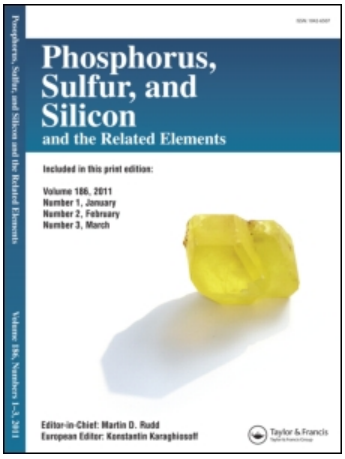

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Structural Analogues of Bioactive Phosphonic Acids: First Crystal Structure Characterization of Phosphonothioic and Boranophosphonic Acids

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Phosphonothioic and boranophosphonic acids have been structurally characterized for the first time by single X-ray crystallography. These two functional groups, and the corresponding phosphonic acid, were all conveniently synthesized in high yields from trityl H-phosphinic acid ($Ph_3CPO_2H_2$). The resulting trityl-substituted series: $Ph_3CP(O)(OH)_2$, $Ph_3CP(S)(OH)_2$, $Ph_3CP(O)(BH_3^-)(OH)]LH^+$ (L = Lewis base) is fully characterized by spectroscopic methods, and the structural characteristics are compared. The results indicate that boranophosphonic acids should be investigated anytime a bioactive phosphonic acid has been identified. The solid state arrangements of the synthesized compounds are also discussed.

Keywords Boranophosphonic acid; H-phosphinic acid; phosphonic acid; phosphonothioic acid; solid state; X-ray diffraction

INTRODUCTION

Phosphonic acids are an important class of organophosphorus compounds. Numerous biologically-active molecules contain this moiety[1] and various analogues have been evaluated as phosphonic acid replacements in bioactive compounds. Both boranophosphonic acids[2] and phosphonothioic (thiophosphonic) acids[3] have potential or demonstrated bioactivities; phosphonothioic acids have often been employed as phosphatase inhibitors, and recently boranophosphonic acids have been

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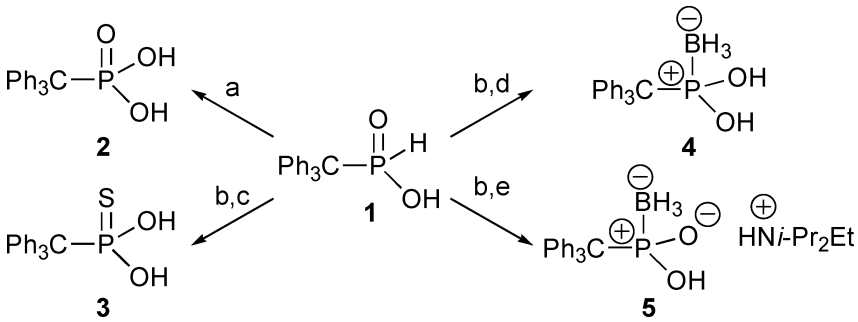


SCHEME 1 Synthesis of compounds **2–5**: (a) O_3, MeOH, 0°C, 82%; (b) N,O-bis(trimethylsilyl)acetamide, THF, RT, 1h; (c) S_8, RT, then MeOH; (d) BH_3Me_2S, RT, then MeOH; (e) $BH_3EtNiPr_2$, then NH_4OH, MeOH.

introduced in search of antiviral activity.[2] Furthermore they might be useful motifs in boron neutron capture therapy (BNCT).[4] Considering their importance it is surprising that, to the best of our knowledge, no X-ray crystal structures have been reported for compounds containing either functional group.[5]

RESULTS AND DISCUSSION

Synthesis

Herein, we report the synthesis, structural characterization, and comparison, of trityl phosphonic **2**, phosphonothioic **3**, and boranophosphonic acids **4** and **5**. All four compounds are prepared from facile syntheses from the known trityl-H-phosphinic acid **1**[6] in excellent yields (Scheme 1). To enable structural comparisons and to allow the introduction of various functionalities we employed a divergent synthetic approach for all three functional groups from **1**, thus providing additional examples of the utility of H-phosphinic acids in organophosphorus chemistry.[7]Simple oxidation of **1** with ozone[8] delivered **2** cleanly. Silylation of **1** and trapping of the resulting phosphonite with elemental sulfur, or with borane-dimethylsulfide complex, followed by methanolysis, afforded **3** and **4**, respectively. The boranophosphonic acid salt **5** was obtained analogously to **4**, but using BH_3DIEA followed by treatment with methanolic ammonium hydroxide.[2] Trityl phosphonic acid is typically made by reaction of triphenylmethanol with PCl_3 followed by hydrolysis.[9,10] Phosphonothioic acids have been prepared on occasion from H-phosphinic acids through silylation followed

