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The Structure of Tetramethyl μ-Monothiopyrophosphate

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ABSTRACT

The compound tetramethyl μ-monothiopyrophosphate ($C_4H_{12}O_6P_2S$) crystallizes in the monoclinic space group C 2/c, with (at −130°C) a = 10.322 Å, b = 8.229 Å, c = 12.062 Å, β = 98.44°, and D_{calc} = 1.639 g/mL³ and Z = 4. The crystal structure has been determined by single crystal X-ray diffraction to give a final R value of 0.0329 for 614 independent observed reflections [$F_o > 2.5\sigma(F_o)$]. The sulfur atom resides on a crystallographic two-fold axis. The P–S–P bond angle is 105.4° and the P–S bond lengths are 2.093 Å. The bond angles around phosphorus range from 99.1° to 118.2°. The terminal P=O bond is 1.465 Å, and the methoxyl P—O bond is about 1.556 Å. The H_3C–O–P bond angle is about 119.5°. Many structural features are interpreted in terms of π-bonding to phosphorus. Comparisons with the structures of pyrophosphate and related compounds indicate that the combined effects of increased acuteness of the P—S—P bond and the increased length of the P—S bonds lead to an increase of about 0.4 Å in the separation of phosphorus atoms in the sulfur-bridging compound. These facts, together with the weakness of the P—S bond, must be taken into account in the interpretation of kinetic data for enzymatic reactions of phosphorothiolates as substrates in place of phosphates.

INTRODUCTION

The structures of bridging-sulfur monothiopyrophosphates are of interest as potential substrates for enzymes because of their high chemical reactivity and their relation to naturally occurring substrates for enzymes that catalyze phosphoryl and phosphoryl ester group transfer reactions. μ-Monothiopyrophosphate (MTP) is a phosphoryl donor substrate for several enzymes, despite the fact that its steric requirements are expected to be significantly greater than those of pyrophosphate. The magnitude of the steric difference is important as essential information on which to base interpretations of comparative kinetic data.

Pyrophosphate and its derivatives are also of biological interest; for example, adenosine triphosphate (ATP) is among the most ubiquitous compounds in biochemical reactions. Analogues to such compounds are important enzyme inhibitors that have greatly aided the study of the structure and function of enzymes that catalyze phosphoryl group transfer [1]. Recently, a number of compounds of the form R—S—PO_3^{2-}, which are analogues to biological phosphate esters, have been prepared and tested as substrates of and inhibitors against a number of enzymes. MTP, in particular, is known to be a substrate of at least two enzymes whose normal substrate is pyrophosphate, inorganic pyrophosphatase [2] and pyrophosphate-dependent phosphofructokinase [3], which catalyzes phosphoryl group transfer from MTP to fructose 6-phosphate. To interpret the enzymatic rates for MTP and pyrophosphate, one must be able to relate these molecules in both structural and electronic terms, and for this it is essential to have bond lengths and angles for the P—O and P—S bonds in such molecules.

Since the preparation of bridging-sulfur thiodiphosphate tetraesters (tetraesters of MTP) by Edmundson and by Michalski and co-workers [4,5], the structure of only one such compound, bis(5,5′-

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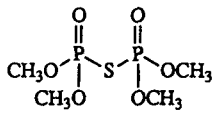

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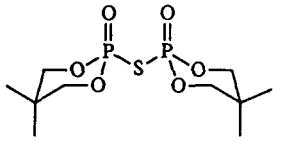

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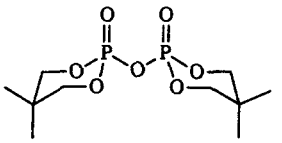

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dimethyl-2-oxo-1,3,2-dioxaphosphorinanyl) sulfide **2**, has been solved [6]. The structure of the analogous ester of pyrophosphate **3** has also been solved by x-ray crystallography [7]. In this article we report the crystal and molecular structure of **1**, the tetramethyl ester of μ-monothiopyrophosphate. In this compound the P—S bond lengths and P—S—P bond angle are similar to those in **2.**

