

# Sustainable Production of Reduced Phosphorus Compounds: Mechanochemical Hydride Phosphorylation Using Condensed Phosphates as a Route to Phosphite

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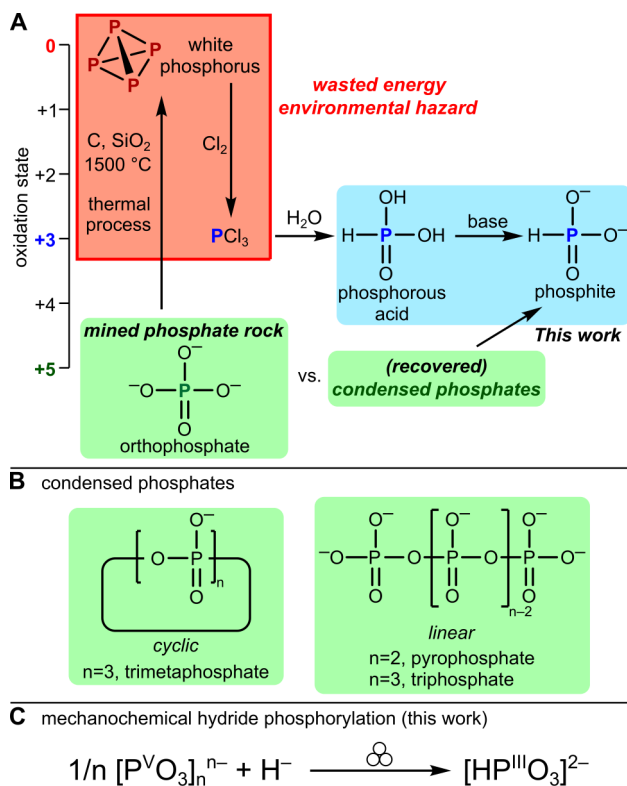
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**Abstract:** Phosphorus removal and recovery technologies have been implemented to tackle the anthropogenic eutrophication caused by phosphate runoff into waterways. In pursuit of a better utilization of the phosphates recovered from waste water treatment, we herein report that condensed phosphates can be employed to phosphorylate hydride reagents under solvent-free mechanochemical conditions to furnish phosphite ( $\text{HPO}_3^{2-}$ ), a versatile chemical with phosphorus in the +3 oxidation state. Hydride phosphorylation, as a two-electron one-proton reduction of a main group element oxide, constitutes a direct parallel with  $\text{CO}_2$  reduction to formate. Using potassium hydride as the hydride source, sodium trimetaphosphate ( $\text{Na}_3\text{P}_3\text{O}_9$ ), triphosphate ( $\text{Na}_5\text{P}_3\text{O}_{10}$ ), and pyrophosphate ( $\text{Na}_4\text{P}_2\text{O}_7$ ) engendered phosphite in 44, 58, and 44% yields based on total P content, respectively, under their optimal conditions. Formation of overreduced products including hypophosphite ( $\text{H}_2\text{PO}_2^-$ ) was identified as a competing process, and mechanistic investigation revealed that hydride attack on in situ generated phosphorylated phosphite species is a potent pathway for overreduction. The phosphite generated from our method could be easily isolated in the form of barium phosphite, a useful intermediate for production of phosphorous acid. This method circumvents the need to pass through white phosphorus ( $\text{P}_4$ ) as a high energy intermediate and mitigates involvement of environmentally hazardous chemicals. A bioproduced polyphosphate from baker's yeast was demonstrated to be a viable starting material for the production of phosphite. This example demonstrates the possibility of accessing reduced phosphorus compounds in a more sustainable manner, and more importantly, closing the modern phosphorus cycle.