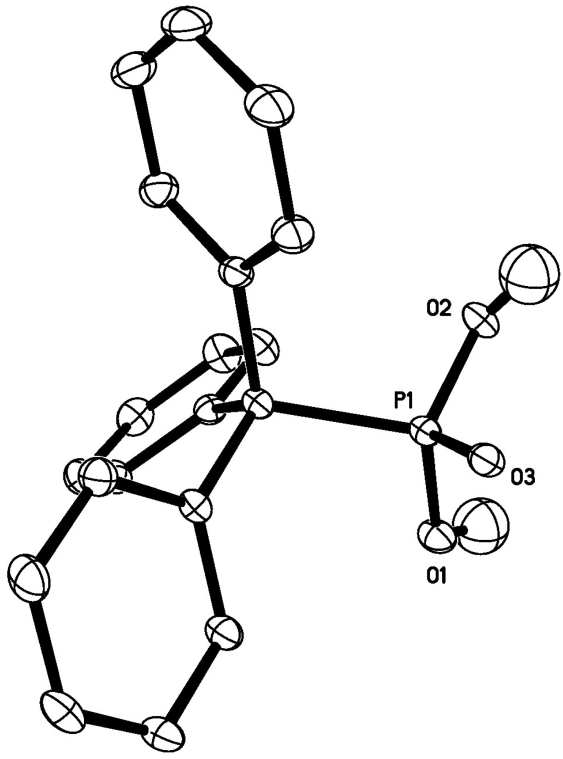


FIGURE 1 X-ray structure of $Ph_3CP(O)(OH)_2$ **2**. Selected bond distances (Å) and angles (deg): P(1)-O(3), 1.5070(10); P(1)-O(1), 1.5386(10); P(1)-O(2), 1.5518(11); P(1)-C(1), 1.8588(14); O(3)-P(1)-O(1), 111.36(6); O(3)-P(1)-O(2), 112.41(6); O(1)-P(1)-O(2), 108.29(6); O(3)-P(1)-C(1), 110.73(6); O(1)-P(1)-C(1), 105.90(6).

by trapping with elemental ulphur,[11] or more generally via multistep pathways.[12]

The crystal structures of compounds **2**–**5** are shown in Figures 1–4. Although phosphonic acid **2** is a well-known and widely used compound[9] its crystal structure has not been reported and is included to allow structural comparisons to be drawn. Compound **2** has a P═O bond length of 1.5070(10) and P─OH bond lengths of 1.5386(10) Å and 1.5518(11) Å. Although phosphonic acids have been structurally characterized, data are limited. But these values compare well with those observed in *t*-butyl phosphonic acid that has a P═O bond length of 1.5083(16) and P─OH bond lengths of 1.5544(17) Å and 1.5448(16) Å.[13] Not surprisingly, the P═S bond in **3** is much longer (1.9513(9) Å). The P-B bond

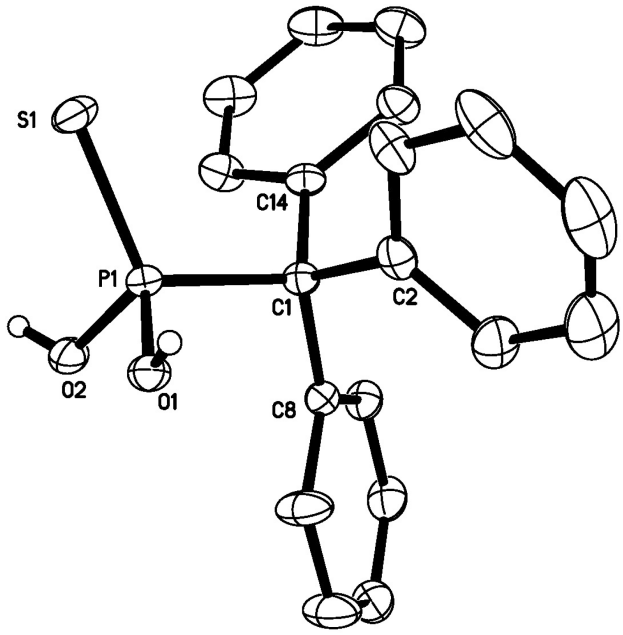


FIGURE 2 Crystal structure of $Ph_3CP(S)(OH)_2$ **3**, the first structurally characterized example of a thiophosphonic acid. Selected bond distances (Å) and angles (deg): P(1)-S(1), 1.9513(9); P(1)-O(1), 1.560(2); P(1)-O(2), 1.565(2); P(1)-C(1), 1.884(3); O(1)-P(1)-O(2), 101.88(11); O(1)-P(1)-C(1), 105.76(11); O(2)-P(1)-S(1), 113.44(8); C(1)-P(1)-S(1), 114.30(8).

