## Functionalization of Intact Trimetaphosphate: A Triphosphorylating Reagent for C, N, and O Nucleophiles

# Functionalization of Intact Trimetaphosphate: A Triphosphorylating Reagent for C, N, and O Nucleophiles

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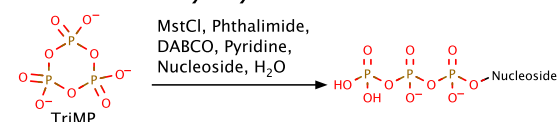
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***Abstract:*** Trimetaphosphate (TriMP, $[P_3O_9]^{3-}$) reacts with PyAOP ($[(H_8C_4N)_3PON_4C_5H_3][PF_6]$), to yield an activated TriMP, $[P_3O_9P(NC_4H_8)_3]^-$ (**1**), incorporating a phosphonium moiety. Anion **1** is isolated as its bis(triphenylphosphine)iminium (PPN) salt in 70% yield and phosphorylates nucleophiles with elimination of phosphoramide $OP(NC_4H_8)_3$. Treatment of **1** with amines $HNR^1R^2$ generates $[P_3O_8NR^1R^2]^{2-}$ (**2a**: $R^1 = R^2 = Et$; **2b**: $R^1 = H$, $R^2 = {}^tBu$) in greater than 70% yield as mixed PPN and alkyl ammonium salts. Treatment of **1** with primary alcohols in the presence of a tertiary amine base results in salts of intact TriMP alkyl esters $[P_3O_9R]^{2-}$ (**3a**, R = Me; **3b** R = Et) in greater than 60% isolated yield. Reaction of **1** with $[PPN][H_2PO_4]$ provides orthophosphoryl TriMP (**4**, $[P_4O_{12}H_2]^{2-}$) in 40% yield as the PPN salt. Treatment of **1** with Wittig reagent $H_2CPPh_3$ (2 equiv) provides phosphorus ylide $[P_3O_8CHPPh_3]^{2-}$ (**5**), in 61% yield as a mixed salt. Ylide **5** reacts with water to provide $[P_3O_8Me]^{2-}$ (**6**) and with aldehydes to give olefins $[P_3O_8CHCHR]^{2-}$ (**7a**: R = H, **7b**: R = 4-$C_6H_4Br$), products in which one TriMP oxygen is replaced by a phosphonate P–C linkage. Treatment of intact TriMP derivatives **2a**, **2b**, **3a**, and **7a** with aqueous tetrabutylammonium hydroxide results in ring-opening to linear triphosphate derivatives. X-ray crystal structures are provided for salts of **1**, **2a**, **3a**, and **4**.

Trimetaphosphate ($[P_3O_9]^{3-}$, TriMP) is of interest for triphosphorylation of nucleosides.[1–3] Protocols require electrophilic activation of TriMP, for example with mesitylenesulfonyl chloride (MstCl), but no active triphosphorylating agent has been identified conclusively, and linear triphosphate products are typically obtained upon hydrolytic workup (Scheme 1).[1] Smith and Khorana, in their work on the synthesis of nucleoside polyphosphates, noted that an attractive hypothesis to explain the accumulation of the triphosphate is that "it may exist in the reaction medium as a stable entity, for example, as the cyclic metaphosphate".[4] We have been interested in the preparation of metaphosphate salts,[5,6] which are solubilized in polar aprotic organic media using lipophilic counter cations; with the present work we bring this strategy to bear on the synthesis, isolation, and structural characterization of an activated trimetaphosphate reagent (anion **1**, Figure 1). The utility of anion **1** as a triphosphorylating agent is demonstrated by reactions with simple nitrogen and oxygen nucleophiles. Furthermore, anion **1** also effects triphosphorylation of the Wittig reagent, a carbon nucleophile, illustrating a novel synthetic pathway to phosphonate C–P linkages. Hydrolysis of the resulting phosphoramidates, organophosphates, and phosphonates opens the trimetaphosphate ring, resulting in linear triphosphate derivatives.
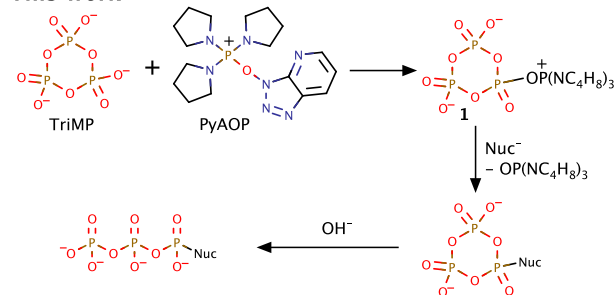
**Scheme 1.** Phosphate functionalization strategies[1,7]