Phosphorous acid ( $\text{H}_3\text{PO}_3$ ) and its conjugate base, phosphite ( $\text{HPO}_3^{2-}$ ), have found applications as reducing agents, as the starting material for preparing basic lead phosphite,<sup>1</sup> a stabilizer for chlorine-containing plastics, as cathode materials for lithium- and sodium-ion batteries,<sup>2–4</sup> as well as the starting material for other commercially important reduced phosphorus compounds, such as glyphosate.<sup>5</sup> Phosphite and related *H*-phosphonate esters are a family of key intermediates to organophosphorus compounds via elaboration of the P–H function into P–C bonds.<sup>6–12</sup> Recent advances in biotechnology have also cleared out a path for phosphite to act as an environmentally friendly herbicide, biostimulant, and biocide in modern agriculture owing to its minimal toxicity to humans and animals, biodegradability in soil, and



**Figure 1.** (A) Thermal process for manufacture of phosphorous acid and phosphite (red) versus the envisioned new process to produce phosphite (cyan) from phosphate inputs (green) without traversing the lower oxidation states; (B) structures of cyclic and linear condensed phosphates; (C) reaction design of mechanochemical phosphorylation of hydrides using condensed phosphates (this work).

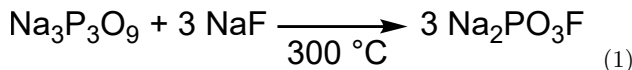
inability to trigger eutrophication of natural water bodies through agricultural runoff.<sup>13</sup> The development of transgenic crops that metabolize phosphite rather than phosphate has allowed phosphite to serve as both fertilizer and herbicide.<sup>14,15</sup> Additionally, phosphite is thought to have been a potential major nutrient in the pre-oxygenated Archaean oceans.<sup>16</sup>

However, current production of phosphorous acid relies on an energy-intensive process known as the thermal process in which the phosphorus in phosphate rock is first reduced at 1500 °C to P(0) (white phosphorus, P<sub>4</sub>), followed by oxidation back to P(III) as PCl<sub>3</sub> using chlorine gas. Subsequent

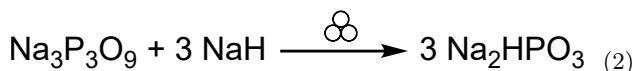
hydrolysis provides phosphorous acid (Figure 1A).<sup>1,17</sup> This carbothermal legacy process is very energy intensive and involves substances that are environmentally hazardous. In addition to phosphate rock, the primary source of phosphorus, phosphate recovery from waste streams is becoming an increasingly important method to obtain phosphorus,<sup>18</sup> as phosphorus is a nonrenewable resource<sup>19–21</sup> and high concentrations of phosphate in a water body lead to eutrophication.<sup>22</sup> Among those phosphate recovery methods, one well-established process, known as enhanced biological phosphorus removal (EBPR), utilizes microorganisms to take up phosphate from waste water and store it in intracellular polyphosphate granules.<sup>23–25</sup> In the “Heatphos Process”, polyphosphate can be released from bacteria by heating at 70 °C for 1 hour.<sup>26,27</sup> The recovered phosphate can be used as a raw material for the fertilizer industry.

Recently we showed that phosphate is a suitable precursor to chemicals traditionally synthesized from white phosphorus.<sup>28–33</sup> Building upon these principles, we sought to develop a process for the reduction of recovered phosphate to phosphite, bypassing hazardous white phosphorus and chlorine and minimizing energy waste (Figure 1A).<sup>34</sup> The envisioned reaction, hydride phosphorylation, can be considered as directly analogous to the canonical two-electron, one-proton reduction of a main-group element oxide: for instance, CO<sub>2</sub> reduction to formate.<sup>35,36</sup>

Our curiosity in regard to this topic was piqued by the industrial synthesis of sodium fluorophosphate (Na<sub>2</sub>PO<sub>3</sub>F), an active ingredient in toothpaste. In a 100% atom-efficient reaction, sodium trimetaphosphate (Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub>) and three equivalents of sodium fluoride are heated to 300 °C resulting in a melt and the formation of Na<sub>2</sub>PO<sub>3</sub>F:<sup>37</sup>