in **4** at 1.89(5) Å is slightly longer than in a $PhP(BH_3)(OR)_2$ compound (1.851(6) Å),[14] and essentially the same as in the boranophosphates, $(MeO)_2P(O)BH_3^-/i\text{-}Pr_2NH_2^+$ (1.887(3) Å),[15] and $(MeO)_2P(BH_3)OK$ (1.895(6) Å).[16] For all compounds, the P—O single bonds are similar and range from 1.560(2)-1.60(3) Å. The P—C bond lengths increase slightly from **2** to **5** (1.8588(14)-1.9212(17) Å). It is interesting to note that phosphonothioic compound **3** exists in solution and in the crystalline state, only as the thiono P(=S)OH tautomer and not the thiolo P(=O)SH tautomer, consistent with the structure usually assumed to predominate in this equilibrium when a C—P bond is present.[3]

Compounds **2**–**5** were also fully characterized by IR, mass spectrometry, and NMR spectroscopy. The ^{31}P NMR chemical shifts in $CDCl_3$ are: **1**, 40.9 ppm; **2**, 32.7 ppm; **3**, 92.5 ppm; **4**, 108.1 ppm (93.3 ppm in water at pH 11.2, similar to other reported boranophosphonate salts[2]); and **5**, 108.0 ppm. The very large downfield shift in **3** versus **2** upon

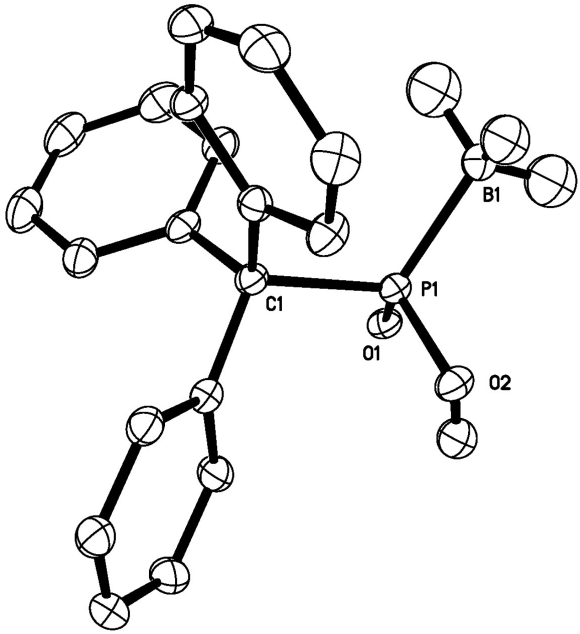


FIGURE 3 Crystal structure of **4,** the first structurally characterized example of a boranophosphonic acid. Selected bond distances (Å) and angles (deg): P(1)-O(1), 1.53(3); P(1)-O(2) 1.60(3); P(1)-B(1) 1.89(5); P(1)-C(1), 1.91(4); B(1)-H(1), 1.2(6); O(1)-P(1)-O(2), 108.9(16); O(1)-P(1)-B(1), 115(2); O(2)-P(1)-B(1), 106(2); O(1)-P(1)-C(1), 107.9(17); O(2)-P(1)-C(1), 104.4(16); B(1)-P(1)-C(1), 114(2).

replacement of the oxygen with sulfur is typical.[17] The signals for boranophosphonates **4** and **5** are consistent with literature values indicating phosphoryl character, and less as a bonding description as a P(III) borane complex.[14] The almost identical ^{31}P NMR chemical shifts observed with **4** and **5** support the solid-state structural analogy between the two compounds. Boranophosphonate **4** has a formally negatively charged boron atom, as would be expected for the representation $RP(^{+})(BH_3^{-})(OH)_2$. Despite careful examination of the residual electron density map, locating the hydrogen for O(1) proved unsuccessful. It is likely that the hydrogen atom is disordered or located between the phosphonate oxygen and lattice ethanol, with significant ionization of one OH bond in **4** (Scheme 2). Indeed, one of the P—O bond is shortened significantly, and in the range of a formal phosphoryl P=O group.[18] To clarify this, **5** was prepared and structurally characterized. The hydrogen atoms on the amine nitrogen N(1), and the phosphorus oxygen O(2), were located from the difference map. Comparison of bond lengths and