EXPERIMENTAL

Preparation and Crystallization of **1**

Hexane and toluene (Mallinckrodt) were purified by fractional distillation after stirring with CaH_2. The synthesis of **1** was as previously described with minor modifications [5]. Crystals suitable for X-ray diffraction studies were obtained by slowly evaporating the hexane supernatant under a stream of N_2 at room temperature. Crystals also formed from 3:1 mixtures of hexane and toluene cooled slowly to −20°C. The crystals were deliquescent and dissolved within 2–3 minutes upon removal from the solvent and exposure to air.

X-Ray Data Collection, Structure Determination, and Refinement for **1**

Crystal Data: formula, $C_4H_{12}O_6P_2S$; molecular weight, 250.1; crystal system, monoclinic; T = −130°C; unit cell dimensions a = 10.322(3) Å, b = 8.229(3) Å, c = 12.062(4) Å, β = 98.44(3)°, V = 1013.4(6) Å^3; Z = 4; D_{calc} = 1.639 g/mL^3; μ(Cu-K_α) = 0.5912 cm^{-1}; F(000) = 520; λ(Cu-K_α) = 1.5418 Å; space group C2/c.

Under argon, a clear crystal (0.15 × 0.20 × 0.40) of the compound was mounted on a glass fiber and placed on a goniometer under a stream of cold nitrogen gas (−130°C). The final lattice parameters were determined from a least-squares refinement for 24 reflections (50° > θ > 45°) accurately centered on the diffractometer. Data were collected on a Syntex P-1 diffractometer with graphite-crystal-monochromated Cu-K_α radiation by the θ–2θ scan technique. A total of 1367 reflections were collected for a 2θ range of 3.5° to 110°; 614 of which were independent observed reflections [$F_o > 2.5\sigma(F_o)$]. The intensities were corrected for Lorentz and polarization effects.

Calculations were carried out with Siemans SHELXTL PLUS system of computer programs. The function $\Sigma w(F_o - F_c)^2$ was minimized. An extinction correction of x = 0.0079(12), where $F^* = F[1 + .002\chi F^2/\sin(2\theta)]^{-1/4}$, was made. Neutral atom scattering factors for S, P, O, C, and H were taken from known values [8].

The structure was solved by direct methods. A difference-Fourier map revealed the positions of the hydrogen atoms. Full-matrix least-squares refinement of the nonhydrogen atoms with anisotropic thermal parameters and the hydrogen atoms with B fixed at 5.5 Å^2 led to final values of R = 3.29 and wR = 5.51 (goodness of fit, 1.1). The largest peak in the final difference-Fourier map was 0.36 eA^{-3}. The weighting scheme was based on $w - 1 = \sigma 2(F) + pF2$, where p = 0.0015; no systematic variation of $w(|F_o| - |F_c|)$ versus IF_cI or (sin θ/λ) was noted.

RESULTS AND DISCUSSION

Structure of **1**

The molecular structure of **1** is illustrated in Figure 1, which also gives the numbering scheme. The atomic coordinates are given in Table 1, the bond lengths in Table 2, and the bond angles in Table 3. The sulfur atom resides on a crystallographic 2-fold axis. The P–S bond length is 2.093 Å, which is typical of single phosphorus–sulfur bonds in tetravalent phosphorus compounds [9]. The P–S–P angle of 105° is somewhat more acute than tetrahedral. The geometry around the phosphorus is a distorted tetrahedron, in which the bond angles about the phosphorus atoms average 109.4° (Table 3). The P–O bond lengths for the two methoxyl groups on a single phosphorus atom are the same, but the bond angles relating the methoxyl groups to the phosphoryl oxygen differ slightly. The angle for O(1)–P(1)–O(5) is 117.2°, while that for O(3)–P(1)–O(5) is 118.2°. These angles, and that of 99.1° for O(1)–P(1)–O(3) between the methoxyl groups, show the greatest deviations from tetrahedral around phosphorus. The angles between the sulfur and