Sodium trimetaphosphate (Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub>), readily produced by the dehydration of phosphoric acid with sodium chloride,<sup>38</sup> is the smallest cyclic phosphate with a O:P ratio of three (Figure 1B), identical to that in phosphite. It is therefore an attractive starting material for reduction to produce phosphite. In analogy to the industrial production of Na<sub>2</sub>PO<sub>3</sub>F, we hypothesized that the reaction of Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub> with a metal hydride such as sodium hydride (NaH) might give rise to the formation of sodium phosphite (Na<sub>2</sub>HPO<sub>3</sub>):

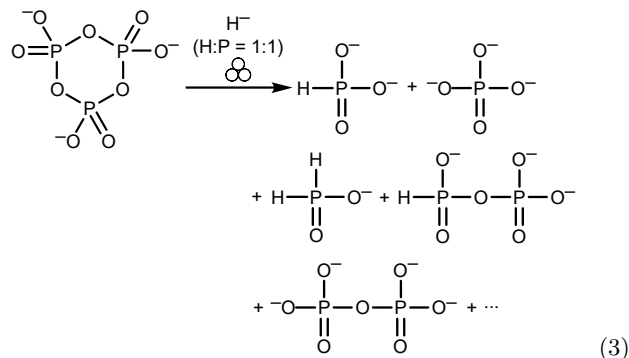


Along the lines of the synthesis of Na<sub>2</sub>PO<sub>3</sub>F, our initial strategy involved the thermal reaction between NaH and Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub> (neat, 3:1 molar ratio) at 300 °C, and we were pleased to observe the formation of the desired phosphite by <sup>31</sup>P NMR spectroscopy. However, the presence of unreacted trimetaphosphate as the major phosphorus-containing species at the end of the reaction sequence pointed toward poor conversion. Additionally, the formation of an unusual phosphinophosphate, [H<sub>2</sub>P–OPO<sub>3</sub>]<sup>2–</sup>, which is tentatively assigned based on data from NMR spectroscopy, suggested poor mixing of the solid reagents and high local concentrations of hydride, plausibly leading to overreduction.

In order to overcome this issue, we turned to

mechanochemistry. Protocols in which reagents are subjected to intimate mixing and grinding using ball mills have become increasingly popular in recent years, affording reaction products that cannot be obtained using traditional solution-based methods.<sup>39–45</sup> Additionally, the use of mechanochemistry obviates the need for solvent and can give short reaction times, good scalability, and even opportunities for in situ reaction monitoring.<sup>46,47</sup> Mechanochemical protocols have been applied to phosphorylate natural and synthetic polymers.<sup>48,49</sup>

Ball-milling reactions were conducted in a shaker mill using steel jars and ball bearings, using commercial hydride sources and thoroughly dehydrated phosphates. All water-soluble phosphorus-containing products were quantified by <sup>31</sup>P NMR analysis of an aqueous extract of the solid reaction mixture, and percentage yields and recovery rates of extraction are based on total P content in the phosphate input. The reaction of Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub> with three equivalents of NaH (H:P = 1:1) led to the formation of the desired product in short reaction times (within 60 min) with almost complete consumption of the starting material (Table 1). Other major products included pyrophosphate and orthophosphate. Control experiments confirmed that these phosphate materials did not appear simply by ball-milling Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub> alone under otherwise identical conditions, although Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub> was partially converted to a variety of cyclic and linear phosphates (see SI).



**Table 1.** Optimization of hydride source<sup>a</sup>

hydride	phosphite yield <sup>b,c,d</sup> (%)	conversion <sup>b</sup> (%)
LiH	17	99
NaH	10(16)	95
KH	23	>99
NaBH <sub>4</sub>	11(18)	92
LiAlH <sub>4</sub>	6(9)	82

<sup>a</sup> Reaction conditions: Na<sub>3</sub>P<sub>3</sub>O<sub>9</sub> (1.0 mmol), alkali metal hydrides (3.0 mmol) or NaBH<sub>4</sub> (0.75 mmol) or LiAlH<sub>4</sub> (0.75 mmol), 30 Hz, 60 min. <sup>b</sup> Determined by <sup>31</sup>P NMR spectroscopy.