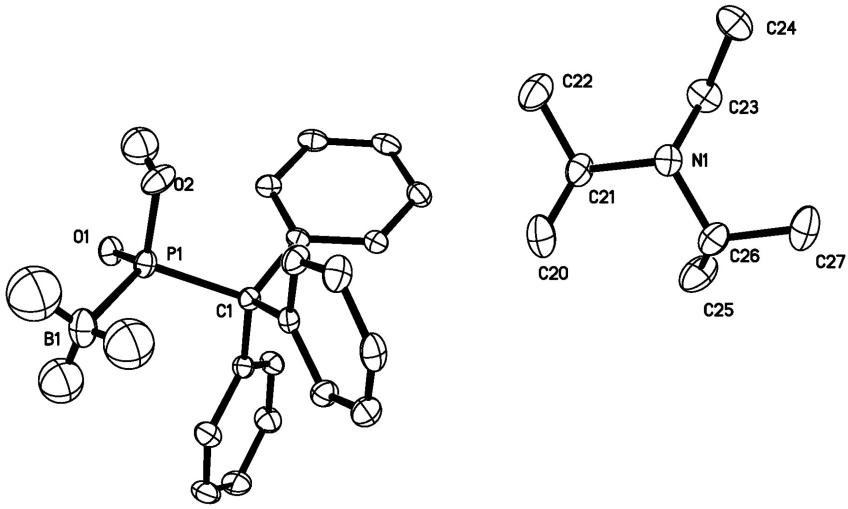
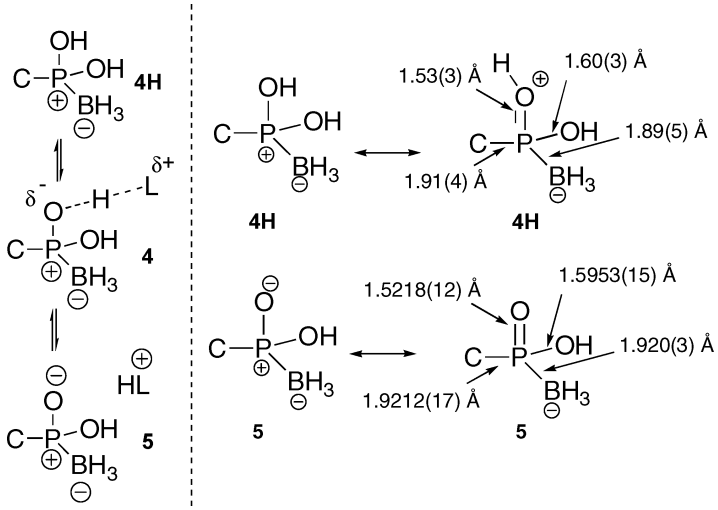


FIGURE 4 Crystal structure of **5**. Selected bond distances (Å) and angles (deg): P(1)-O(1), 1.5218(12); P(1)-O(2), 1.5953(15); P(1)-B(1), 1.920(3); P(1)-C(1), 1.9212(17); B(1)-H(4); 1.07(3); O(1)-P(1)-O(2), 108.55(8); O(1)-P(1)-B(1), 116.91(10); O(2)-P(1)-B(1), 106.13(11); O(1)-P(1)-C(1), 108.45(7); O(2)-P(1)-C(1), 102.17(8); B(1)-P(1)-C(1), 113.47(10); P(1)-B(1)-H(2), 108.8(17).

angles show excellent structural agreement with **4**. This indicates that $RP(^{+})(BH_3^{-})(OH)_2$ is a much stronger acid than **2**, and therefore **4** is better represented as $RP(O)(BH_3^{-})(OH)H^{+}$, where partial protonation of lattice ethanol is probably occurring, and P═O bond character is very pronounced (Scheme 2). The P—B bond in **4** is also intermediate between that of $PhP(BH_3)(OR)_2$ and $(MeO)_2P(O)BH_3^{-}$, but closer to the latter.

M.p. The measured pKas for **2** are 5.6 and 9.8, and for **3** are 4.4 and 8.9, confirming the previously observed lower pKas for phosphonothioic acids versus the corresponding phosphonic acids. The only measurable pKa for **4** was 5.9. This was independently verified by titrating **5**, suggesting that the first pKa for boranophosphonates is much lower than in **2** and **3**, also in agreement with the X-ray data. Some decomposition of **4** (~10%) leading to the H-phosphinate salt of **1** is observed at high pH. Structural studies of boranophosphates[15,16,20] have shown that although the P—B bond is much longer than in the corresponding phosphate, the compounds are good phosphate mimics and capable of entering an enzyme active site, much like phosphonothioates. Similarly, the structural data of boranophosphonate **4** indicate good mimicry for a phosphonate, in spite of the long P-B bond. Therefore,



SCHEME 2 Bonding representations and structural comparisons for **4** and **5.**

boranophosphonates might be useful pharmacophores, although there are limited studies currently available.[2]

Discussion of the Solid-State Arrangement of 2–5

Phosphinic and phosphonic acids are known to form strong hydrogen bonds and can act simultaneously as proton donor and acceptor. Phosphinic acids usually dimerize[20] or form one-dimensional polymers,[21] while phosphonic acids typically crystallize as polymeric aggregates.[22] In the solid state, the trityl phosphonic acid, **2**, adopts a motif in which the molecules are interlinked by hydrogen bonds to the solvent lattice molecules, for example, H(8)-O(5) are H-bonded at a distance of 1.567, and H(1)-O(4) at 1.675 (Figure 5). The phosphonothioic acid, **3**, has a different packing arrangement compared with **2**, **4** and **5**. Here, H-bonding to the acetone (solvent) occurs but no intermolecular phosphonic packing is observed (Figure 6).

