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Methylene insertion into the exocyclic P–N bonds of bis(amido)cyclodiphosphazane, *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$

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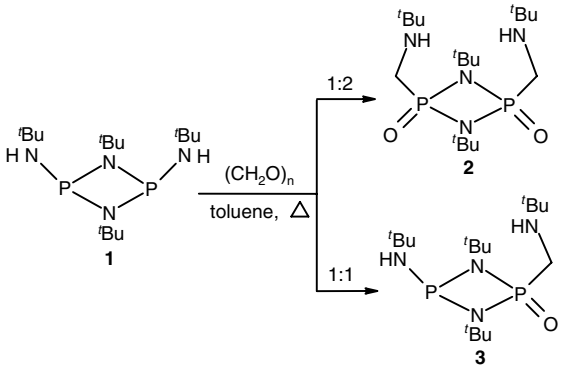
Abstract—The 1:2 and 1:1 reactions of *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$ (**1**) with paraformaldehyde afforded α-aminophosphonates, *cis*-[^{t}Bu(H)NCH$_2$(O)P(μ-^{t}BuN)]$_2$ (**2**) and *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)$_2$P(O)CH$_2$N(H)^{t}Bu] (**3**), respectively, through the insertion of a methylene moiety into the P–N bonds. The X-ray crystal structure of **2** reveals that the insertion reaction occurs selectively at the exocyclic P–N bonds of bis(amido)cyclodiphosphazane.

Over the past years, several ligands containing P–N bonds have been synthesized and utilized for stabilizing various transition metals.[1] However, the reactivity concerning P–N bonds is less explored.[2] Recently, we reported[3] the insertion of carbon fragments into P–N bonds in the reaction of aminophosphines with aldehydes, which leads to the formation of α-aminophosphonates. Several mono- and bis(aminophosphines) showed similar reactivity with various aldehydes and ketones. These α-aminophosphonates are biologically important as they are the key precursors for synthesizing numerous antibacterial, antiviral, and antifungal active α-aminophosphonic acid derivatives.[4] The insertion reaction is driven by the formation of thermodynamically stable P=O bonds similar to other phosphorus based reactions such as Wittig, Michaelis–Arbuzov, and Mitsunobu reactions. Recently, we observed a sigmatropic rearrangement driven by P=O bond formation in which the amine arm-containing cyclodiphosphazane or phosphite derivatives undergo [1,3]-sigmatropic rearrangement in the presence of elemental sulfur (or) selenium to produce the thio- or selenophosphates.[5] These reactions of cyclodiphosphazanes prompted us to investigate their reactivity with aldehydes. Bis(amino)cyclodiphosph(III)azane, *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$ contains both exocyclic and endocyclic P–N bonds, and it would be interesting to examine the selectivity of these P–N bonds toward methylene insertion reactions.

The reaction of *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$ (**1**) with 2 equiv of paraformaldehyde in toluene under reflux conditions gave methylene-inserted product **2** as shown in Scheme 1.[6] The mono inserted product **3** was obtained selectively from the 1:1 reaction between *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$ and $(CH_2O)_n$ under similar reaction conditions. The ^{31}P NMR spectrum of **2** showed a single resonance at 27.3 ppm, which is highly shielded compared to the bis(amido)cyclodiphosph(III)azane **1** (δ_P: 88.5 ppm) but at relatively higher frequency than the dioxo derivative, *cis*-[^{t}Bu(H)N(O)P(μ-^{t}BuN)]$_2$ (δ_P: −3.3 ppm).[7] The ^{31}P NMR spectrum of **3** exhibited two doublets at 74.8 ppm and 25.5 ppm with a $^2J_{PP}$ value of 5.3 Hz. The high frequency chemical shift was assigned to the unreacted phosphorus(III) center, whereas the signal at low frequency was due to the methylene



Scheme 1. Reactivity of cyclodiphosphazane with $(CH_2O)_n$.

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inserted phosphorus(V) center. The IR spectrum of **2** showed a band at 3235 cm^{-1} for ν_{NH}, which is about 70 cm^{-1} lower than that in *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$ ($\nu_{NH} = 3302\ cm^{-1}$). In the ^{1}H NMR spectrum of **2**, the inserted methylene protons appeared as a doublet at 3.03 ppm with $^2J_{PH} = 12.8$ Hz. The structural compositions of **2** and **3** were further confirmed from mass spectrometric data and elemental analyses.