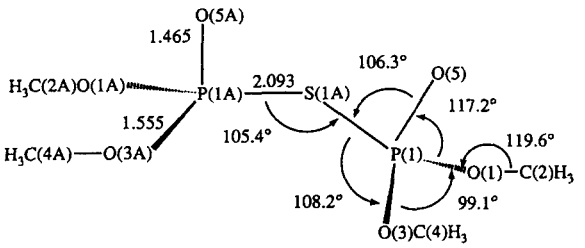

FIGURE 1 The bond lengths and angles in crystalline tetramethyl μ-monothiopyrophosphate **1.**

TABLE 1 Final Fractional Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients

	X/a	Y/b	Z/c	U (eq)[a]
S(1A)	0	−236(1)	7500	0.0245(4)
P(1)	1366(1)	1306(1)	8425(1)	0.0217(4)
O(1)	2171(2)	2125(2)	7582(2)	0.0257(7)
C(2)	3009(3)	1138(4)	6989(2)	0.0316(11)
O(3)	626(2)	2826(2)	8772(1)	0.0252(7)
C(4)	−84(3)	2723(4)	9727(2)	0.0304(11)
O(5)	2089(2)	307(2)	9314(1)	0.0300(7)

[a] U (eq) = $(U_{11} + U_{22} + U_{33})/3$

TABLE 2 Bond Lengths of Tetramethyl μ-Monothiopyrophosphate **1**

Bond	Bond Length (Å)
S(1A)–P(1)	2.093(1)
P(1)–O(1)	1.557(2)
P(1)–O(3)	1.555(2)
P(1)–O(5)	1.465(2)
O(1)–C(2)	1.450(4)
O(3)–C(4)	1.456(3)
S(1A)–P(1A)	2.093

TABLE 3 Bond Angles of Tetramethyl μ-Monothiopyrophosphate **1**

Bond	Bond Angle
P(1)–S(1A)–P(1A)	105.4(1)
S(1A)–P(1)–O(1)	107.3(1)
S(1A)–P(1)–O(3)	108.2(1)
S(1A)–P(1)–O(5)	106.3(1)
O(1)–P(1)–O(3)	99.1(1)
O(1)–P(1)–O(5)	117.2(1)
O(3)–P(1)–O(5)	118.2(1)
P(1)–O(1)–C(2)	119.6(2)
P(1)–O(3)–C(4)	119.3(2)

phosphoryl group oxygen, S(1A)–P(1)–O(5), and between the sulfur and the methoxyl group oxygens are much closer to the tetrahedral angle, 106.3° and 107°–108°, respectively.

Comparison of **1** *to* **2**

The structure of **1** is similar to that of **2** with regard to the lengths of the P—S bonds (Table 1); however, the angle defined by the P–S–P system (Table 2), is more obtuse by about 3° in **1** compared with **2** (Table 4). This difference apparently arises from the decreased constraints placed on the phosphorus–oxygen angles in the methyl ester **1** compared with the cyclic ester **2.** The angle O(1)–P(2)–O(3) in **2** is 106.2° [6], and the corresponding angle of 99.1° between the methoxyl groups in **1** is considerably further from tetrahedral. The angle S(1A)–P(1)–O(5) bond is 106.3° in **1** versus 110° in **2,** and it is the only bond angle from O(5) in **1** that is less than tetrahedral. The length of the bond linking phosphorus and unalkylated oxygen, O(5), is similar in the two compounds, 1.465 Å for **1** and 1.45 Å for **2** [6]. The bond angle P(1)–O(1)–C(2) is 119.6° in **1,** which is slightly more acute than the angles for the corresponding bonds in **2** (120°–121°) [6]. In the P–O–C linkages, the average P—O bonds are of nearly equal length for **1** and **2** (1.556 Å vs. 1.564 Å), although the average O—C bonds are shorter in **1** (1.453 Å) than in **2** (1.485 Å).