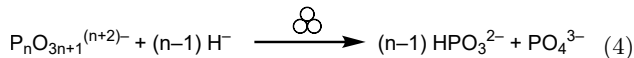
<sup>c</sup> Based on total P content. <sup>d</sup> Parenthesized value includes phosphite in free and phosphorylated forms when phosphorylated phosphites were observed.

Having observed formation of the desired product, we set out to optimize the hydride reagent. An initial survey of hydride sources at stoichiometric loading (H:P = 1:1) showed that potassium hydride (KH) gave superior results to other common hydride reagents in regard to conversion of phosphate input and yield of phosphite (Tables 1 and S1). The lower lattice energy of KH likely contributes to its higher reactivity at the crystal surface.<sup>50</sup> On account of the higher yields obtained using KH, we chose to use it as the hydride source to continue our study. Use of KH as the reduc-

tant also avoided the accumulation of phosphorylated phosphite (isohypophosphate,  $[\text{O}_2\text{HP}-\text{OPO}_3]^{3-}$ )<sup>51–54</sup> which was formed using other hydride reagents.

During the course of optimization, we also identified hypophosphite ( $\text{H}_2\text{PO}_2^-$ ), a species containing phosphorus in the +1 oxidation state, as a product of ball milling. In addition, a phosphorus recovery rate of only 81% suggested formation of insoluble or gaseous side products (presumably elemental phosphorus and phosphine gas, respectively). These findings pointed toward a non-negligible portion of  $\text{Na}_3\text{P}_3\text{O}_9$  undergoing overreduction to yield species in the lower oxidation states. Overreduction consumes hydride equivalents, thereby reducing the yield of phosphite, and also poses a danger to the environment as phosphine gas is known to be highly toxic.<sup>1</sup>

In pursuit of better yield and selectivity of reduction to phosphite, we explored the scope of phosphate sources (Tables 2 and S2). We first tried linear phosphates (pyrophosphate and triphosphate) that are industrially accessible by dehydration of hydrogen or dihydrogen phosphate at 300–900 °C.<sup>1</sup> Unlike cyclic phosphates, each polyphosphate molecule  $\text{P}_n\text{O}_{3n+1}^{(n+2)-}$  contains only  $(n-1)$  P-units that are susceptible to hydride attack, namely, in theory, a polyphosphate with  $n$  P-units can only produce  $(n-1)$  equivalents of phosphite with one equivalent of orthophosphate as byproduct:

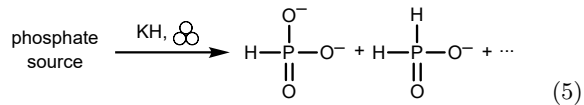


The reaction of sodium pyrophosphate ( $\text{Na}_4\text{P}_2\text{O}_7$ ) with one equivalent of KH (H:P = 1:2) furnished phosphite in 37% yield within 60 min of mixing. While elongating the reaction time at the same hydride loading did not improve the yield, an increased yield of phosphite (44%), which corresponds to 88% of reactive P-units, was obtained when a higher hydride loading (H:P = 1.5:2) was used followed by 90 min of mixing. A similar trend was observed in the reduction of sodium triphosphate ( $\text{Na}_5\text{P}_3\text{O}_{10}$ ) by KH. Mixing  $\text{Na}_5\text{P}_3\text{O}_{10}$  with two equivalents of KH (H:P = 2:3) yielded phosphite in 44% yield within 60 min, while an increased yield of phosphite (58%), which corresponds to 87% of reactive P-units, was obtained at a higher hydride loading (H:P = 1:1) after 90 min. Only a very low degree of overreduction was observed. Potassium phosphate salts react with KH in a similar fashion to sodium salts, but more slowly.