M.p. Complexes **4** and **5** exhibit similar structural arrangements. Each P═O and P─OH oxygen atoms participate in hydrogen bonding, the P─OH group H bonds to P═O affording dimeric interactions as depicted in Figures 7–9. In **4** the lattice solvent molecules show little intermolecular interaction with the phosphonic acid and are present to fill the voids in the crystal lattice. However, in **5**, the protonated amine occupies a position between two phosphonic acid moieties allowing O(1) (P═O) to form a second hydrogen bond with the amine proton (N─H).

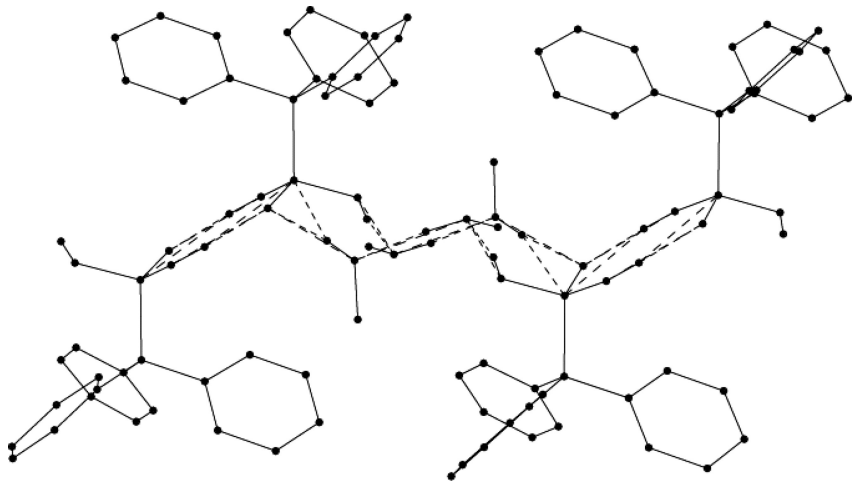


FIGURE 5 Packing Diagram of **2.**

This double hydrogen accepting of P═O results in weaker hydrogen bonding,[23] which is confirmed through the O..O intermolecular separations of **4** and **5**. The measured intermolecular O..O bond lengths and O-H..O angles that characterize the H-bond strength are found to be 2.573/151.41 for **4** and 2.710 /151.41 for **5**. These values are consistent with corresponding literature values.[13,24]

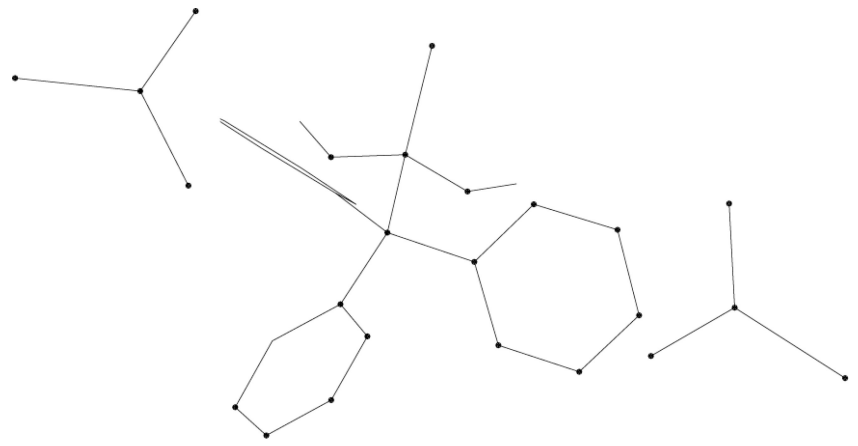


FIGURE 6 Solid-State Arrangement of 3.

FIGURE 7 Packing Diagram of **5**.

EXPERIMENTAL

General Chemistry

^{1}H NMR spectra were recorded on a Varian Mercury-300 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported (in parts per million [ppm]) relative to internal tetramethylsilane (Me_4Si, $\delta = 0.00$ ppm) with $CDCl_3$ or DMSO-d_6 as solvent. ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts for ^{13}C NMR spectra are reported (in parts per million) relative to $CDCl_3$ ($\delta = 77.0$ ppm) or to DMSO-d_6 ($\delta = 40.0$ ppm). ^{31}P NMR spectra were recorded at 121 MHz on a Varian Mercury-300 spectrometer and chemical shifts reported (in parts per million) relative to external 85% phosphoric acid ($\delta = 0.0$ ppm). Mass spectrometry was provided by the the Mass Spectrometry Facility of the University of South Carolina. Organic solutions of products were dried over anhydrous $MgSO_4$.

