Dihydrogen Tetrametaphosphate, \([P_{4}O_{12}H_{2}]^{2-}\) –: Synthesis, Solubilization in Organic Media, Preparation of Its Anhydride \([P_{4}O_{11}]^{2-}\) and Acidic Methyl Ester, and Conversion to Tetrametaphosphate Metal Complexes via Protonolysis.” Journal of the American Chemical Society, vol. 136, no. 34, Aug. 2014, pp. 11894–97. © 2014 American Chemical Society

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Dihydrogen Tetrametaphosphate, \([P_4O_{12}H_2]^{2-}\): Synthesis, Solubilization in Organic Media, Preparation of its Anhydride \([P_4O_{11}]^{2-}\) and Acidic Methyl Ester, and Conversion to Tetrametaphosphate Metal Complexes via Protonolysis

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Supporting Information

ABSTRACT: Dihydrogen tetrametaphosphate \([P_4O_{12}H_2]^{2-}\) (1) can now be synthesized and isolated as its PPN salt ([PPN]⁺ = [N(PPh₃)₂]⁺) via treatment of [PPN][P₄O₁₂] with trifluoroacetic anhydride in wet acetone; this simple procedure affords the oxoacid salt in 94% yield. A pKₐ of 15.83 ± 0.11 in acetonitrile was determined. \([P_4O_{12}H_2]^{2-}\) reacts with the dehydrating agent \(N,N\)-dicyclohexylcarbodiimide to afford tetrametaphosphate anhydride \([P_4O_{11}]^{2-}\) (2) in 82% yield, also as the PPN salt. From 2 a monohydrogen tetrametaphosphate ester \([P_4O_{10}(OH)(OMe)]^{2-}\) (3, 96%) was derived by addition of methanol, illustrating that 2 can function as a reagent for chemical phosphorylation. Addition of water to 2 regenerates 1 quantitatively. Deprotonation of 1 by metal amides in the +2 oxidation state led to the unconventional monomeric \(\text{tin(II)}\ k^6\) tetrametaphosphate \([Sn(P_4O_{12})]^{4-}\) (4, 78%, a molecular analog of SnO) and binary dimeric chromium(II) bis(\(\mu_2\)k₂\(\kappa^2\)) derivative \([Cr_2(P_4O_{12})]^{4-}\) (5, 82%). Structural data stemming from single-crystal X-ray diffraction studies for the PPN salts of anions 1–5 are also reported.

The study of cyclic phosphates was initially undertaken almost two centuries ago coinciding with the advent of modern chemistry. The early interest in this fundamentally important research area has not yet translated into a modern chemistry. The early interest in this fundamentally important research area has not yet translated into a modern chemistry.2 The early interest in this fundamentally important research area has not yet translated into a modern chemistry.3 This class of molecules, the cyclic phosphates, is also strongly implicated in prebiotic chemistry.4 Recognizing that a significant opportunity for the expansion of cyclic phosphate chemistry could be realized by synthesizing an organic-media soluble acid form of tetrametaphosphate,5 we set out to investigate if a convenient entry point into this domain could be identified. Herein, we report a simple and high-yielding procedure for the preparation of a previously unknown organic-soluble form of dihydrogen tetrametaphosphate,6 which is demonstrated to be a potent precursor not only to its corresponding anhydride and methyl ester but also to metal tetrametaphosphates. This is a powerful new strategy in cyclic phosphate chemistry: the synthesis of tetrametaphosphate metal complexes via protonolysis.