Sodium fluorophosphate ( $\text{Na}_2\text{PO}_3\text{F}$ ) engendered a moderate yield (47%) and a notable degree of overreduction. Commercial “sodium hexametaphosphate” or Graham’s salt, which is a mixture of cyclic and linear phosphates (Figure S10), afforded a low yield of 29%. Lastly, orthophosphate gave rise to no phosphite, confirming that the presence of phosphoanhydride bonds is key to such reduction reactivity by loss of phosphate as a leaving group. The reactivity of phosphoanhydride bonds predominates biological phosphorylation processes, which involve removal of a terminal  $\text{PO}_3^-$  group, such as in processes that consume ATP and produce ADP.<sup>55</sup>

Mechanochemical reduction of  $\text{Na}_4\text{P}_2\text{O}_7$  by KH followed by treatment with deuterium oxide ( $\text{D}_2\text{O}$ ) resulted in no detected deuterium incorporation in the formed phosphite as determined by  $^{31}\text{P}$  NMR spectroscopy, indicating that KH was the only source of hydrogen atom. This result confirmed

phosphorylation of hydride as the exclusive mechanism of phosphite P–H bond formation in the current system, ruling out a mechanism of KH reduction of phosphates to yield H-free low-oxidation-state phosphorus intermediates followed by protonation during aqueous workup.

