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Mechanochemistry Made It Possible: The First Synthesis of Sterically Encumbered Adamantoid Phosphazane $P_4(N^tBu)_6$

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Dedication ((optional))

Abstract: All reported attempts to synthesize the *tert*-butyl-substituted adamantoid phosph(III)azane $P_4(N^tBu)_6$ have failed, leading to the classification of this molecule as inaccessible and a literature example of steric control in chemistry of phosphorus-nitrogen compounds. We now demonstrate that this structure is readily accessible by a solvent-free mechanochemical milling approach, highlighting the importance of mechanochemical reaction environment in evaluating chemical reactivity.

Carbon-based covalent structures have been extensively studied and developed across a myriad of applications, involving small molecules as well as polymeric and extended frameworks.^[1] In contrast, the chemistry of covalent structures based on non-carbon backbones is much less advanced, with the exception of specific compound families that are based on strong covalent bonds of the Si-O (silicate minerals, zeolites, silicone polymers), P-O (e.g. phosphate ceramics and biologically occurring phosphates) or P-N (e.g. phosphazane polymers) type.^[2] However, most non-carbon based covalent arrangements are labile and highly air- and moisture-sensitive, making their synthesis challenging. Hence, the design and synthesis of complex inorganic covalent structures still remains an underdeveloped area in comparison to their organic counterparts.^[3]

Since the isolation of the first phosphorus-nitrogen (PN) heterocycle,^[4] there has been growing interest in such systems, and especially in cyclophosphazanes based on a saturated PN backbone. Importance of cyclophosphazanes arises from their structural versatility,^[5-10] with applications as multidentate ligands,^[11] asymmetric^[12] and organic catalysts,^[13] and antitumor drugs.^[14] The structure of the PN backbone in cyclophosph(III)azanes is controlled by steric and stoichiometric factors. A classic illustration of strict steric control is the $[XP(\mu-NR)]_2$ dimers (I, Figure 1a), observed for sterically demanding groups (e.g. R = ^tBu), whereas trimers $[XP(\mu-NR)]_3$ and larger structures are obtained with smaller substituents (e.g. R = Me, Et) (Figure 1a, II-V).^[6,15] Steric demand of the nitrogen substituent is thought to control the stability and accessibility of different cyclophosph(III)azane isomers, which can interconvert under suitable conditions,^[16] for example *via* the *twist*

mechanism found in the formation of type IV phosphazane $[[CIP(\mu-Npy)]_2]_2[P_2(\mu-Npy)]$ (Figure 1b).^[17] The *twist* mechanism was also proposed in the conversion of type V macrocycles, $[[P(\mu-NR)]_2(\mu-NR)]_2$, into the thermodynamically preferred type VI adamantoid isomer $P_4(NR)_6$ (Figure 1c).^[17] For the *iso*-propyl (ⁱPr) substituted macrocycle $[[P(\mu-N^iPr)]_2(\mu-N^iPr)]_2$ (1), conversion into the adamantoid isomer 2 is achieved by prolonged heating in a sealed tube (Scheme 1).^[18] However, over the past two decades all reported attempts to convert the *tert*-butyl (^tBu) substituted double-decker macrocycle $[[P(\mu-N^tBu)]_2(\mu-N^tBu)]_2$ (3) into its adamantoid isomer (4) have failed (Scheme 1).^[19]

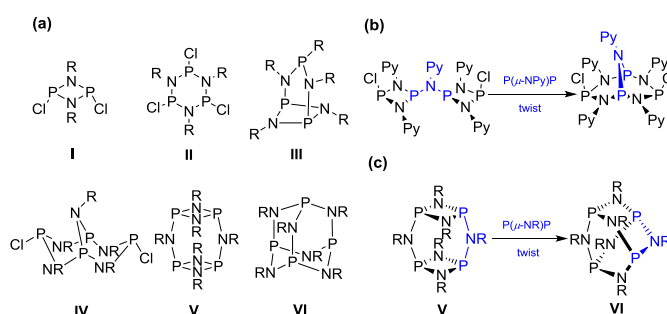


Figure 1. (a) Selected PN backbones; (b) and (c) *twist* isomerization mechanism in cyclophosphazanes.¹⁷

Furthermore, while the direct synthesis of adamantoid $P_4(NR)_6$ backbones by reaction of PCl_3 with RNH_2 was successful for less sterically hindered amines (i.e., R = Me, Et, ⁱPr), it failed for bulky ^tBuNH₂. These results led to a conclusion that the type V macrocyclic backbone is the more stable one in the presence of bulky ^tBu groups.^[20] Thus, 4 has been classified as inaccessible on steric grounds and is usually cited as an example of steric control in PN compounds.^[17,21,21]

Herein, we demonstrate that this so far elusive molecular structure is readily accessible by adopting a mechanochemical approach based on ball milling.^[22] Our study indicates that previous inability to access this molecule is not due to steric effects, but to inherent limitations of chemical reactivity in solution.