Reagents and Solvents

Triphenylmethanol was purchased from TCI, N,O-bis(trimethylsilyl) acetamide was purchased from Gelest, Inc., Borane-*N*, *N*-diisopropylethylamine complex was purchased from Aldrich, Borane-methyl

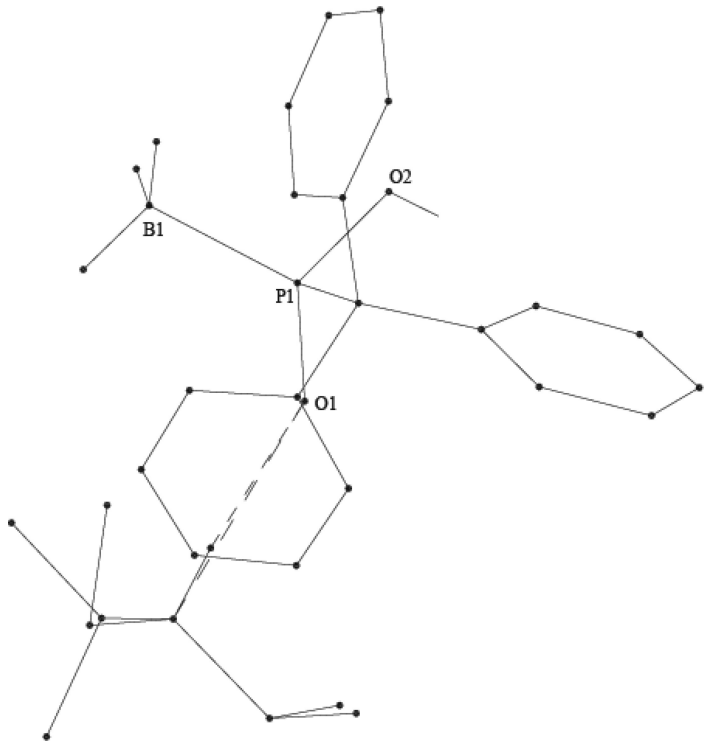


FIGURE 8 Diagram showing H-bonding between the ions in **5.**

sulfide complex was purchased from Alrdich, aqueous hypophosphorous acid (50 wt.%) was obtained from Aldrich, and all were used as received. Anhydrous THF was freshly distilled from NaH and benzophenone prior to use. All other reagents were used as received. Reagent or HPLC grade solvents (toluene and MeOH) were used throughout this study and were not dried prior to use.

Trityl H-Phosphinic Acid 1

A mixture of triphenylmethanol (100 g, 384 mmol), aqueous H_3PO_2 (845 mmol) and toluene (770 mL) was prepared at room temperature. The resulting mixture was heated at reflux under N_2 for 12 h with continuous water-removal using a Dean-Stark trap. The reaction was monitored by ^{31}P NMR. The reaction mixture was concentrated under vacuum, the residue was partitioned between CH_2Cl_2 and H_2O, the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The resulting residue was diluted in EtOAc

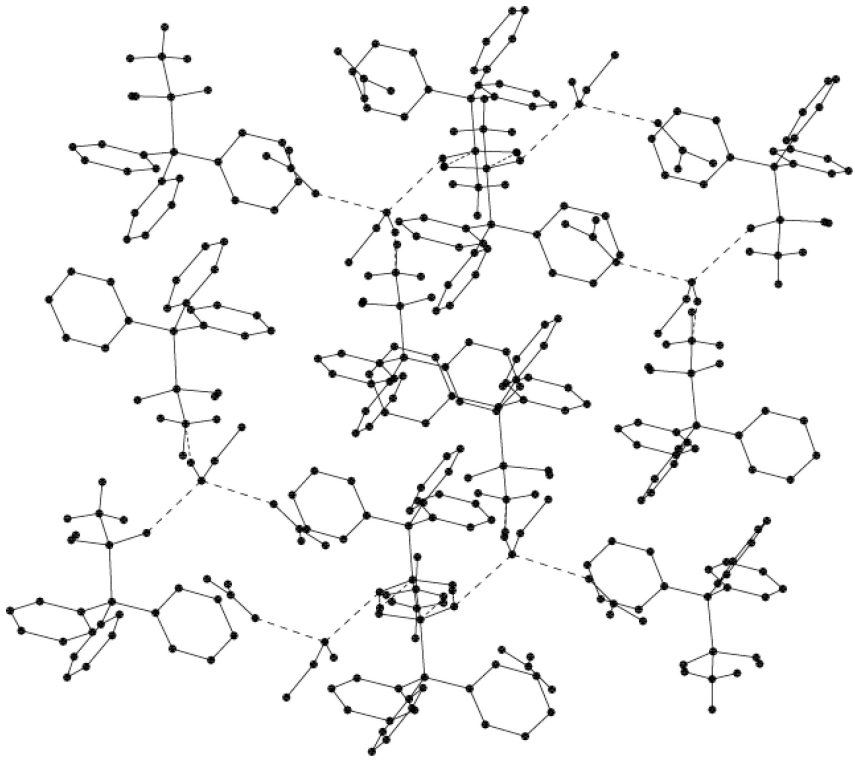


FIGURE 9 Packing diagram of **4.**

and washed several times with EtOAc, afforded the H-phosphinic acid (44 g, 37%) as a white powder by simple vacuum filtration. M.p. 207–210°C.