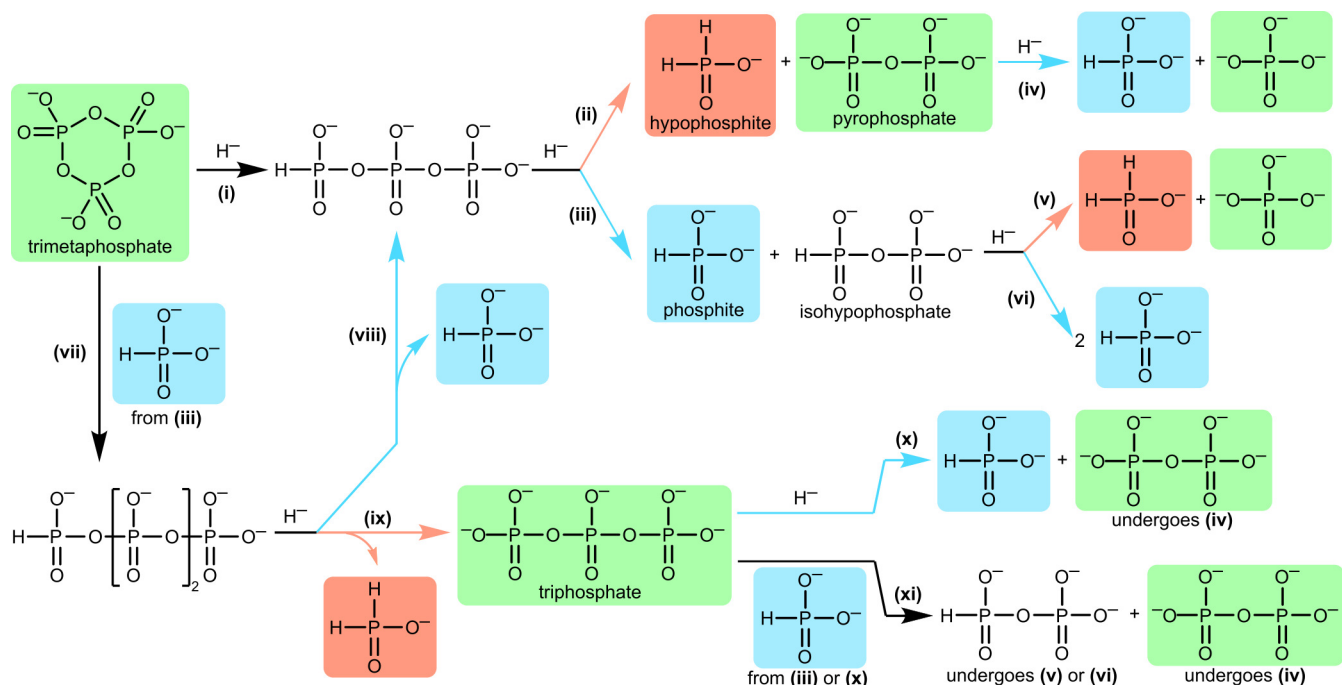


**Table 2.** Scope of phosphate sources and effects of hydride loading<sup>a</sup>

phosphate	H:P	yield <sup>b</sup> (%)		recovery <sup>c</sup> (%)
		$\text{HPO}_3^{2-}$	$\text{H}_2\text{PO}_2^-$	
$\text{Na}_3\text{P}_3\text{O}_9$	1:1	23	2	81
$\text{K}_4\text{P}_2\text{O}_7$	1:2	30[60] <sup>e</sup>	0	98
$\text{Na}_4\text{P}_2\text{O}_7$	1:2	37[74] <sup>e</sup>	0	98
$\text{Na}_4\text{P}_2\text{O}_7^d$	1.5:2	44[88] <sup>e</sup>	0	97
$\text{K}_5\text{P}_3\text{O}_{10}$	2:3	31[47] <sup>e</sup>	0	98
$\text{Na}_5\text{P}_3\text{O}_{10}$	2:3	44[66] <sup>e</sup>	trace	96
$\text{Na}_5\text{P}_3\text{O}_{10}^d$	1:1	58[87] <sup>e</sup>	0	98
$\text{Na}_2\text{PO}_3\text{F}$	1:1	47	2	93
Graham’s salt	1:1	29	2	85
$\text{K}_3\text{PO}_4$	1:1	0	0	97

<sup>a</sup> Reaction conditions: 1.0–3.0 mmol P, 30 Hz, 60 min. <sup>b</sup> Based on total P content; determined by  $^{31}\text{P}$  NMR spectroscopy. <sup>c</sup> Defined as recovery efficiency of total P content by aqueous extraction, determined by  $^{31}\text{P}$  NMR spectroscopy. <sup>d</sup> 90 min. <sup>e</sup> For polyphosphates  $\text{P}_n\text{O}_{3n+1}^{(n+2)-}$ , bracketed value of yield is based on  $(n-1)$  reactive P-units according to Eq. 4 (two for triphosphate, one for pyrophosphate).

To further improve the yield and alleviate generation of hazardous side products, we set out to seek the chemical origin of overreduction. First, we investigated the stability of phosphite toward hydride. No conversion was observed when sodium phosphite ( $\text{Na}_2\text{HPO}_3$ ) was ball-milled alone or treated with KH under typical reaction conditions, which rules out disproportionation<sup>56,57</sup> or hydride attack on phosphite as an overreduction pathway. We then studied the reactions of polyphosphates with various equivalents of hydride (Table S3). Treatment of pyrophosphate with half an equivalent of KH (H:P = 0.5:2) furnished phosphite in a good efficiency (74% based on hydride) without detected overreduction. However, reactions of sodium triphosphate ( $\text{Na}_5\text{P}_3\text{O}_{10}$ ) with substoichiometric KH (H:P = 1:3) resulted in a decreased yield of phosphite (60% based on hydride after 60 min, Table S3, entries 7 and 8) and observation of hypophosphite ( $\text{H}_2\text{PO}_2^-$ ), an overreduction product not detected when higher hydride loadings were applied (Table S3). Also identified in the reaction were isohypophosphate ( $[\text{O}_2\text{HP}-\text{OPO}_3]^{3-}$ ) and other phosphorylated phosphites, from which hypophosphite is generated via nucleophilic substitution with hydride (Figure 2(ii),(v),(ix)). These results suggested that, counterintuitively, reducing the amount of hydride employed has led to an increasing tendency for overreduction. A plausible rationale for this is that phosphite, the desired product, can undergo phosphorylation under the reaction conditions (Figure 2(xi)) thereby activating it for a second reduction by hydride (Figure 2(v)). While direct hydride attack at the bridging P-group in triphosphate as a pathway toward phosphorylated phosphite cannot be ruled out at this point, such rise in overreduction is primarily attributed to phosphorylation of generated phosphite. Char-



**Figure 2.** Proposed pathways for phosphite (cyan) and hypophosphite (red) formation from select condensed phosphates (green) applied as phosphate input and/or involved as intermediates.

acterization of the reaction of  $\text{Na}_2\text{HPO}_3$  with  $\text{Na}_5\text{P}_3\text{O}_{10}$  by  $^{31}\text{P}$  NMR spectroscopy revealed that phosphite is susceptible to phosphorylation by triphosphate under typical reaction conditions to afford isohypophosphate which may give rise to overreduction. Because this process is in competition with phosphate reduction (Figure 2(vi),(x)), adding excess KH mitigates phosphorylation of phosphite by depleting reactive polyphosphates in the system and thus leads to diminished overreduction. In contrast, pyrophosphate was found to be inefficient at phosphite phosphorylation under these conditions (see SI), which explains the lack of overreduction in its reactions. The observed behavior can be attributed to the diminished leaving group capacity of orthophosphate relative to linear condensed phosphates.