Structural Comparison of **1** *to Pyrophosphates*

The bond angle P–X–P is much more obtuse when oxygen bridges the two phosphorus atoms than when sulfur is the bridge. Moreover, the difference of about 30 degrees is much greater than the difference between the central H_3C–X–CH_3 bond angle of 111.7° for dimethyl ether and 99.1° for dimethyl sulfide [10]. The similarity in the P–O–P angles holds for tetraesters of pyrophosphate, dianionic pyrophosphate, and tetraanionic pyrophosphate (Table 4).

Phosphorus and other third-row elements are thought to undergo π-bonding with the lone pairs

TABLE 4 P–X Bond Lengths, P–X–P Bond Angles, and P-to-P Distances for Derivatives of Pyrophosphate and its Analogues

Compound	P–X–P Angle (°)	Ave. P–X Bond Length (Å)	P–P Distance, Å	Source
1	105.4	2.093	3.31	this work
2	102.2	2.105	3.28	[6]
3	132	1.63	2.98	[7]
$Na_4P_2O_7 \cdot 10H_2O$	130.2	1.612	2.925	[1]
$K_2H_2P_2O_7$, anhydrous	131.0	1.618	2.945	[27]
$Mn_2P_2O_7 \cdot 2H_2O$	127.5	1.613	2.893	[28]
$NH(PO_3Na_2)_2 \cdot 10H_2O$	127.2	1.678	3.006	[1]
$CH_2(PO_3H_2)_2$	117	1.79	3.05	[1]

of electrons of oygen and nitrogen [11]. For example, the cause of the planarity of trisilylamine is controversial; however, delocalization of the unshared electron pair on nitrogen into the silicon atoms is thought to be a major contributor. The angle of the central bond in disiloxane ($H_3Si–O–SiH_3$) is 144°, much greater than that of dimethyl ether. The openness of the bond angle supports the concept of π-bonding in disiloxane [12, 13], although steric interactions in the series of compounds $(R_3Si)_2O$ with various R groups may also play a role [14]. Electron-delocalization from the bridging oxygen into the phosphoryl groups would likewise be favored by an obtuse angle for P–O–P [15].

The length of the P—O bonds versus the P—C bond (Table 4) is also consistent with π-bonding from the central oxygen in pyrophosphates. The lengths of the P—O bonds are near 1.61–1.62 Å, which is much shorter than the 1.71 Å predicted for a single (no π-bonding) P—O bond [15]. The P—C bond is 1.79 Å, close to the predicted value of 1.83 Å [16].

Bond Lengths for Bridging Atoms

The reason that the P–S–P angle in **1** is more acute than the P–O–P angle in **2** may be that the larger radius of sulfur makes π-bonding less favored. Dittmer et al. discussed the possibility that sulfur participates in resonance delocalization less extensively than oxygen in neutral acids of the monoesters of phosphate and thiophosphate [17], and Frey and Sammons explained the physicochemical properties of phosphorothioate anions on the basis that electron pairs on sulfur are not significantly delocalized by resonance [18]. The latter interpretation of the properties of phosphorothioate anions implied that π-bonding between sulfur and phosphorus is much less favored than between oxygen and phosphorus. The π-bonding in hypervalent molecules such as phosphates and phosphorothioates has often been attributed to d_π-p_π bonding; however, in a recent paper Reed and Schleyer attributed it mainly to p_π-σ^* negative hyperconjugation [19].