IR (KBr) 3420.4 (OH), 3086.5-3021.8 (CH), 1180.0 (P═O), 980.4 (P─OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.48 ($^1J_{PH} = 572$ Hz, 1H), 7.3–7.1 (m, 15H, Ar*H*); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 57.1, 126.5, 127.6, 128.5, 128.6, 129.7, 130.6 (d, $^2J_{PCC} = 28$ Hz), 140.1(d, $^3J_{PCCC} = 13$ Hz); ^{31}P NMR δ 40.9 (d, $^1J_{PH} = 572$ Hz); HRMS (FAB) calcd. For $C_{19}H_{17}O_2P$, (M) 308.0966, found 308.0959.

Tritylphosphonic Acid 2

Ozone was bubbled into a solution of trityl-H-phosphinic acid[5] (500 mg, 1.62 mmol) in MeOH (25 mL), at 0°C. After 3 h, the ice bath was removed and N_2 was bubbled into the reaction mixture for 2 h. The white precipitate was removed via centrifugation. The filtrate was concentrated in vacuo, and the residue partitioned between EtOAc and

brine. The aqueous layer was extracted with EtOAc (3x). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford **2** (431 mg, 82%) as a white solid. M.p. 248–250°C. IR (KBr) 2800.0 (OH), 1142.6 (P═O), 965.7 (P─OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–7.18 (m, 15H, Ar*H*), 4.12 (bs, 2H, O*H*); ^{13}C NMR δ 61.2 (d, $^1J_{PC} = 141$ Hz), 127.3, 128.2, 130.5 (d, $^3J_{PCCC} = 7$ Hz), 141.2 (d, $^2J_{PCC} = 5$ Hz); ^{31}P NMR δ 32.7 (s); HRMS (ES) calcd. For $C_{19}H_{17}O_3P$, (M─H) 323.0837, found 323.0843. Crystals of **2** were obtained from MeOH.

Trityl Phosphonothioic Acid 3

A solution of **1** (462 mg, 1.5 mmol) in anhydrous THF (15 mL) under N_2, was treated with BSA (1.85 mL, 7.5 mmol) at room temperature (RT) for 1 h. Sulfur (96 mg, 3 mmol) was then added at RT, and the mixture stirred for 1 h. After addition of MeOH (15 mL), the mixture was stirred for 2 h, then concentrated in vacuo. The residue was diluted in MeOH, giving a heterogeneous mixture. A precipitate was separated from the yellowish filtrate via centrifugation. The filtrate was concentrated in vacuo, affording **3** (510 mg, 100%) as a pale yellowish solid. M.p. 84–89°C. IR (KBr) 3327.5 (OH), 3174.6 (OH), 949.8 (P─OH), 700.1 (P═S) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.33–7.10 (m, 15H, Ar*H*), 6.69 (bs, 2H, O*H*); ^{13}C NMR δ 126.9, 127.9, 129.0, 129.7, 131.1 (d, $^3J_{PCCC} = 6$ Hz), 144.5 (d, $^2J_{PCC} = 5$ Hz); ^{31}P NMR δ 92.5 (s); HRMS (ES) calcd. For $C_{19}H_{17}O_2PS$, (M-H) 339.0609, found 339.0616. Crystals of **3** were obtained from toluene/CH_2Cl_2/MeOH (6:3:1).

Trityl Boranophosphonic Acid 4

A solution of **1** (308 mg, 1 mmol) in anhydrous THF (15 mL) was treated with BSA (1.23 mL, 5 mmol) at RT for 1 h, under N_2. A solution of $BH_3.Me_2S$ (1 mL, 2.0 M solution in THF) was then added at RT, and the resulting mixture stirred for 1 h. After addition of MeOH (15 mL), the mixture was stirred for 2 h, then concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O and the organic phase was washed with H_2O (3x). The combined aqueous layers were concentrated in vacuo, affording **4** (319 mg, 99%) as a white powder. M.p. 119–122°C. IR (KBr) 3421.1 (OH), 3173.9 (OH), 2356.3 (BH), 1040.4 (PO_2H), 702.0 (P-B) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.36–7.11 (m, 15H, Ar*H*), 6.7 (bs, 2H, O*H*), 2.59 (bq, $J = 7$ Hz, 2H, CH_2), 1.10 (bt, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR δ 125.9, 127.5, 131.5 (d, $^3J_{PCCC} = 4$ Hz), 146.2; ^{31}P NMR δ 108.1 (bs). HRMS (ES) calcd. For $C_{27}H_{39}BNO_2P$, (M-) 321.1216, found 321.1216. Crystals of **4** were obtained from CH_2Cl_2/EtOH.