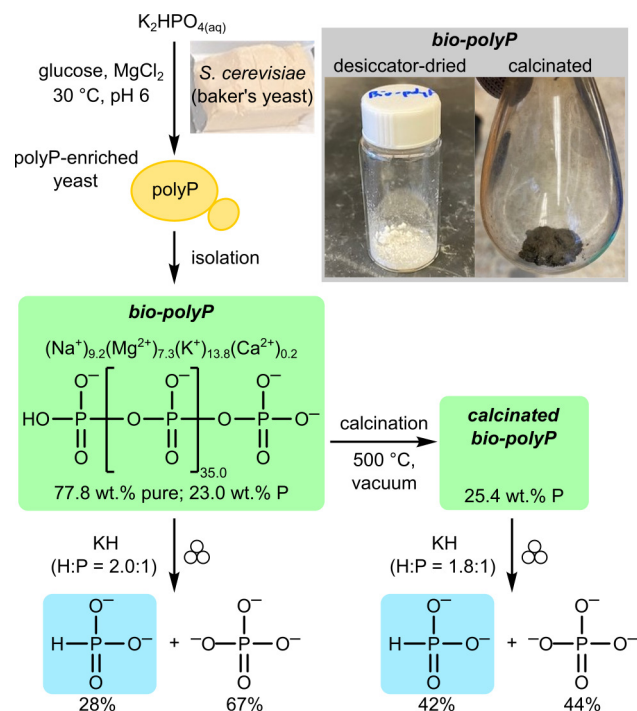
The reactions of sodium trimetaphosphate ( $\text{Na}_3\text{P}_3\text{O}_9$ ) with KH displayed a higher degree of overreduction (with up to 7% yield of hypophosphite; Table S3, entries 1–6) compared to the reactions of pyrophosphate and triphosphate. When  $\text{Na}_3\text{P}_3\text{O}_9$  was treated with substoichiometric KH (H:P = 1:3), phosphorylated phosphites of various chain lengths were the major reduction products instead of free phosphite, pointing toward a mechanism of hydride phosphorylation through ring opening followed by stepwise cleavage of terminal phosphates (Figure 2(i),(iii)). The ring opening reactivity of trimetaphosphate was further demonstrated by the facile mechanochemical reaction between  $\text{Na}_3\text{P}_3\text{O}_9$  and  $\text{Na}_2\text{HPO}_3$ , affording phosphorylated terminal phosphites of various chain lengths (Figure 2(vii)), which were assigned based on a combination of 1D- and 2D- $^{31}\text{P}$  NMR spectroscopic techniques (see SI). These results suggest that the ring-opening reactivity of trimetaphosphate provides additional pathways to form phosphorylated phosphites and thus significantly increases the degree of overreduction.

Despite having only one reactive P-unit per molecule, sodium pyrophosphate is a useful phosphate source due to its highly selective and efficient conversion to phosphite.

Therefore, we carried out phosphite isolation studies using  $\text{Na}_4\text{P}_2\text{O}_7$  as starting material. Isolation of phosphite from phosphates in the crude mixture was achieved through precipitating orthophosphate as struvite ( $\text{NH}_4\text{MgPO}_4 \cdot 6\text{H}_2\text{O}$ ), taking advantage of the low solubility of this mineral.<sup>58</sup> This method led to a 34% isolated yield of phosphite (67% based on reactive P) in the form of a barium phosphite salt  $\text{BaHPO}_3 \cdot \text{H}_2\text{O}$  (see SI). Phosphorous acid solutions can be prepared by treatment of the barium phosphite salt with sulfuric acid,<sup>59</sup> and protocols for separation of phosphorous acid from phosphoric acid on an industrial scale are well established.<sup>60–63</sup>

