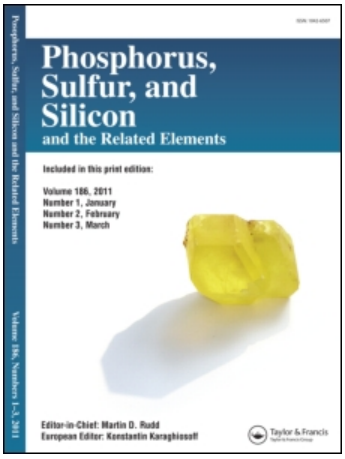

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article McClard, Ronald W. and Jackson, Steven A.(1988) 'SYNTHESIS OF AN UNREACTIVE YLID DESIGNED AS A -C-P-C-P DIPHOSPHATE ISOSTERE SYNTHON', Phosphorus, Sulfur, and Silicon and the Related Elements, 39: 1, 27 — 31
To link to this Article: DOI: 10.1080/03086648808072851
URL: http://dx.doi.org/10.1080/03086648808072851

Phosphorus and Sulfur, 1988, Vol. 39, pp. 27–31
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SYNTHESIS OF AN UNREACTIVE YLID DESIGNED AS A —C—P—C—P DIPHOSPHATE ISOSTERE SYNTHON

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(Received January 25, 1988; in final form January 25, 1988)

The complex phosphonium salt **3** was synthesized from bis(hydroxymethyl)phosphinic acid in five steps. The ylid, **2a**, produced *in situ* from **3a**, did not react as expected with aldehydes to give the desired phosphonylphosphinyl derivative. Since **2a** is actually more basic than the homologous **1**, the observed lack of reactivity is apparently not a result of electronic factors.

Key words: Analog; diphosphate; phosphinate; phosphonate; phosphonium salt; ylid.

INTRODUCTION

Many phosphonate analogs of important metabolites and putative transition-states have been synthesized and studied; the literature is vast and will not be reviewed here. In addition, some analogs of polyphosphates have been made as well. Two major types of phosphonate analogs of diphosphates have been previously reported: 1) methylene bisphosphonate analogs such as 5-phosphoryl-ribose 1-α-(methylenebisphosphonate),[1,2] and the related analog of ADP;[3] 2) phosphonylphosphate analogs such as 5′-deoxyuridine-5′-phosphonylphosphate,[4] 2′,5′-dideoxythymidine 5′-phosphonylphosphate[5] and the similar analog of isopentenyl diphosphate.[6] Our intent was to produce a synthetic reagent that possessed the properties required to produce phosphonylphosphinyl (P—C—P—C—) analogs that, as a class, had not yet been described. Since it was shown that the ylid **1**[7] reacted nicely with the protected sugar 2,3-*O*-isopropylidene-5-*O*-trityl-ribose to give the desired ring-closed sugar phosphonate[8] it seemed reasonable that ylid **2a** should provide a good reagent for delivering the —C—P—C—P moiety.

$$R_3P=CH—R'$$

1 R = Ph, R′ = —P(O)(OPh)$_2$

2a R = Ph, R′ = —P[(O)(OPh)]CH$_2$P[(O)(OPh)$_2$]

2b R = nBu, R′ = —P[(O)(OPh)]CH$_2$P[(O)(OPh)$_2$]

Below we describe the preparation and properties of these more complex ylids and their corresponding phosphonium salts.

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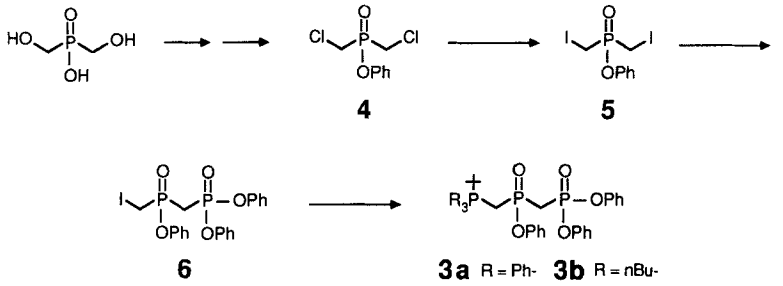
RESULTS AND DISCUSSION

