**) could be obtained from the mixture spectrum and the spectrum of **8**. ^{31}P NMR:[15,17] $\delta_{\equiv P(NHR)N(CH_3)_2}$ 23.8, $^3J_{PP}$ = 42.7; $\delta_{\equiv[N(CH_3)_2]_2}$ 27.3.

Attempted Preparation of 2,2,4,4-$N_3P_3[N(CH_3)_2]_2[NHCH_2CH_2N(CH_3)_2]_4$. This reaction was allowed to proceed as the other dimethylaminolyses with use of 2.0 g (0.044 mol) of dimethylamine and 0.5 g (0.001 mol) of **5**. Only degradation products were obtained.

Preparation of 2,4-$N_3P_3Cl_4(NHCH_2CH_2OCH_3)_2$ (10). A solution of 15.02 g (0.2 mol) of 2-methoxyethylamine in 100 mL of diethyl ether was slowly added to a stirred solution of 34.8 g (0.1 mol) of $N_3P_3Cl_6$ and 20.2 g (0.2 mol) of triethylamine in 150 mL of diethyl ether at room temperature. After an additional 24 h of stirring, the mixture was filtered and the solvent removed to yield a clear oil which gradually turned yellow. The oil was placed on a silica gel column and eluted with hexane until the $N_3P_3Cl_6$ was removed. A 60:40 benzene[12]:hexane mixture was used to elute the product. The resulting oil was dissolved in hexane, and 7.0 g (18% of theory) of a white crystalline solid, mp 87 °C, was obtained at 0 °C. Anal. Calcd for $N_3P_3Cl_4(NHCH_2CH_2OCH_3)_2$: C, 16.94; N, 16.48; H, 3.70; mol wt, 387. Found: C, 16.60; N, 17.07; H, 3.94; mol wt, 387 (mass spectrum).[14] ^{31}P NMR:[15] $\delta_{\equiv PCl_2}$ 22.0, $^3J_{PP}$ = 47.7; $\delta_{\equiv PCl(NHCH_2CH_2OCH_3)}$ 22.8.

Preparation of 2,2-$N_3P_3Cl_4(OCH_2CH_2Cl)_2$ (11). A solution of 1.6 g (0.02 mol) of 2-chloroethanol[11] in 50 mL of chloroform was slowly added to a solution of 3.47 g (0.01 mol) of $N_3P_3Cl_6$ and 2.0 g (0.02 mol) of triethylamine in 50 mL of chloroform. The reaction was allowed to stir for an additional 48 h. Workup as previously noted yielded 0.8 g (18.5% of theory) of a clear oil, which was very heat- and moisture-sensitive. Anal. Calcd: mol wt, 433. Found: mol wt, 433 (mass spectrum).[14] ^{1}H NMR:[15] δ_{OCH_2} 3.7 (2 H); δ_{CH_2Cl} 4.4 (2 H). ^{31}P NMR: $\delta_{\equiv PCl_2}$ 23.6; $\delta_{\equiv P(OCH_2CH_2Cl)_2}$ 16.2.

Results and Discussion

Preparation and Characterization. The reactions of 2-haloethylamines with hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, led to modest yields of the ((2-haloethyl)amino)chlorocyclotriphosphazenes. These reactions are carried out most conveniently and safely by generating the 2-haloethylamine in situ with use of the reaction of the amine hydrohalide with triethylamine:

$$N_3P_3Cl_6 + n NH_2CH_2CH_2X\cdot HX + 2n(C_2H_5)_3N \rightarrow N_3P_3Cl_{6-n}(NHCH_2CH_2X)_n + n(C_2H_5)_3N\cdot HX + n(C_2H_5)_3N\cdot HCl$$

X = Br, n = 1,2 (**1**, **2**)
X = Cl, n = 1, 2, 4 (**3**–**5**)

Although reactions in nonpolar solvents were slow and gave fewer decomposition products while reactions in more polar solvents were faster with more decomposition, all reactions were accompanied by the formation of resinous materials. Furthermore, the ((2-haloethyl)amino)cyclotriphosphazenes (**1**–**5**) produced in these reactions are very sensitive to both heat and moisture, especially in the pure state. Formation of large amounts of resinous materials in the reactions of primary amines with $N_3P_3Cl_6$ has been noted in previous studies.[6,18] These side reactions are believed to arise from intermolecular elimination of hydrogen chloride from two (or more) aminocyclotriphosphazenes.[19–21] In addition to this mode of reactivity, the ((2-haloethyl)amino)cyclophosphazenes (**1**–**5**) could also undergo reactions associated with the alkyl halide such as hydrogen halide elimination, quaternization of triethylamine by the alkyl halide, and endocyclic or exocyclic nitrogen atom alkylation. Another unwelcome aspect of the reactivity of these derivatives was the interaction with silica gel. A significant amount of material remained irreversibly bound to the silica gel in either column or preparative-layer chromatography. The sensitivity of these materials, along with their toxic[10] and probable mutagenic character, requires that extreme care be exercised in their handling.