Trityl Boranophosphonic Acid Diisopropylethylamine Salt 5

1 (481 mg, 1.56 mmol) in anhydrous THF (20 mL) was treated with BSA (1.92 mL, 5 mmol) for 1 h at RT under N_2. A solution of

DIPEA.BH_3 (543 μL, 3.12 mmol) was then added at RT. After 1 h, conc. NH_4OH in MeOH (20 mL, 1:1, v/v) was added, stirring continued for 1 h, then concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O, and the organic phase was washed with H_2O (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo, affording **5** (660 mg, 94%) as a white powder. M.p. 104–107°C. IR (KBr) 3440.2 (OH), 3379.3 (NH), 2371.5 (BH), 2329.7 (PO_2), 1105.1 (C-N), 1032.8 (P–OH), cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46–7.11 (m, 15H, Ar*H*), 3.53 (sept, $J = 7$ Hz, 2H, C*H*(CH_3)$_2$), 2.83 (q, $J =$ 7 Hz, 2H, CH_2), 2.35 (s, OH), 1.26-1.21 (m, 15H, CH_3); ^{13}C NMR δ 12.2, 41.7, 53.0, 66.1 (d, $^1J_{PC} = 29$ Hz), 126.0, 127.5, 131.5 (d, $^3J_{PCCC} = 5$ Hz), 144.8; ^{31}P NMR δ 109 (q, $J_{PB} = 133$ Hz); HRMS (ES) calcd. For $C_{27}H_{39}BNO_2P$, (M-) 321.1216, found 321.1224. Crystals of **5** were obtained from toluene/CH_2Cl_2/MeOH (6:3:1).

Crystallographic Parameters

Thermal Ellipsoids at 50% probability, H atoms on the phenyl groups have been omitted for clarity. Crystal Data for complexes **2–5**:[25] **(2)** $C_{21}H_{25}O_5P$ (M = 388.38), T = 213(2) K, Triclinic, P-1, a = 9.0901(6) Å, b = 9.7482(6) Å, c = 12.3042(7)Å, $\alpha = 94.8300(10)°$, $\beta = 108.3390(10)°$, $\gamma = 105.2350(10)°$, Z = 2, Reflections Collected = 6210, Independent reflections = 4416, R (int) = 0.0143, Final R indices [$I > 2\sigma(I)$] R1 = 0.0376, wR2 = 0.0996 **(3)** $C_{25}H_{29}O_4PS$ (M = 456.51), T = 213(2) K, Monoclinic, P 21/n, a = 9.5308(11) b = 18.182(2) c = 14.0754(16) $\beta =$ 93.703(2)° V = 2434.1(5) Å^{3}Z = 4, Reflections Collected = 15181, Independent reflections = 5716 [R(int) = 0.0327], Final R indices [$I > 2\sigma(I)$] R1 = 0.0582, wR2 = 0.1545 **(4)** $C_{24}H_{31}BO_4P$, (M = 425.27), T = 213(2) K, triclinic, P-1, a = 9.5549(9) Å, b = 10.7293(10) Å, c = 12.7101(11) Å, $\alpha = 73.331(2)°$, $\beta = 83.598(2)°\gamma = 74.864(2)°$ V = 1204.00(19) Å^{3}Z = 2, Reflections Collected = 10251, Independent reflections = 4322 [R(int) = 0.0229], Final R indices [$I>2\sigma(I)$] R1 = 0.0527, wR2 = 0.1462 **(5)** $C_{27}H_{39}BNO_2P$ (M = 451.37), T = 213(2) K, Monoclinic, P 21/n, a = 15.737(2) Å, b = 11.0004(16) Å, c = 15.760(2) Å, $\beta = 111.509(2)°$, Z = 4, Reflections Collected = 14562, Independent reflections = 4560 [R(int) = 0.0249], Final R indices [$I > 2\sigma(I)$] R1 = 0.0382, wR2 = 0.0970

Conclusions

In summary, we have characterized for the first time both a phosphonothioic acid RP(=S)$(OH)_2$, and boranophosphonic acids [RP(O)(BH_3^-)(OH)]LH^+ (where L is a Lewis base) by X-ray diffractometry. The pKa measurements for **4** and **5** indicate that at physiological pH, complete deprotonation would be achieved. All compounds were

synthesized in excellent yields from the same H-phosphinic acid precursor. Since structural parameters are important to the design of bioactive compounds, and compounds of the type **2**–**5** have demonstrated or potential value for this purpose, this work provides sets of comparable structural data, and thus should be useful to future medicinally-related applications.

Crystal data for compounds **1**–**5** is available free of charge from the CCDC, reference numbers: 664468 – 664472.

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