Mechanochemistry has emerged as an excellent solvent-free and atom-efficient alternative to conventional solution-based chemistry,^[23] enabling access to novel organic transformation and the synthesis of otherwise inaccessible molecules.^[24,25] However, mechanochemistry has been hardly explored in the context of non-carbon backbones and organometallics.^[26] We now demonstrate how the application of mechanochemistry resolves a long-standing challenge of cyclophosphazane chemistry by enabling the formation of adamantoid $P_4(N^tBu)_6$ (4) by isodesmic isomerization of its sterically encumbered cyclic dimeric phosph(III)azane counterpart 3 (Scheme 1).^[21]

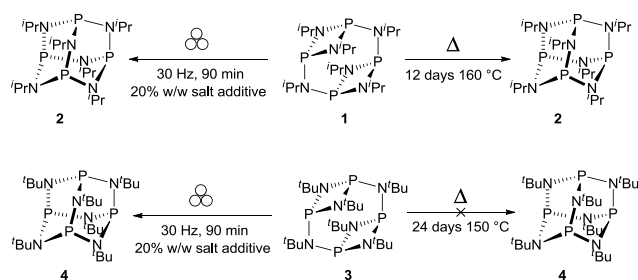
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Scheme 1. Herein described isodesmic isomerization of $[\{P(\mu\text{-NR})_2(\mu\text{-NR})\}_2]$ (V) into $P_4(\text{NR})_6$ (VI) by ball milling (left) has so far been difficult (for **2**) or impossible (for **4**) to achieve *via* solution methods (right). The symbol for mechanical milling has been proposed by Hanusa *et al.*^[26a]

Our first goal was the conversion of **1** into its adamantoid isomer **2** *via* ball milling. Previously, Wolmerhäser *et al.* reported this rearrangement occurs only upon prolonged heating at high temperature (12 days at 160 °C).^[18] An attempt to conduct the isomerization of **1** by milling for 90 minutes in a Retsch MM400 mixer mill operating at 30 Hz loaded with a 10 mm stainless steel ball (4 gram weight) was unsuccessful, as evidenced by the $^{31}\text{P}\{^1\text{H}\}$ nuclear magnetic resonance (NMR) spectrum of the milled material recorded in tetrahydrofuran (THF). Next, we explored modified mechanochemical approaches, by milling in the presence of a small amount of a liquid (liquid-assisted grinding, LAG) or salt additive, which has previously shown to enhance and direct mechanochemical transformations.^[27] Milling of **1** in the presence of toluene or THF (100 μL per 100 mg of solid reactant, corresponding to parameter^[28] $\eta = 1 \mu\text{L}/\text{mg}$) led to so far unprecedented room-temperature formation of adamantoid **2**. Conversion to **2** was ca. 20%, but screening of a series of different liquid and solid milling additives (Table S1, SI) revealed that the presence of 20% by weight of LiCl in the milling mixture leads to almost quantitative production of **2** after 90 min milling. This is in stark contrast to extensive time and harsh reaction conditions required in solution (*vide supra*).^[18] Formation of **2** was confirmed by ^1H , ^{13}C and ^{31}P NMR spectroscopy in solution and in the solid state (see SI). The obtained spectroscopic data are fully consistent with the literature,^[18,20] and formation of **2** was fully ascertained by single crystal X-ray diffraction after recrystallization from CH_3CN (Figure 3).

Next, we also explored milling **3** in the presence of additives (see SI). Similarly to the mechanochemical isomerization of **1**, milling of **3** in the presence of 20% LiCl by weight readily and quantitatively yielded **4**, which was previously thought inaccessible, after 90 min. This is particularly remarkable considering that **3** was reported not to isomerize even after heating for 24 days at 150 °C.^[19] To further evaluate the influence of standard reaction conditions on formation of **4**, we refluxed **3** in various solvents (*e.g.*, ether, hexane, THF, toluene, DMF) with identical amounts of salt additive. In all cases – with the exception of DMF, where **3** decomposed upon prolonged heating – the formation of **4** was not observed in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the sample even after extended reaction times, supporting the view that this adamantoid structure is not accessible by solution methods.