The principal characterization methods for **1**–**5** were ^{31}P NMR spectroscopy and mass spectrometry. Infrared and ^{1}H NMR spectrometry were sufficient only to establish the presence of the cyclophosphazene and (2-haloethyl)amino functions, respectively. The broad-band-decoupled ^{31}P NMR spectra were either AB_2 or AX_2 spin systems. The chemical shift assignments were facilitated by comparison of spectra with and without broad-band decoupling since resonances attributed to environments containing the (2-haloethyl)amino moiety attached to a phosphorus atom are simplified by removal of phosphorus–proton coupling. The monosubstituted derivatives **1** and **3** exhibited AB_2 spectra with the chemical shifts of the $\equiv PCl_2$ and $PCl(NHCH_2CH_2X)$ centers falling in the ranges found in $N_3P_3Cl_5NHC_2H_5$ and other primary amine–pentachlorocyclotriphosphazene compounds.[22] In disubstituted derivatives **2** and **4**, AX_2 spectra are observed with the A resonance corresponding to the $\equiv P(NHCH_2CH_2X)_2$ and X to the $\equiv PCl_2$ centers, thus establishing the geminal configuration.

The products of the reaction leading to the bis((2-chloroethyl)amino)tetrachlorocyclotriphosphazenes vary with the solvent used in their preparation. In chloroform, only the geminal isomer **3** is observed both as the final product and in the ^{31}P NMR spectrum of the crude reaction mixture. When a more polar solvent (e.g. acetonitrile) is used, the ^{31}P NMR spectrum of the crude reaction mixture shows both the geminal AX_2 pattern and an A_2B pattern corresponding to the nongeminal isomer(s). The separation of the resonance lines was sufficient to obtain an approximate measure of the geminal to nongeminal ratio for the reaction mixture (2:1). Enrichment to a 1:1 mixture could be achieved by preparative-layer chromatography. The tetrakis((2-chloroethyl)amino) derivative **5** exhibits an A_2X ^{31}P NMR spectrum with the A resonance corresponding to the $\equiv P(NHCH_2CH_2Cl)_2$ centers. The ^{31}P NMR spectrum of the crude reaction mixture shows the presence of a trace amount of the

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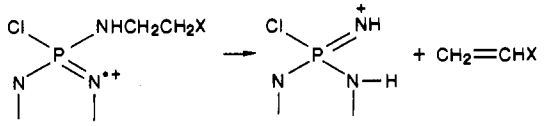
geminal tris derivative **6**. Attempts to prepare larger quantities of **6** were unsuccessful.

The mass spectra of **1**–**5**[14] were useful for determination of the degree of substitution and to demonstrate the absence of contamination by other phosphazene derivatives. Identification of ions was convenient due to the characteristic chlorine and bromine isotope distributions.[23] The molecular ions were observed for all the derivatives examined, and the major fragmentation pathways involve the exocyclic substituents rather than the N_3P_3 ring. In the monosubstituted derivatives **1** and **3**, the base peak is the $N_3P_3Cl_5(NHCH_2)^+$ ion. The cleavage of a carbon–carbon bond adjacent to a carbon–nitrogen bond is the dominant process in the mass spectra of primary aliphatic amines.[24] Other significant processes include phosphorus–chlorine, phosphorus–exocyclic nitrogen, and carbon–halogen cleavage and the McLafferty rearrangement leading to the $N_3P_3Cl_5(NH)H^+$ ion.



The vinyl halides that are eliminated in this rearrangement are also observed in the mass spectrum. The McLafferty rearrangement has been shown to play an important role in the fragmentation processes of a wide variety of organo-[25] and aminophosphazene[26] derivatives. The mass spectra of the geminal disubstituted derivatives **2** and **4** exhibit the same general processes observed for **1** and **3**. It is of interest to note that the base peak in **2** is the $N_3P_3Cl_4(NHCH_2CH_2Br)^+$ ion, while in **4** the corresponding ion is not observed and the base peak, $N_3P_3Cl_4(NHCH_2CH_2Cl)(NH)H^+$, arises from a McLafferty rearrangement. The mass spectrum of the geminal tetrasubstituted derivative **5** follows the patterns seen in **1**–**4**.