The PPN salt of TriMP has been investigated in organic solvents as a ligand for transition metals.[5,6,9–11] It has properties favorable for functionalization studies including a lack of acidic protons, solubility in polar organic solvents, and crystallinity of reaction products. TriMP is also the obvious choice for synthesizing triphosphorylated biomolecules;[12] notable recent advances in this area using MstCl as activator are due to Mohamady and Taylor.[1,3,13] Phosphonium based condensing reagents have also been used as activators for phosphates and phosphonates for coupling with alcohols (Scheme 1).[7,14]

By analogy with a powerful methodology for carboxylate activation, we find that TriMP reacts smoothly with peptide coupling reagent PyAOP,[15,16] to provide anion **1** (Figures 1 and 2). Anion **1** is a potent electrophile, as the phosphonium group is able to leave as the neutral phosphoramide $OP(NC_4H_8)_3$. The PPN salt of **1** is readily isolated on a multigram scale under open air conditions. Anion **1** is analogous to the phosphorylation intermediates proposed in several previous publications,[7,14] but the present work represents the first isolation and characterization of such a phosphonium-phosphate. As a crystalline solid, the PPN salt of anion **1** is stable for weeks.

The structure of **1** as revealed by X-ray crystallography contains several interesting features (Figure 2). Notably, the P2–O4 and P2–O6 bond lengths of 1.555(1) and 1.554(1) Å are much shorter than the corresponding P4–O4 and P3–O6 bond lengths of 1.678(1) and 1.674(1) Å. The contraction of
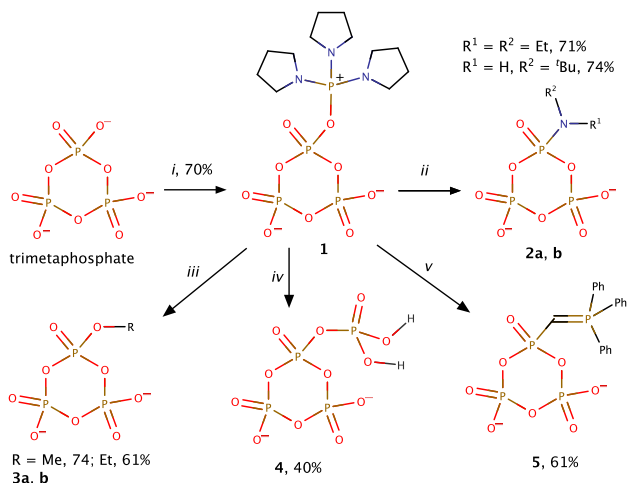
**Figure 1.** Synthesis of anions **1** through **5** as their PPN salts: *i*, one equivalent PyAOP in acetone for 30 minutes at 25 °C; *ii*, 5 equivalents amine in acetonitrile for 15 minutes at 25 °C; *iii*, 5 equivalents alcohol, 2 equivalents pyridine, and 2 equivalents triethylamine in acetonitrile for 2 hours at 25 °C; *iv*, one equivalent [PPN][$H_2PO_4$][8] in acetonitrile for 15 minutes at 25 °C; *v*, 4 equivalents $H_2CPPh_3$ in acetonitrile for 24 hours under an inert atmosphere at 25 °C.
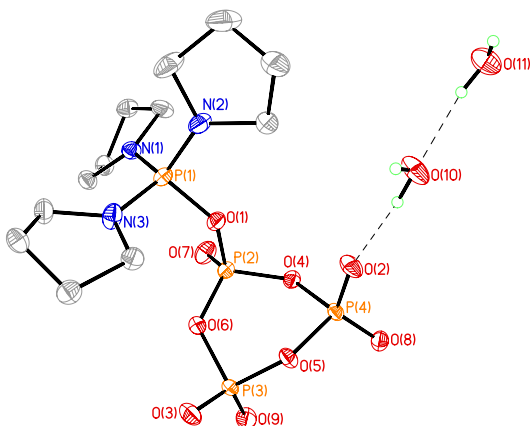