The synthesis of **3a**, the conjugate phosphonium salt of **2a**, was achieved in five steps from bis(hydroxymethyl)phosphinic acid (Scheme 1) which was first converted to the crystalline phenyl bis(chloromethyl)phosphinate, **4**. Compound **5** was obtained by transhalogenation and then converted to the asymmetric phosphonylphosphinate **6** by a controlled Arbusov reaction with diphenyl methyl phosphite. Compound **6** was then converted to **3a** by quaternization with triphenylphosphine. The proton-decoupled ^{31}P NMR spectrum of the asymmetric **3a** is as expected: two doublets for the phosphonium and phosphonyl nuclei and a double-doublet for the central phosphinyl nucleus. The 270 MHz ^{1}H NMR spectrum (Figure 1) yielded the expected resonances plus an additional interesting feature. The four methylene protons are widely separated by about 1 ppm each and the downfield three of these protons give similar splitting patterns. The fourth proton (δ 3.1), presumably positioned between the two phosphinyl P



SCHEME 1

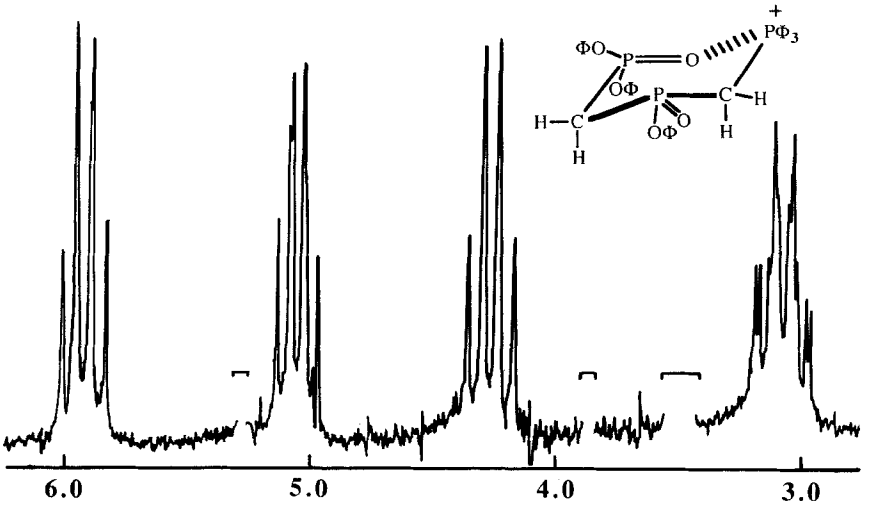


FIGURE 1 Segment of 270 MHz ^{1}H NMR spectrum of compound **3a** in $CDCl_3$ (only the region containing resonances assigned to methylene protons). Brackets indicate where peaks due to minor known impurities were removed. The inset shows a suggested structure of **3a** in $CDCl_3$. Φ = phenyl.

atoms as told from its upfield shift, experiences added splitting which is not easily attributable to a nearby hydrogen or phosphorus nucleus. The most likely conclusion is that **3a** self-associates, in $CDCl_3$, to form a ring-like chair structure; such a structure would provide for "W-coupling" of a distal methylene —H to the phosphonium P. Such coupling could not be readily detected in the ^{31}P spectrum owing to the already complex pattern of splitting caused by the three phenyl groups on the phosphonium phosphorus, but it is evident in the ^{1}H spectrum.

The ylid **2a** was generated *in situ* by addition of base to **3a** in aprotic polar solvents. Attempts to isolate the ylid in crystalline form were unsuccessful, however its existence could be inferred from ^{31}P NMR. Upon treatment of **3a** with base (PhLi) in DMSO, a large increase (16.0 Hz to about 31 Hz) was observed for the coupling constant between the phosphinyl (central) and Ph_3P— phosphorus atoms of the phosphonium salt. A significant downfield shift of about 11 ppm, with only minor changes in the other resonances, was also observed. This is parallel to what happens in the case of the related phosphonium salt form of ylid **1**. We observed that partial neutralization of that phosphonium salt in CH_3CN (using a $CDCl_3$ lock) caused the phosphonyl P to shift from −4.1 ppm downfield to +25.1 ppm with a concommitant increase in P—P coupling constant from 10.4 Hz to 45.1 Hz. The Ph_3P— resonance was shifted only slightly, from 18.7 ppm to 18.5 ppm.

Reaction of **2a**, formed *in situ*, with the protected sugar 2,3-*O*-isopropylidene-5-*O*-tritylribose did not occur in various solvents, nor did the ylid react with benzaldehyde. To test the idea that the additional P=O moiety had somehow decreased the nucleophilicity of the ylid, we titrated both **2a** and its homolog **1** in 80% CH_3CN/20% H_2O. Compound **2a** ($pK_a \sim 7.8$) is actually slightly more basic, and presumably inherently more nucleophilic, than **1** ($pK_a \sim 7.4$). Thus the apparent lack of reactivity of **2a** is either due to some unknown steric problem or perhaps a solution self-association phenomenon as is proposed for pure **3a**.[9] The tri-n-butyl phosphonium compound **3b** was also prepared, converted to the corresponding ylid **2b**, which was also found to not react with an aldehyde. The only products recovered were $Ph_3P{=}O$ (or $Bu_3P{=}O$), unreacted **2a** (or **2b**), **3a** (or **3b**), and $CH_3P(O)OPhCH_2P(O)(OPh)_2$, **7**, presumably because the ylid reacted faster with traces of water in the solvent than with an intended electrophile.