In their work identifying the key intermediate in ATP synthetic routes developed by Todd and Khorana,7 Glonek, Kleps, and Myers (GKM) definitively characterized cyclic adenosine triphosphate which rapidly decomposed to ATP upon contact with water.8 GKM concluded that “it is likely that trimetaphosphate esters including that of adenosine will be found only in a nonaqueous milieu, such as the lipid portions of cell organelles”.9 The requirement of anhydrous media for the preparation of cyclic phosphate esters is universal not only in the synthesis of phosphate nucleosides but also in previous attempts to access the acid forms of cyclic phosphates. In 1956, Griffith reported that under furnace conditions the reaction of phosphoric acid with sodium dihydrogen phosphate afforded cyclic phosphate acids.9 However, an unrefined structure was reported,10 and there was an ensuing debate on the composition of the obtained polycrystalline form.11 Structurally well-characterized cyclic phosphate acids are a tetras(3,5-xylidinium) dihydrogen cyclohexaphosphate dihydrate12 and a sodium monohydror trimetaphosphate.13 Why are the acid forms of metaphosphate rings so rare? One reason could be associated with their essentially strong acidity, as implicated by the titration of sodium tri- and tetrametaphosphate with nitric acid.14 Following the “anhydrous principle”, we investigated whether a lipophilic organic cation, such as \([PPN]^+\) ([PPN]⁺ = bis(triphenylphosphine)iminium), could facilitate access to dihydrogen tetrametaphosphate in nonaqueous media by protonation of its tetrametaphosphate salt with a strong acid. Treatment of \([PPN][P_4O_{12}]\cdot5H_2O\) with 1 equiv of trifluoroacetic anhydride in acetone at 23 °C resulted in the formation of a single new cyclic phosphate species 1, which exhibits a singlet resonance at -25.6 ppm in its \(^{31}\text{P}\{^{1}H\} NMR spectrum. Upon addition of a dehydrating agent such as DCC (DCC = \(N,N\)-dicyclohexylcarbodiimide) to the reaction mixture, the \(^{31}\text{P}\{^{1}H\} NMR spectrum...
NMR spectrum displayed two triplet signals at −24.4 and −32.5 ppm in an A2B2 spin system, characteristic for the small ultraphosphate \([\text{P}_4\text{O}_{11}]^{2−}\) (Scheme 1). These results suggest that 1 is the oxoacid dianion dihydrogen tetrametaphosphate \([\text{P}_4\text{O}_{12}\text{H}_2]^{3−}\). Indeed, we were able to isolate the PPN salt of 1 as an analytically pure solid in 94% yield. The presence in 1 of acidic P−OH groups is evidenced by a broad singlet at 14.03 ppm in the \(^1\)H NMR spectrum recorded in CD\(_3\)CN at 23 °C. However, in solution these terminal acidic hydrogens are mobile; this being a general property of hydrogen-bonded oxoacids. The fluxional behavior of 1 is reflected in its \(^{31}\)P\(^{1}\)H) NMR spectrum which displays a single singlet resonance.

It should be emphasized that the synthesis of 1 is so facile that the reaction can be carried out on gram scales under open air conditions using commercial solvents and reagents as received. Trifluoroacetic acid reacts with H\(_2\)O from either the solvent or \([\text{PPN}]_4[\text{P}_4\text{O}_{12}]_4\cdot5\text{H}_2\text{O}\) to in situ generate trifluoroacetic acid (TFA), which can then protonate \([\text{P}_4\text{O}_{12}]^{4−}\). Acetone was identified as the most convenient solvent as it delivers a simple purification process. The simplicity of the purification procedure in acetone is primarily attributed to the lower solubility of \([\text{PPN}]_4\cdot1\) (this precipitates out of or crystallizes from the reaction mixture) relative to the byproduct \([\text{PPN}]_4\cdot[\text{CF}_3\text{COO}]_4\). It should be noted that strong Bronsted acids such as TFA, triflic acid, and triflic anhydride also react with \([\text{P}_4\text{O}_{12}]^{4−}\) to afford 1 in good isolated yields. In comparison, no formation of 1 was observed when \([\text{P}_4\text{O}_{12}]^{5−}\) was treated with a weaker Bronsted acid such as acetic acid.