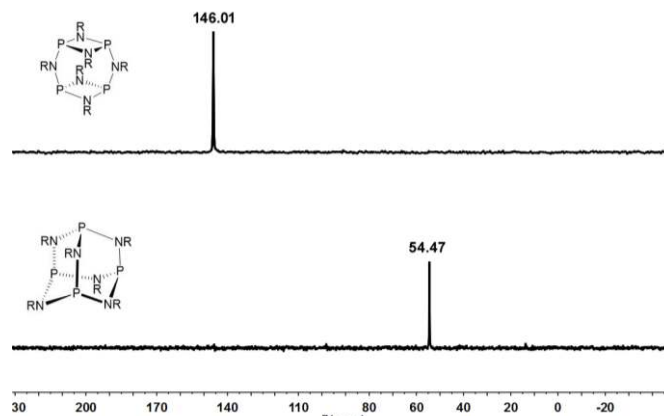


Figure 2. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of $[\{P(\mu\text{-N'Bu})_2(\mu\text{-N'Bu})\}_2]$ (**3**) (top) and $P_4(\text{N'Bu})_6$ (**4**) (bottom) in C_6D_6 . Further NMR spectra for compounds **1-4** are given in the SI.

After recrystallization from toluene, **4** was characterized by ^1H , ^{13}C and ^{31}P NMR spectroscopy in solution, as well as by X-ray powder diffraction and solid-state NMR spectroscopy (see SI). The $^{31}\text{P}\{^1\text{H}\}$ NMR chemical shift for **4** at room temperature exhibits a singlet at δ 54.47 ppm (Figure 2), which is comparable to that found for its 'Pr counterpart, δ 84.41 ppm (*cf.*, 117.2 ppm in **3**). The ^{13}C NMR spectrum shows two single resonances at δ 59.29 and δ 31.38 ppm (*cf.*, δ 58 and δ 29 ppm in **3**, see SI). In contrast to its precursor **3**, the room-temperature ^1H NMR spectrum of **4** shows only one single resonance at δ 1.51 ppm (*cf.*, 1.57 and 1.53 ppm in **3**, see SI), which is diagnostic of isomerization to an adamantoid structure. Low temperature single crystal structures of **2** and **4**, obtained from diffraction studies of crystals grown from CH_3CN and toluene, respectively, are in agreement with the initial spectroscopic analyses (Figure 3). The average P–N bond distance in **4** (1.72 Å) is comparable to that in analogous compounds containing less sterically demanding N-substituents (*cf.*, 1.69 Å and 1.71 Å in $P_4(\text{NMe})_6$ and $P_4(\text{NEt})_6$, respectively), which supports our view that previous inability to synthesize **4** was not due to steric constraints^[8a,29]

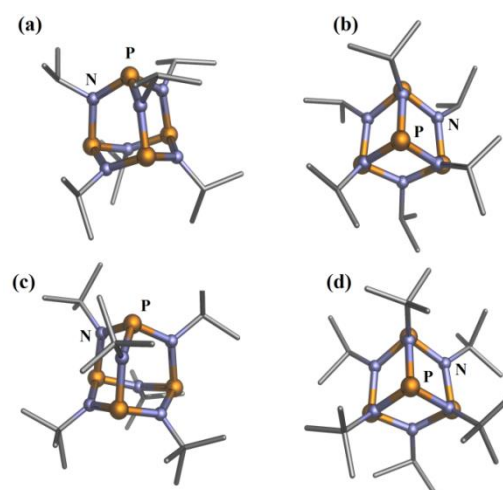


Figure 3. Views of molecules of **2** (a and b) and **4** (c and d), as established by single crystal X-ray diffraction. For selected bond lengths and angles, see SI. Hydrogen atoms are omitted for clarity. Nitrogen, phosphorus and carbon atoms are shown in blue, orange and grey, respectively.

The efficiency of the mechanochemical isomerization appears strongly dependent on the amount of LiCl present in the reaction mixture: at 10% by weight the reaction did not take place within 90 min of milling, while at 30% the conversion was less than quantitative. The lack of reactivity at a lower LiCl loading may be explained by the low concentration of salt, while the reduction in reactivity upon increasing the amount of LiCl above 20% is tentatively explained by dilution and less efficient mechanical impact onto the phosphazane reactant. As the formation of **4** is surprising and in contrast to the established understanding of cyclophosphazane chemistry, we decided to verify the viability of the isodesmic **3**→**4** isomerization by single molecule density functional theory (DFT) calculations (see SI). In contrast to our initial expectation that such an isomerization should proceed *via* the twist mechanism,^[17] the computational study suggests a stepwise mechanism in which the first step entails the formation of a P–N bond, while two more are cleaved, passing through the transition state **TS1** (Figure 4). The resulting postulated intermediate **Int1** adopts a bicyclic [3,1,1] structure resembling a type **III** backbone (Figure 1). Although we have so far not been able to experimentally confirm the existence of **Int1**, such cyclophosph(III)azane structures have been previously reported, *e.g.* for R = Cl, N₃, N(SiMe₃)₂,^[30] supporting the plausibility of the proposed mechanism. In the next step, the reaction passes through the transition state **TS2** to form the final adamantoid structure. The overall reaction is exothermic (~43 kJ·mol⁻¹), but involves very high-energy barriers (~160 and ~114 kJ·mol⁻¹ for **TS1** and **TS2**, respectively) (Figure 4). Such high energy barriers provide a potential explanation on why this molecule has remained inaccessible for so long. The calculated values of free relative energy ΔG for **Int1** and compound **4**, relative to reactant are ~62 and -44.8 kJ·mol⁻¹, respectively. Calculations performed on the reaction modelled in the presence of lithium chloride suggest that the salt additive does not lower the activation barrier (see SI).