The foregoing interpretation is supported by the fact that the lengths of the P—S bonds in **1** and other compounds containing a P–S–P linkage are near that predicted on the basis that no π-bonding is involved [9], in contrast to the case of P—O—P bonds. Parenthetically, we note that the bond lengths are in accord with the bond strengths; the bond dissociation energies for P—S bonds are 45–50 kcal mol^{-1}, whereas those for P—O bonds are 95–100 kcal mol^{-1} [20].

Bond Lengths and Angles of the Esterified Oxygen Atoms

The P–O–C bond angles in tetraesters of pyrophosphate and MTP are all near 120°; such open bond angles may indicate the presence of π-bonding interactions between the phosphorus atoms and the oxygen atoms of the alkoxy group. For **2**, the values are near 120°–121°, for **3** they lie between 118°–122°, and for **1** they are 117°–118°. It is interesting that the values for **3** are about half as distorted from tetrahedral as is the P–O–P angle of 132°. The P–O bond lengths in these compounds fall in the range 1.54–1.57 Å and are much shorter than either the predicted value for a P—O single bond of 1.71 Å [15] or the bridging P—O bonds (Table 4). The short length of these P—O bonds supports resonance delocalization of nonbonding electrons between phosphorus and oxygen; the bond is much shorter than predicted, and no reasonable alternative to π-bonding can be invoked to explain its length.

Further, the P–O–CH_3 bond angles and P–O–CH_3 bond lengths in dimethyl α-hydroxyiminobenzylphosphonate are similar to those in **1**, **2**, and **3** [21], and the exocyclic P–O bond lengths and P–O–C bond angles are also similar in methyl ethylene phosphate and methyl pinacol phosphate [22, 23]. Values near 120° for the P–O–C bond angle appear to be normal for monoesters as well, and π-bonding is invoked to explain these and other data [23].

Based on Cruickshank's correlation of P–O bond length with π-bond order [15], Bukowska-Strzyzewska and Dobrowolska assigned bond orders to all the P—O bonds in **3** [7]. The P—O bonds in the alkoxyl groups are slightly shorter in **3** than in **2** or **1**. Together with the phosphoryl group bond lengths, which average 1.41 Å for **3** [7], these data imply a greater overall π-bond order in **3** than in **2** or **1**.

The Phosphoryl Group

It is well-established that the stretching frequency of the P=O bond in compounds of the form $R_1R_2R_3P{=}O$ is a linear function of the sum of the electronegativities of the substituents [24, 25]. For three acyclic esters of pyrophosphate, the average stretching frequency of the P=O bond is 1287 cm^{-1} [26], whereas for four acyclic esters of MTP the average frequency is 1271 cm^{-1} [5]. Thus, the lower value of the P=O frequency in the case of tetraesters of MTP implies that the —$SP(O)(OR)_2$ group is less electronegative by 0.3–0.5 unit than the —$OP(O)(OR)_2$ group, as determined from the correlations found by a number of workers [23, 26]. The *apparent* electronegativity of a group is partly a function of its π-bonding ability [24, 25]; the calculated difference in electronegativities may, therefore, be more important qualitatively than quantitatively.

Importance of Structure to Reactivity

The structures of **1** and the derivatives of μ-monothiopyrophosphates and pyrophosphates listed in Tables 1 through 4 suggest that the P—S bonds are

essentially single bonds in this series, whereas the P—O bonds appear to have π-bond character. Thus, the P—S bonds in derivatives of MTP are weaker and longer than P—O bonds in comparable pyrophosphates; and the P–S–P angles are much more acute than the comparable P–O–P angles. The weakness of the P—S bond is a factor contributing to increased reactivity in nucleophilic substitution on phosphorus to the extent that P—S cleavage is important in the transition state. The combined effects of the greater length of the P—S bond, and the more acute P–S–P bond angle in **1** and **2** compared with **3** and other pyrophosphates, place the two phosphorus atoms about 0.4 Å further apart in derivatives of MTP compared with pyrophosphates. These differences must be taken into account in the interpretation of kinetic data obtained in enzymatic and nonenzymatic experiments.

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