In biological systems, long-chain polyphosphate (polyP) is involved in ATP synthesis catalyzed by polyP kinases in which polyP is the source of a third  $\text{PO}_3^-$  group leading to ATP.<sup>64,65</sup> Inspired by the biochemical reactivity of polyP, we turned our attention to the application of bioproduced polyP as a source of  $\text{PO}_3^-$ . A recent protocol of polyP accumulation using *Saccharomyces cerevisiae* (baker's yeast) followed by isolation allowed us to obtain bioproduced polyP (bio-polyP, Figure 3) in multigram quantities.<sup>66,67</sup> The composition and structure of the isolated bio-polyP was analyzed by  $^{31}\text{P}$  NMR spectroscopy in conjunction with several elemental analytical methods. Linear phosphates (with  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  as counterions) constitute 77.8 wt.% of bio-polyP with an average degree of polymerization of 37, whereas residual orthophosphate and trimetaphosphate are <1.5 wt.%. The measured metal composition and average chain length of the isolated bio-polyP are similar to those of intracellular polyphosphates in bacteria in EBPR systems.<sup>68,69</sup> Major impurities include residual organic substances (protein and nucleic acid), water, and NaCl.

Mechanochemical reduction of bio-polyP with excess KH (H:P = 2.0:1) on a 0.2 g-scale afforded phosphite in 28% yield, far lower than the theoretical yield (97% P-units are reactive). Instead, a high yield of orthophosphate (67%) was observed and is mainly attributed to the interference from



**Figure 3.** Biotechnological production, properties, and mechanochemical reactivity of bio-polyP. Inset: photos of a bio-polyP sample dried in a desiccator at 25 °C (left) and a bio-polyP sample after calcination (right).

oxygen-containing impurities including water and residual organic mass.

Preliminary experiments revealed that the affecting impurities can be partially removed through vacuum calcination. While bio-polyP is labile upon heating under air at 120 °C as well as under ball milling conditions, affording orthophosphate and short-chain polyphosphates (see SI), calcination of bio-polyP at 500 °C under reduced pressure pyrolyzes organic impurities and removes the water content. The resulting dark material (Figure 3 inset) cannot be effectively extracted with water, but a <sup>31</sup>P NMR spectrum of its aqueous extract still confirmed long-chain polyphosphate as the predominant form of P. Calcinated bio-polyP engendered an increased phosphite yield of 42%.

In conclusion, we have demonstrated that phosphite can be accessed via direct reduction of polyphosphates by simple metal hydrides, using mechanochemical methods. Unlike the thermal process, this direct process bypasses the hazardous intermediate white phosphorus, and ostensibly does not traverse lower phosphorus oxidation states than +3. Optimization of reaction conditions revealed that high phosphite production yields and good selectivity can be achieved when employing linear phosphates as phosphate sources with KH as the hydride source. The optimized protocol employing pyrophosphate, which contains only the poor leaving group orthophosphate, gives high selectivity for the targeted P(V)→P(III) reduction. Mechanistic studies revealed that (poly)phosphorylated phosphite species that are generated through either ring opening of cyclic phosphates by hydride or phosphorylation of formed phosphite are key intermediates in the overreduction pathways observed when not using pyrophosphate as the P source. By using bioproduced polyphosphate from baker's yeast, we demonstrated that polyphosphates recovered from microorganisms could be promising starting materials for sustainable production

of phosphite, while certain impurities may be detrimental to the efficiency of production. With this case study we lay down an idealized framework for generating an industrially useful P(III) chemical that bypasses toxic and high-energy intermediates and presents an opportunity to move toward a 'closed-loop' phosphorus industry.

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## Competing Interests

The authors declare no competing interests.

## Supporting Information

Experimental details of mechanochemical reactions, characterization data, and protocol for accumulation and isolation of bio-polyP from baker's yeast are provided in the Supporting Information document.

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# Graphical TOC Entry