The solid-state structure of \([\text{PPN}]_4\cdot1\) was established using single-crystal X-ray diffraction, and the resulting model of the dianion in C\(_2\) symmetry is depicted in Figure 1. The hydrogen atoms (placed at calculated positions and refined using a riding model) are arranged in a mutual 1,5 disposition. The most prominent feature is the presence of intramolecular hydrogen bonds between the protons and neighboring P−O−hydrogen-bond acceptors showing a short O21⋯O12A distance of 2.731(5) Å. Such hydrogen-bonding interactions may contribute to the stability of 1 in both the solid state and in organic solvents. The P−OH bond length of 1.5096(19) Å is intermediate between the long bridging P−O distances and the short external P−O distances.

Dihydrogen tetrametaphosphate 1 is not stable in aqueous solution in that it generates an acidic medium in which the formation of linear phosphates and phosphoric acid can be detected by \(^{31}\)P\(^{1}\)H) NMR spectroscopy. However, 1 shows significant stability toward H\(_2\)O in organic solvents such as acetonitrile and acetone, as no decomposition was detected after 48 h at 23 °C for an acetone solution of 1 containing 50 equiv of H\(_2\)O. The dianionic character of 1 serves to inhibit nucleophilic attack at the phosphorus atoms. Such an stabilization effect is commonly observed in the chemistry of general anionic phosphate diesters.

The instability of 1 in aqueous solution hampers measurement of its acidity in water. Nevertheless, the pK\(_a\) of 1 in acetonitrile was determined by UV−vis spectrophotometric titration of \([\text{PPN}]_4[\text{P}_4\text{O}_{12}\text{H}_2]\) coupled with 2,4-dinitrophenol (pK\(_a\) = 16.66 in MeCN) as a chromophore. A pK\(_a\) value of 15.83 ± 0.11 was thereby obtained for 1 in acetonitrile, corresponding to an intermediate acidity between that of TFA (pK\(_a\) = 12.65 in MeCN) and acetic acid (pK\(_a\) = 23.51 in MeCN), this being in agreement with the experimental observation that 1 can be prepared by protonation of tetrametaphosphate with TFA but not with acetic acid.

We further pursued the isolation of the observed small ultraphosphate 2. It was reported to be an important intermediate in the hydrolysis of \(\text{P}_4\text{O}_{10}\) and a key phosphorylating precursor to esters of orthophosphate and linear polyphosphate. However, neither an isolation procedure nor structural characterization was available until now. The reaction of 1 with a stoichiometric amount of DCC in acetonitrile led to the quantitative formation of 2 (as its PPN salt), which was isolated as an analytically pure solid in 82% yield after removing the byproduct dicyclohexylurea (DCU) that precipitated from the reaction mixture. Since ultraphosphate was originally defined as "an infinite cross-linked polymer of high viscosity," 2 would be more aptly described as the anhydride of dihydrogen tetrametaphosphate.

The solid-state structure of 2 was established via an X-ray diffraction study and is shown in Figure 1. The two negatively charged terminal phosphates are bent away from each other but with concomitant rupture of the phosphoanhydridic P−O3−P3 bridge adopt boat and chair conformations.

Treatment of 2 with acetone (H\(_2\)O content ≤0.5 w/w%) at 23 °C regenerates 1 in quantitative in situ yield and in a 68% isolated yield. The reaction likely occurs via nucleophilic attack of H\(_2\)O with concomitant rupture of the phosphoanhydridic P1−O3−P3 bridge. In a similar manner, the P1−O3−P3 bridge of 2 can also be cleaved by other hydroxy nucleophiles such as methanol, in that case yielding an acidic tetrametaphosphate methyl ester (Scheme 2). The reaction of 2 with 50 equiv of methanol at 23 °C afforded within 30 min the quantitative formation of methanolysis product \([\text{P}_4\text{O}_{10}(\text{OH})(\text{OMe})]^{2−}\) (3). The \(^{31}\)P\(^{1}\)H) NMR spectrum of 3 revealed a triplet at −24.6 ppm.