Selected derivativization reactions of the ((2-chloroethyl)amino)phosphazenes (**3**–**5**) were attempted. Dimethylaminolysis reactions lead to the replacement of chlorine atoms with dimethylamino groups at both phosphorus and carbon sites for the mono and bis derivatives.

$$N_3P_3Cl_{6-n}(NHCH_2CH_2Cl)_n \xrightarrow{HN(CH_3)_2} N_3P_3[N(CH_3)_2]_{6-n}[NHCH_2CH_2N(CH_3)_2]_n$$
$$n = 1, 2 \text{ (7–9)}$$

Attempts to prepare water-soluble ((2-chloroethyl)amino)phosphazenes[27] by amination only at phosphorus atoms were unsuccessful. Dimethylaminolysis of the tetrasubstituted derivative **5** only gave degradation products. The ^1H and ^{31}P NMR spectra of the mono (**7**), bis geminal (**8**), and bis nongeminal (**9**) derivatives were consistent with the structures deduced fro their chloro precursors. The value of $^3J_{PNCH}$ in (dimethylamino)phosphazenes is often used as a probe to local environment,[1] and the magnitude of this coupling constant in **8** and **9** is in keeping with the assignments made from the ^{31}P NMR spectra. The mass spectra of **7** and **8**,[14] while showing molecular ions, are complex due to the occurrence of McLafferty rearrangements involving each of the exocyclic substituents.

Aziridines may be prepared by dehydrohalogenation reactions of 2-haloethylamines and related materials. Given the interest that has been shown in aziridinocyclophosphazene derivatives,[8,9,26,28,29] the conversion of the ((2-haloethyl)amino)phosphazenes to the aziridino derivatives by treatment with bases that could serve as hydrohalide acceptors was attempted. In order to circumvent nucleophilic attack on the phosphorus centers, a variety of proton-specific bases were employed. However, in all cases, a large number of unidentified products were obtained in low yields.

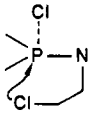
In order to examine further the characteristics that are operative in the reactions of $N_3P_3Cl_6$ with bases functionalized in the 2-position, two additional systems were investigated. In one of these the amino group was retained and the halogen was replaced with a methoxy group (2-methoxyethylamine) while in the other the halogen was retained and the amino group was replaced by a hydroxy function (2-chloroethanol):

$$N_3P_3Cl_6 + 2HECH_2CH_2X + 2N(C_2H_5)_3 \rightarrow N_3P_3Cl_4(ECH_2CH_2X)_2 + 2N(C_2H_5)_3{\cdot}HCl$$
$$E = NH, X = OCH_3 \text{ (10)}$$
$$E = O, X = Cl \text{ (11)}$$

The bis((2-methoxyethyl)amino) derivative **10** exhibits an A_2B ^{31}P NMR spectrum with the B resonance corresponding to the $\equiv P(NHCH_2CH_2OCH_3)Cl$ centers, and consequently, **10** is assigned a nongeminal structure. The 2-chloroethoxy derivative **11** exhibits an A_2X ^{31}P NMR spectrum with the doublet corresponding to the $\equiv PCl_2$ centers and the triplet to the $\equiv P(OCH_2CH_2Cl)_2$ center, and consequently, **11** is assigned a geminal structure. The mass spectrum[14] of **11** is of interest in that apparently each of the 2-chloroethoxy substituents can enter into the McLafferty rearrangement, providing a large amount of the $N_3P_3(O)_2(H)_2Cl_4^+$ ion.

Mechanistic Considerations. The observations reported in this paper provide additional complications to the already complex models required for rationalization of the stereochemical pathways followed in the reactions of amines with halocyclophosphazenes.[3] The reaction of ethylamine with $N_3P_3Cl_6$ has been examined in detail and found to provide the nongeminal bis isomers, a trace of the nongeminal tris isomer, and the geminal tetrakis derivative.[6] The introduction of a chlorine or bromine atom in the 2-position of ethylamine results in exclusive formation of the geminal bis isomer (**2**, **4**) in relatively nonpolar solvents while in polar solvents formation of the nongeminal bis material is observed but the geminal isomer still predominates. In the reactions of 2-chloroethylamine, a trace of the tris isomer (**6**) and reasonable amounts of the geminal tetrakis material (**5**) are also obtained. Two different models, one based on a substituent effect and the other on an incoming reagent effect, could be considered as providing reasonable rationalizations for these and related observations.

The first of these models involves assistance in chlorine displacement by a weak association of the exocyclic chlorine (or bromine) atom and the phosphorus center



thus lowering the energy of the dissociative reaction transition state. Exocyclic group participation in halogen displacement in nongeminal substitution reactions of $N_3P_3Cl_6$ have previously been proposed.[30,31] Given the ready formation of spirocyclic phosphazenes with bifunctional reagents such as ethanolamine,[32] there does not appear to be any geometrical restraints on the formation of the five-membered ring. The formation of the geminal bis(2-chloroethoxy)cyclophosphazene (**11**) while nongeminal replacement is the predominant mode of reaction of $N_3P_3Cl_6$ with

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alkoxy,[33] vinyloxy,[34] and aryloxy[30,35] reagents can also be rationalized by the substituent effect model. The formation of the nongeminal derivative (**10**) by 2-methoxyethylamine may reflect steric crowding by the methyl group decreasing the ability for effective oxygen-phosphorus interaction.