Although, the methylene insertion into the P–N bonds in bis(amido)cyclodiphosph(III)azane **1** was confirmed by spectroscopic and analytical data, the selectivity of P–N bonds for the insertion reaction was inconclusive and attempts to grow suitable single crystals for X-ray studies were unsuccessful. However, we prepared the amine-dihydrochloride of **2** by passing HCl gas through a methanol solution of **2** for 10 min. Upon storing the concentrated solution for two days at room temperature X-ray quality crystals were obtained and the formation of the hydrochloride adduct was confirmed by low temperature X-ray study.[8]

The molecular structure of **2** with atom numbering scheme is shown in Figure 1 along with pertinent bond distances and angles. The molecular structure of **2** reveals that the methylene insertion reaction occurs selectively at the exocyclic P–N bonds. Also, the exocyclic nitrogen centers are protonated, while the endocyclic nitrogen centers remain neutral. The two P=O bonds present in **2** are arranged mutually cis to each other with P=O bond lengths of 1.470(2) Å. The P–C bond distance of 1.819(2) Å is comparable with the literature values.[9] The endocyclic P–N bond distance of 1.679(1) Å is slightly shorter than those present in *cis*-[^{t}Bu(H)NP-(μ-^{t}BuN)]$_2$ (1.726(2) Å)[10] and *cis*-[ClP(μ-^{t}BuN)]$_2$ (1.689(9) Å).[11] The interesting feature of **2** is the presence of strong hydrogen bonding interactions between the N–H and Cl of the amine-dihydrochloride (N2–H2NA···Cl: 3.111(2) Å, 168.00°, N2–H2NB···Cl: 3.091(2) Å, 167.00°). The N–H···Cl hydrogen bonding leads to the formation of an eight-membered ring above the four-membered P_2N_2 plane.

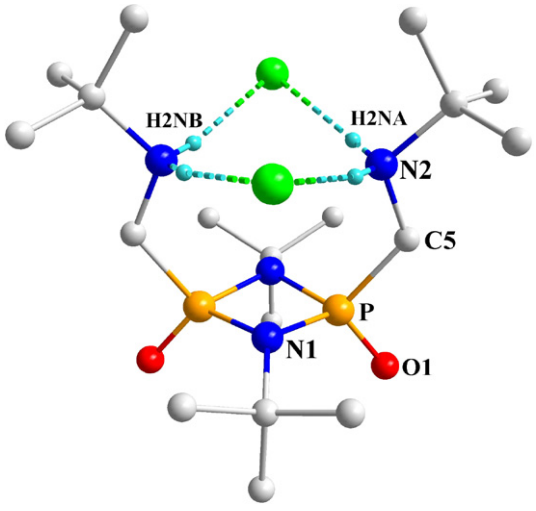


Figure 1. Molecular structure of **2**·2HCl. For clarity, hydrogen atoms except at N2 have been omitted. Selected bond lengths (Å) and angles (°): P–O1: 1.470(2), P–N1: 1.679(1), P–C5: 1.819(2), N1–C1: 1.503(2), N2–C5: 1.482(3), N2–C6: 1.546(2); O1–P–C5: 104.69(8), O1–P–N1: 120.46(8), P–C5–N2: 121.86(11), P–N1–C1: 127.89(11), C5–N2–C6: 114.61(12), P–N1–P^i: 93.89(7).

Previously, we suggested a mechanism for the methylene insertion into the P–N bonds in aminophosphines involving a Staudinger–Wittig pathway, in which proton transfer occurs from nitrogen to the phosphorus center to give $R_2P(O)H$ as an intermediate.[3a] However, this mechanism fails to explain the insertion observed in non-proton containing aminophosphines such as $RN(PPh_2)_2$ and $Ph_2PN(C_2H_4)_2NPPh_2$, hence we concluded that the presence of the NH group is not a necessary requirement for the insertion reactions.[3] The reactivity of bis(amido)cyclodiphosph(III)azane toward paraformaldehyde indicates that the preferential exocyclic P–N bond insertion is due to the relatively more basic nature of the amide nitrogens compared to the ring nitrogen atoms. The strained four-membered ring does not undergo ring expansion via an insertion reaction. Generally, the amines (R_3N) or phosphines (R_3P) react with CS_2 to produce respective dithioformate derivatives of the type R_3N–CS_2 (**I**) and R_3P–CS_2 (**II**) (Chart 1).[12] In contrast, the reactions of aminophosphines with CS_2 lead to the insertion of CS_2 into the P–N bonds; interestingly, compounds containing P(V) centers also show similar reactivity.[13] In bis(amido)cyclodiphosphazanes, competition exists between the phosphorus and the nitrogen lone pair for nucleophilic attack by CS_2. The reaction of *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$ with CS_2 gives selectively the phosphonium salt (**III**) as proved by single crystal X-ray diffraction studies.[14] These observations suggest that the aldehyde would interact first with the phosphorus center to form a betaine intermediate similar to CS_2. Based on this information, the following tentative mechanism is proposed for the insertion reaction involving a phosphaoxirane intermediate (Scheme 2). The existence of three-membered