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**Scheme 1. Synthetic Route to the PPN Salts of Dihydrogen Tetrametaphosphate 1 and Tetrametaphosphate Anhydride 2**

**Figure 1. Solid-state molecular structures of \([\text{P}_4\text{O}_{12}\text{H}_2]^{3−}\) (1) and \([\text{P}_4\text{O}_{11}]^{2−}\) (2) with ellipsoids at the 50% probability level.**
Scheme 2. Methanolysis of 2 to Monohydrogen Tetrametaphosphate Methyl Ester 3

Scheme 3. Protonolysis Route to Anionic (P₄O₁₂)⁴⁻ Complexes of Tin(II) and Chromium(II)

Figure 2. Solid-state molecular structure of [P₄O₁₀(OH)(OMe)]²⁻ (3) with ellipsoids at the 30% probability level.

In the structure of 3 (Figure 2), the hydroxyl and methyl residues are located on opposing phosphoryl residues and intramolecular O–H···O hydrogen bonding between the hydroxyl and neighboring P–O⁻ bond is indicated, with an O₃2···O₂1 distance of 2.617(9) Å.

Since 1 can be delivered in anhydrous form and is soluble in organic solvents, it is uniquely suitable for synthesizing metal tetrametaphosphate complexes by protonolysis leading to replacement of simple basic ligands. Moreover, due to its diacidic nature it is commensurate for reaction with metals in the +2 oxidation state. Herein we tested the reactivity of 1 with a pair of metal(II) bis(hexamethyldisilazide) complexes leading to exemplary binary metal(II) tetrametaphosphate systems.

The reaction of [PPN]₂[Cr(HMDS)₂(THF)] and tin(II) oxide SnO has tin(II) in nearly an identical structural environment as reported by Moore and Pauling., making 4 an excellent molecular mimic of a known solid oxide material. To the best of our knowledge, 4 also represents the first example of η⁴ tetrametaphosphate coordination to a metal. The lone pair electrons at the tin(II) center are expected to be localized in an orbital very rich in s character in view of Bent’s rule considerations.

We further examined the reactivity of 1 toward the d-block metal(II) amide Cr(HMDS)₂(THF). Addition of 1 equiv of [PPN]₂[Cr(HMDS)₂(THF)] to a purple-brown solution of Cr(HMDS)₂(THF) at 23 °C rapidly afforded a pale-green solution. The [P{¹H}] NMR spectrum of this new species is silent in the phosphate region, suggesting that the tetrametaphosphate is coordinated to a paramagnetic chromium(II) center. After workup, a pale-gray solid was isolated in 82% yield. The solid-state structure of 5 was identified as a binary chromium(II) tetrametaphosphate dimer [Cr₂(P₄O₁₂)₄]²⁻ (5, Scheme 3, Figure 3) by X-ray diffraction. Each chromium adopts a square planar configuration. The Cr···Cr distance of 2.9020(13) Å suggests a very weak Cr···Cr...
interaction.31 Compound 5 represents the first example of a binary metal(II) tetrametaphosphate dimer. In the case of most other k1 tetrametaphosphate complexes, such as those bearing d0 Rh and Ir centers, typically only one tetrametaphosphate ligand is involved with two metal moieties bonded on either side of the P2O7 mean plane.33 However, an example of the M₂(P2O7)2 configuration observed here for anion S with approximate D₃h symmetry has been reported previously for titanium.36

We have described a simple preparative procedure for an organic-media soluble salt of the strong Brønsted acid dihydrogen tetrametaphosphate [P4O12H₂]²⁻ (1). This diacid dianion serves as precursor to numerous derivatives. The use of available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENTS

The authors declare the following competing financial interest(s): A provisional patent containing the material in this paper has been filed by MIT.

REFERENCES

(1) "The development of the chemistry of cyclophosphates was very slow, spreading along almost two centuries." Quote from André Durif, ref 32; see also references therein.


(5) The term "metaphosphate" is defined 32,118 as PO₄⁻³ as phosphorus analog of nitrate which exists as cyclic oligomers (PO₄)₅⁻.

(6) See ref 9 for a preparation of Na₂H₂P₄O₁₂.