**Figure 2.** Thermal ellipsoid (50%) plot of anion **1** (dihydrate).

these bonds can be explained by the increased electrophilicity of P2. We explored this effect computationally with Natural Population Analysis (NPA) at the B3LYP/6-31++G** level of theory.[17,18] NPA reveals a natural charge of 2.67 for P2 compared to 2.58 for both P3 and P4. This difference in charge is small, suggesting that charge buildup on P2 is neutralized by the shortening of the P–O bonds.

Anion **1** reacts rapidly and quantitatively (as monitored by ^{31}P NMR spectroscopy) with the primary and secondary amines $H_2N^tBu$ and $HNEt_2$ to give new phosphoramidate species (Figure 1). These reactions generate an acidic proton, which is scavenged by excess amine to produce an alkyl ammonium counterion that engages in hydrogen bonding with an anionic phosphate ring oxygen, as revealed in a crystallographic study of the salt of **2a** (Figure S78). The acidic proton generated in such reactions should be a useful synthetic handle for introducing functionalized trimetaphosphate molecules into the coordination sphere of transition metals, along the lines of our previous work with monoprotonated TriMP.[6,9,10] As in the case of anion **1**, it is observed for **2a** that the P–O bond lengths of the functionalized phos-

phorus atom are shortened to 1.585(1) Å with elongation of the opposing P–O bond to 1.651(1) Å. This structural effect is somewhat less pronounced than that observed for **1**, as the more electron releasing –$NEt_2$ substituent induces less buildup of positive charge on the phosphorus atom.

As expected,[1] **1** reacts with primary alcohols (Figure 1). The reaction is less facile than for amines owing to the lower reactivity of ROH nucleophiles. It was necessary to add a tertiary amine base to the reaction mixture when functionalizing TriMP with an alcohol, to neutralize the generated acidic proton. Otherwise, an intractable mixture of products forms that contains, according to ^{31}P NMR analysis, symmetric linear triphosphate diesters and lower phosphates. The reaction of **1** with alcohols is slower than with amines, requiring hours rather than minutes to reach completion. However these reactions were found to reach completion faster when pyridine was used as the base rather than triethylamine, a less nucleophilic tertiary amine base. This observation suggests that pyridine may undergo initial phosphorylation, to form $[C_5H_5NP_3O_8]^-$ as a reactive intermediate. However, it was found that addition of triethylamine during the workup was necessary to isolate crystalline products (Figure S79). With these conditions, mixed PPN and triethylammonium salts of the methyl ester, **3a**, and the ethyl ester, **3b**, were obtained with a respectable isolated yield (74% and 61%). The salt of anion **3a** has been crystallographically characterized; hydrogen bonding is observed between the [$HNEt_3$]$^+$ cation and a negatively charged oxygen of the cyclophosphate ring (Fig. S79).