Since completion of the writing of this paper, Gilmore and Park[10] reported the successful synthesis of simple unsaturated phosphonylphosphinyl compounds by the application of symmetric bisphosphonyl phosphinamides in a Wadsworth–Horner–Emmons reaction. Our laboratory has pursued other means for preparing exact (saturated) —CPCP analogs of diphosphate metabolites and now has developed such an approach which had been reported elsewhere.[11] Although we have not pursued the matter further ourselves, it is possible that **2** and **3** may still be of some further synthetic or theoretical interest.

EXPERIMENTAL SECTION

General procedures. NMR spectra were obtained on Varian FT-80, Bruker WH-270, or Varian EM 360 instruments. Positive ^{31}P shifts are taken as ppm downfield of 85% H_3PO_4 and ^{1}H NMR

spectra are referenced to Me_4Si and performed in $CDCl_3$ unless otherwise noted. Mass spectral analysis was performed on a Perkin-Elmer Model RMS-3 instrument. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Melting points and boiling points are uncorrected.

Preparation of diphenyl methyl phosphite. To phosphorus trichloride (50.0 g, 0.363 mol) dissolved in 400 ml anhydrous ether was added a mixture of phenol (68.4 g, 0.726 mol) and pyridine (57.5 g, 0.726 mol) in 150 ml of ether over two hours at 0°. The reaction was allowed to reach room temperature gradually and then heated 1 hr at 40°. An additional 500 ml of ether was added to the reaction mixture and a mixture of methanol (11.6 g, 0.363 mol) and pyridine (28.7 g, 0.363 mol) in 100 ml of ether was then added slowly (1 hr). The mixture was left stirring overnight at room temperature. The precipitated pyridinium chloride was removed by filtration and the filtrates and washings were combined and ether was removed by evaporation. The resultant oil was distilled under reduced pressure to yield 37.9 g (0.153 mol, 42% yield from PCl_3) of product with bp of 103° at 0.1 mm Hg (literature: 169.5–170.5° at 11 mm,[12] 158–162° at 9 mm[13]). ^{31}P NMR: δ + 128.6 (quar, J_{POMe} = 8.8 Hz); literature:[13] +128. ^1H NMR (CCl_4): δ 3.68 (3H, d, —**OCH$_3$**, J_P = 8.8 Hz), 7.0–7.2 (10H, —**OPh**); literature[13]: δ 3.57 (J = 9), 6.9.

Preparation of phenyl bis(chloromethyl)phosphinate, **4**. This was synthesized in two steps from bis(hydroxymethyl)phosphinic acid as described by Ivanov *et al.*,[14] except that the crude product (>90% pure) crystallized spontaneously, thus obviating the need for vacuum distillation. The crude solid was dissolved in hexane at room temperature and allowed to form long low-melting (mp 36.5–37.5°) needles at 0°. ^1H NMR (CCl_4): δ 3.75 (4H, d, Cl**CH$_2$**—, J_P = 9.0 Hz), 7.25 (5H, —**OPh**). ^{31}P NMR: +40.1 (J_{PH} = 8 Hz).

Preparation of phenyl bis(iodomethyl)phosphinate, **5**. This was prepared according to the published procedure[15] which, in our hands, afforded an oil that, when dissolved in hot ligroin and seeded, crystallized overnight. The yield was 82%, mp 84.5–86.5° (lit. 86–87°).[15] ^{31}P NMR: δ + 36.4 ($J_{H,P}$ = 8 Hz).

Synthesis of diphenyl (iodomethylphenoxyphosphinyl)methylphosphonate, **6**. Diphenyl methyl phosphite (3.1 g, 12.5 mmol) and **6** (4.3 g, 10.2 mmol) were combined neat and heated to 155° under N_2 for 3 hr and then an additional 1 g of the phosphite was added followed by continued heating at 170° for 3 hr. The residue was purified by chromatography on silica gel (2/1 petroleum ether/ethyl acetate) to give 2.39 g (44% yield) of **6** as an oil that crystallized upon standing. It was recrystallized from petroleum ether/ethyl acetate (mp 95–96°). ^{31}P NMR revealed the expected two doublets at δ = +34.3 and +8.7 with $J_{P,P'}$ = 1.3 Hz. MS: M+ = 528 (expected, m/e = 528). ^1H NMR: δ 3.15 (2H, dd, P—**CH$_2$**—P, $J_{H,P}$ = 18 Hz, $J_{H,P'}$ = 20 Hz), 3.50 (2H, d, I—**CH$_2$**—P, $J_{H,P}$ = 8.8 Hz), 7.25 (15H,—OPh). Anal. Calcd. for $C_{20}H_{19}IO_5P_2$: 45.48%C, 3.63%H, 11.73%P, 24.02%I. Found: 45.40%C, 3.73%H, 11.75%P, 23.85%I. The chloromethyl homolog of **6** was prepared in low yields by an analogous procedure, using **4** instead of **5**.