Alternatively, the source of the observed geminal selectivity may lie in a decrease in the rate of nongeminal attack. The ratio of geminal vs. nongeminal rates is responsible for the increased amounts of geminal product with increasing steric bulk of primary amines.[2,3] The rate of geminal isomer formation, via a dissociative process, is roughly constant. The rate of nongeminal isomer formation, via an associative process, is very dependent on the steric effects of the incoming reagent; thus, as the rate of the nongeminal process becomes slower, the geminal process becomes competitive. In 2-haloethylamines, the source of the rate retardation is electronic, not steric. It has previously been suggested that only the steric effect of the entering amine is significant but the range of basicity is extended when 2-haloethylamines are considered; e.g. $pK_b(BrCH_2CH_2NH_2) = 8.9$ vs. $pK_b(HCH_2CH_2NH_2) = 10.6$.[37] Thus, the weaker entering nucleophile (assuming nucleophilicity follows basicity) would have a higher activation energy so the alternative (dissociative) mechanism would be dominant, leading to the geminal product. It should be noted that this model does not preclude the operation of the substituent effect (proposed above) in the dissociative process. As one goes to more polar solvents, the rates of associative reactions of amines with $N_3P_3Cl_6$ increase,[3,35,38] hence, the appearance of the nongeminal product. The basicity of 2-methoxyethylamine ($pK_b = 9.44$) is greater than that of the haloethylamines, and hence, the formation of the nongeminal product is observed.

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Supplementary Material Available: Table S1, showing a GC study of the solvent dependence of the reaction of 2-chloroethylamine with $N_3P_3Cl_6$, and Table S2, showing major mass spectral fragments and their intensities (5 pages). Ordering information is given on any current masthead page.

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Organophosphazenes. 21. Synthesis of ((α-Methylethenyl)phenyl)fluorocyclotriphosphazenes[1]

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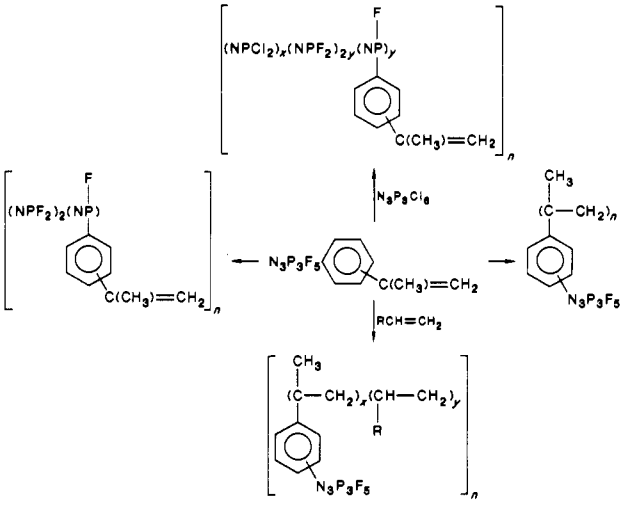
The reactions of (*m*-(α-methylethenyl)phenyl)- and (*p*-(α-methylethenyl)phenyl)lithium with hexafluorocyclotriphosphazene, $N_3P_3F_6$, lead to the formation of a series of ((α-methylethenyl)phenyl)fluorocyclotriphosphazenes, $N_3P_3F_{6-n}[C_6H_4C(CH_3)=CH_2]_n$ ($n = 1, 2$). At the bis stage of substitution both the geminal and non-geminal derivatives are obtained with the cis non-geminal species predominating. The cis to trans ratio is dependent on the position (meta vs. para) of the α-methylethenyl substituent on the phenyl ring. A model for the observed stereochemistry of the reaction is presented. The new compounds were characterized by mass spectrometry along with NMR (^1H, ^{13}C, ^{19}F, ^{31}P) and IR spectroscopy. Examination of the ^{13}C NMR spectra shows the modification in the phenyl charge distribution induced by the fluorophosphazene moiety.

Introduction

Organophosphazenes have become popular targets for synthesis in recent years[2-5] because of the inherent interest in this class of compounds and for more practical reasons, such as the development of new phosphazene monomers, which may be transformed into novel polymers.[3,4] Fundamental aspects of interest involve questions involving the factors that control the stereochemistry of the substitution reactions leading to organophosphazenes[2,6,7] and the synthesis of unique materials such as organometallic phosphazene derivatives.[4,5] Novel polymers from these monomers include polyphosphazenes with organic or organometallic substituents[4,8] and organic copolymers with cyclophosphazenes as substituents.[3] Monomers for this latter type of polymer have been olefinic phosphazenes. The high polarity of the olefin induced by the cyclophosphazene[9-11] has caused some difficulties in the

Scheme I



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