In contrast to the essentially quantitative nature of the reaction between **1** and amines, the reaction with ROH nucleophiles suffers from competing formation of TriMP. This can be ascribed to the reaction of **1** with water becoming competitive with the relatively sluggish ROH triphosphorylation. Excess ROH therefore increases the yield of phosphorylated product by minimizing unproductive conversion of **1** to TriMP. Utilizing one equivalent of methanol in the synthesis of **3a** rather than five equivalents extends the reaction time from two hours to eighteen hours and decreases the isolated yield from 74% to 54%. This problem is not fully mitigated by using anhydrous solvents under an inert atmosphere because the PPN salt of anion **1** crystallizes as a double hydrate, a feature that may be important to its stability or else key to our ability to obtain the salt pure and in crystalline form; efforts to obtain an anhydrous salt of **1** have not yet met with success. The PPN salt of **1**·($H_2O$)$_2$ is not effective for triphosphorylation of 2° or 3° alcohols as such reactions lead exclusively to trimetaphosphate.
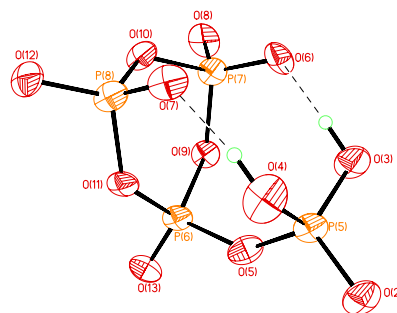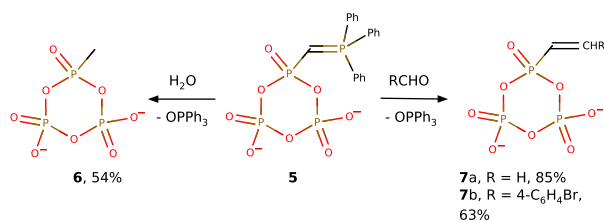


**Figure 3.** Thermal ellipsoid (50%) plot of anion **4**.

Phosphorylation of phosphates is an important reaction class, utilized with TriMP to produce nucleoside tetraphosphates from nucleoside monophosphates.[3] Anion **1** reacts

rapidly with the simplest monophosphate, orthophosphate, delivered as the salt [PPN][H$_2$PO$_4$], to generate anion **4** (Figure 1). Observed previously in complex reaction mixtures and dubbed "orthophosphoryltrimetaphosphate",[8] no pure salt of anion **4** has been reported until now. The crystalline PPN salt of **4**, obtained in 40% yield, was subjected to crystallographic analysis. Anion **4** features an interesting cage structure as a consequence of intramolecular hydrogen bonding with both protons located on the orthophosphate moiety (Figure 3). The $^{31}$P NMR data for **4** are consistent with the anion's solid state structure, with an upfield multiplet ($\delta$ −41.34 ppm) assigned to the branch phosphorus, a doublet for the two ring phosphorus atoms ($\delta$ −23.99 ppm), and another terminal phosphate doublet ($\delta$ −14.58 ppm).

**Scheme 2.** Treatment of **5** with water or aldehydes to generate phosphonates **6**, **7a**, and **7b**
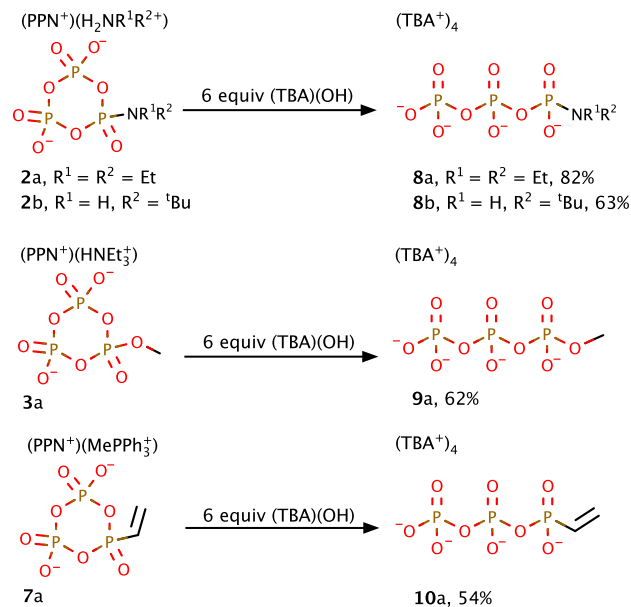