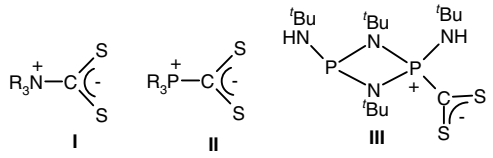
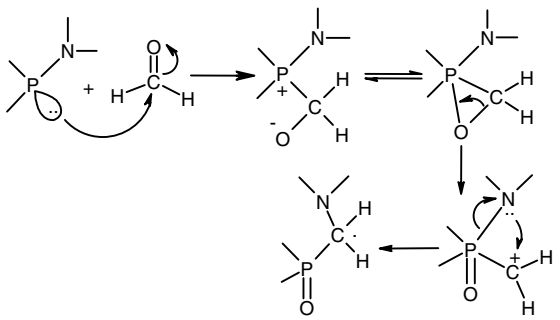


Chart 1.



Scheme 2. A plausible mechanism for the insertion reaction between a P–N bond.

POC rings has been proved structurally.[15] However, at this stage we do not have any spectroscopic evidence for the formation of a phosphaoxirane intermediate.

In conclusion, the exocyclic P–N bonds present in bis(amido)cyclodiphosphazane are reactive toward paraformaldehyde and gave the inserted product, whereas the endocyclic P–N bonds are inert to such reactions. This reaction is stereospecific and exclusively produced *cis*-cyclodiphosphazane derivatives.

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6. A mixture of *cis*-[^{t}Bu(H)NP(μ-^{t}BuN)]$_2$ (**1**) and paraformaldehyde in toluene (35 mL) was stirred under reflux conditions for 24 h. The reaction mixture was then cooled to room temperature and filtered through a frit. The filtrate was concentrated and stored at −30 °C for a day to afford a crystalline product. *Data for* **2**. Yield: 66% (0.87 g). Mp: 206–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (d, CH_2, 4H, $^2J_{PH} = 12.8$ Hz), 2.73 (s, *NH*, 2H), 1.39 (s, ^{t}Bu, 18H), 1.30 (s, ^{t}Bu, 18H). ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$): δ 27.3 (s). FT–IR (KBr disc, cm^{-1}): 3235 [ν(N–H)], 1091 [ν(P═O)]. Anal. Calcd for $C_{18}H_{42}N_4O_2P_2$: C, 52.92; H, 10.36; N, 13.71. Found: C, 52.68; H, 10.43; N, 13.57. MS (EI, *m*/*z*): 409.83 (M+1). *Data for* **3**. Yield: 72% (456 mg). Mp: 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (d, *NH*, 1H, $^3J_{PH} = 7.6$ Hz), 3.02 (d, CH_2, 2H, $^2J_{PH} = 13.6$ Hz), 1.93 (br s, *NH*, 1H), 1.39 (s, ^{t}Bu, 18H), 1.30 (d, ^{t}Bu, 9H, $J_{PH} = 1.2$ Hz), 1.06 (s, ^{t}Bu, 9H). ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$): δ 74.8 (s), 25.5 (d, $^2J_{PP} = 5.3$ Hz). FT–IR (KBr disc, cm^{-1}): 3310 [ν(N–H–)], 3221 [ν(N–H)], 1075 [ν(P═O)]. Anal. Calcd for $C_{17}H_{40}N_4OP_2$: C, 53.94; H, 10.65; N, 14.80. Found: C, 53.79; H, 10.73; N, 15.04%. MS (EI, *m*/*z*): 379.29 (M+1).
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8. Crystal data for **2**·2HCl: $C_{18}H_{44}Cl_2N_4O_2P_2$, $M = 481.41$, trigonal, space group $P3_221$, $a = 10.2364(6)$ Å, $b = 10.2364(6)$ Å, $c = 21.3954(19)$ Å, $\alpha = \beta = 90$, $\gamma = 120$, $V = 1941.5(2)$ Å^3, $Z = 3$, $D_c = 1.235$ g cm^{-3}, μ(Mo Kα) = 0.395 mm^{-1}, $F(000) = 780$, crystal size $0.22 \times 0.25 \times 0.28$ mm, $T = 100$ K. Data were collected on a Bruker APEX CCD diffractometer using Mo Kα radiation. A total of 17,472 reflections ($2.3 < \theta > 28.3$) were processed of which 3170 were unique and considered significant with Inet $> 2\sigma$(Inet). $R_{int} = 0.024$, final R values: $R_1 = 0.0317$, $wR_2 = 0.0817$, GOF ($F2$) = 1.10. CCDC Ref. No. 639466.
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