Synthesis of triphenyl (((diphenoxyphosphinyl)methyl)phenoxyphosphinyl)methylphosphonium iodide, **3a**. Triphenyl phosphine (0.60 g, 1.86 mmol) and **6** (1.20 g, 2.3 mmole) were stirred together under N_2 at 140° for 2 hr. The reaction was cooled to 60° and the residue was dissolved by adding THF. Benzene was added and the product crystallized upon cooling overnight to yield 1.2 g (80%) of fine white powder (mp 168°). ^1H NMR: d 7.1–8.0 (30H, —Ph and —OPh); 3.07 (1H, m), 4.26 (1H, m), 5.06 (1H, m), 5.91 (1H, m), P—**CH$_2$**—P—**CH$_2$**—P (see Figure 1). ^{31}P NMR (assignments from proton-coupled spectra, now shown): δ +22.6 (phosphonium), +36.1 (phosphinyl), and +14.4 ppm (phosphonyl). ^{31}P—^{31}P coupling constants are $J_{(phosphonium,phosphinyl)}$ = 16.4 Hz and $J_{(phosphonyl,phosphinyl)}$ = 9.0 Hz. Anal. Calcd. for $C_{38}H_{34}O_5P_3$: 57.75%C, 4.34%H, 11.75%P. Found: 58.22%C, 4.56%H, 12.11%P. The tri-n-butyl compound **3b** was prepared analogously and gave appropriate analytical data.

Attempted reactions of **2a** *or* **2b** *with aldehydes.* To compound **3a** (1.6 g, 2.0 mmole) in 10 ml dry DMSO was added 50 mg (2.0 mmole) NaH. After 20 min at 23°, evolution of H_2 ceased and benzaldehyde (0.215 g, 2.0 mmole) was added and stirred 24 hr at 23° and a sample was removed for ^{31}P NMR analysis. The reaction mixture was then refluxed 2 hr and another sample was withdrawn. The mixture was then refluxed overnight. The above procedure was applied to 2,3-*O*-isopropylidene-5-*O*-tritylribose instead of benzaldehyde and also for **3b** instead of **3a**. In no case was any evidence of formation of a new C—C bond detected in the ^{31}P NMR.

Synthesis of phenyl ((diphenoxyphosphinyl)methyl)methylphosphinate, **7**. An authentic sample was produced by self-condensation of diphenyl methylphosphonate[16] with the addition of one equivalent of PhLi in THF at −78°. A small yield (17%) of the pure desired product was separated from the predominant polymeric products by chromatography on silica gel (ethyl acetate/CH_2Cl_2, 1/1 followed by ethyl acetate). This material solidified to give a waxy solid that was pure by TLC (ethyl acetate/CH_2Cl_2, 1/1, silica gel, Rf ≈ 0.1). ^{31}P NMR ($CDCl_3$): δ +9.9 (phosphonyl), +40.3 (phosphinyl, $J_{P,P'} = 2$ Hz. ^{1}H NMR: δ 1.90 (2H, d, **CH_3**—P, $J_{HCP} = 14.9$ Hz), 2.87 (2H, dd, P—**CH_2**—P, $J_P = 20.8$ Hz, $J_{P'} = 18.0$ Hz), 7.24 (15H, s, —**OPh**). MS: M+ (m/e) = 402 (expected: 402). Anal. Calcd. for $C_{20}H_{20}O_5P_2$: 59.71%C, 5.01%H, 15.40%P. Found: 59.79%C, 5.27%H, 15.44%P.

ACKNOWLEDGMENTS

This work was funded by the National Cancer Institute, National Institutes of Health (CA 33659 and CA 39560) and a Bristol-Myers Company Grant of Research Corporation. We thank Mr. S. Tsimikas for preparing diphenyl methyl phosphite, the J. Francis Bitter NMR Laboratory, Massachusetts Institute of Technology, where the 270 MHz NMR spectra were obtained, and Dr. Dennis J. Sardella for his help in interpreting the NMR spectra of **3a**.

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