An attractive target is the phosphorylation of carbon nucleophiles. Extant methods for P–C bond formation require the intermediacy of a reduced phosphorus species; it should be recalled that typical phosphorus electrophiles such as PCl$_3$ or POCl$_3$ are derived from P$_4$ (white phosphorus). The idea of making organophosphorus compounds from phosphoric acid without the intermediacy of P$_4$ is a newly articulated objective in phosphorus chemistry.[19–22] In recent decades, the discovery of biological phosphonates has driven the elucidation of phosphonate biosynthesis. The majority of biological phosphonates are derived from phosphoenolpyruvate (PEP) rearrangement to phosphonopyruvate catalyzed by PEP mutase.[23–25] While phosphate esters OP(OR)$_3$ have been used for phosphorylation of carbon nucleophiles such as Grignard reagents,[26] they are typically prepared from phosphorus oxychloride POCl$_3$ by treatment with ROH.[27] Since POCl$_3$ is obtained from P$_4$ by chlorination and oxidation, the phosphate esters OP(OR)$_3$ prepared in this way are downstream of a reduced phosphorus intermediate. In contrast, TriMP can be obtained by thermal dehydration of phosphoric acid with sodium chloride.[28]

The Wittig reagent H$_2$CPPh$_3$ as a C-nucleophile reacts with **1** presumably generating the unobserved intermediate anion [P$_3$O$_8$CH$_2$PPh$_3$]$^{1-}$, which is deprotonated in turn by a second equivalent of the Wittig reagent. This results in anion **5**, itself a phosphorus ylide, delivering a powerful synthetic handle for the synthesis of phosphonates (Figure 1) in the unusual context of a singly functionalized, intact cyclic triphosphate. Due to the synthesis method, novel anion **5** is obtained as a mixed PPN and methyltriphenylphosphonium salt, which has proved difficult to crystallize. This mixed salt of anion **5** is obtained in reasonable purity and is well characterized by NMR spectroscopy and MS methods.

Reaction of **5** with water gives methyl phosphonate **6** (Scheme 2). As a phosphorus ylide, **5** undergoes the Wittig reaction with aldehydes to form alkenyl phosphonates **7**; the olefins generated from 4-BrC$_6$H$_4$CHO are a mixture of $E$ and $Z$ isomers (Scheme 2). Anion **5** is unreactive towards acetone and similar ketones at room temperature, a result

that is typical for stabilized phosphorus ylides. Phosphorus ylides stabilized by an adjacent phosphonate group are well known and have been employed previously in the synthesis of simple alkenyl monophosphonates.[29,30] The closest reported analogue to **5**, Ph$_3$PCHP(O)(OPh)$_2$,[30,31] has been utilized in the synthesis of 6'-deoxyhomonucleoside-6'-phosphonic acids from 5'-nucleoside aldehydes.[32]

**Scheme 3.** Ring-opening of anions **2a**, **2b**, **3a** and **7a** by treatment with aqueous tetrabutylammonium hydroxide



Selected examples of the isolated phosphoramidate (**2a** and **2b**), organophosphate (**3a**), and phosphonate (**7a**) trimetaphosphate derivatives were converted to linear forms by treatment with aqueous tetrabutylammonium hydroxide in acetonitrile (Scheme 3). Although excess hydroxide reacted with the phosphorus-containing cations to give side products, these were easily separated by extraction with dichloromethane. Accordingly, tetra-anionic linear triphosphate derivatives **8a**, **8b**, **9a**, and **10a** were isolated as water-soluble TBA salts in good purity without the need for chromatographic separation.

Previously, activated forms of TriMP were generated in situ with their chemical identities not well established. The synthesis and isolation of **1** shows that such molecules can be brought into the realm of well defined reagents and should encourage the preparation and characterization of analogs based upon TriMP with different leaving groups, or employing entirely different phosphates.

# Supporting Information Available

Experimental details, further characterization data, and X-ray crystallographic information are provided in the Supporting Information document. X-ray crystallographic information can also be accessed through the Cambridge Crystallographic Data Centre (CCDC), deposition numbers 1877207, 1877206, 1877205, and 1877204.

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# Graphical TOC Entry



C, N, O **Nuc**    **OH⁻**

Activated Trimetaphosphate    **LG** = Leaving Group    **Nuc** = Nucleophile