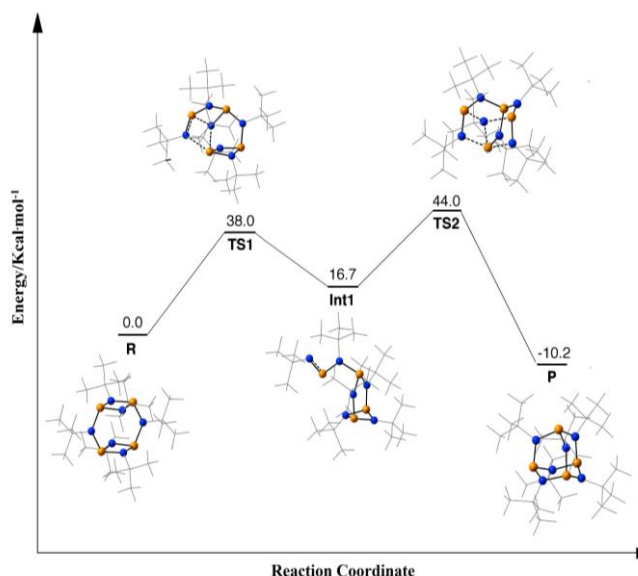


Figure 4. Energy diagram (in kcal·mol⁻¹) for the isodesmic isomerization of **3**→**4**, calculated at the B3LYP/B2/B3LYP/B1 +ZPE level. Nitrogen, phosphorus and carbon atoms are shown in blue, orange and grey, respectively.

In summary, we have demonstrated the first application of mechanochemistry for the transformations of non-carbon covalent backbones. The application of ball milling enabled the

rapid room temperature synthesis of the adamantoid iso-propyl-substituted cyclophosphazane **2**, a molecule that was previously accessible only by extended harsh heating of the starting bicyclic isomer. Most importantly, mechanochemistry permitted, for the first time, the synthesis of the tert-butyl-substituted adamantoid cyclophosphazane, **4** so far considered a textbook example of a sterically inaccessible molecule in main group chemistry. It is tempting to rationalize the unprecedented formation of **4** by milling due to effect of mechanical shear onto the electronic structure of reactants.^[31] However, such effects of shear on chemical reactivity have so far been reported only for polymers and extended frameworks, wherein pulling onto a molecular chain can cause a mechanical effect on a reactive (mechanophore) site.^[32] For materials based on small molecules, milling is more likely to cause the formation of short-lived 'hot spots' or a high-energy amorphous phase that can serve as a non-conventional, continuously agitated reaction environment.^[27,33] We believe that the herein presented formation of a previously inaccessible molecule is a breakthrough in main group chemistry. Our results illustrate the transformative potential that switching to a solvent-free or solvent-reduced mechanochemical environment can have on established chemical syntheses.

Acknowledgements

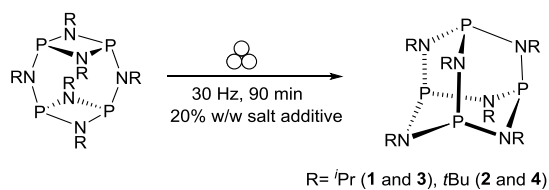
F. G. would like to thank NTU start-up grant (M4080552) and MOE Tier 1 grant (M4011441) for financial support. J. K. C. thanks the Australian Research Council for support. T. F. acknowledges support of W. S. Dawson Scholarship, McGill University. Crystallographic data for **2** and **4** is available from the Cambridge Crystallographic Database Centre (CCDC 1417218 and 1035873).

Keywords: phosphazane • rearrangement • main group • mechanochemical milling • green chemistry

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COMMUNICATION



All previous reported attempts to synthesize the tert-butyl-substituted adamantoid phosph(III)azane $P_4(N^tBu)_6$ have failed. This molecule has therefore, been classified as inaccessible and is cited as an example of steric control in the chemistry of phosphorus-nitrogen (P–N) compounds. Here, we demonstrate that this structure is readily accessible through a room temperature mechanochemical milling approach free of bulk solvent.

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