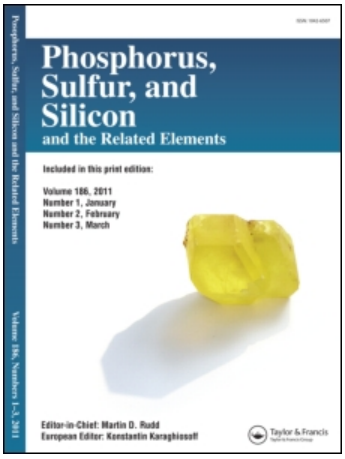

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

PHOSPHONIC SYSTEMS. PART 17. SOLUTION AND SOLID STATE STUDIES ON DIMETHYL 2-HYDROXY-3-BENZOYLPROPYLPHOSP

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To cite this Article Bourne, Susan , Modro, Agnes M. and Modro, Tomasz A.(1995) 'PHOSPHONIC SYSTEMS. PART 17. SOLUTION AND SOLID STATE STUDIES ON DIMETHYL 2-HYDROXY-3-BENZOYLPROPYLPHOSP', Phosphorus, Sulfur, and Silicon and the Related Elements, 102: 1, 83 — 90
To link to this Article: DOI: 10.1080/10426509508042546
URL: http://dx.doi.org/10.1080/10426509508042546

Phosphorus, Sulfur, and Silicon, 1995, Vol. 102, pp. 83–90
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PHOSPHONIC SYSTEMS. PART 17. SOLUTION AND SOLID STATE STUDIES ON DIMETHYL 2-HYDROXY-3-BENZOYLPROPYLPHOSPHONATE

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(Received November 1, 1994)

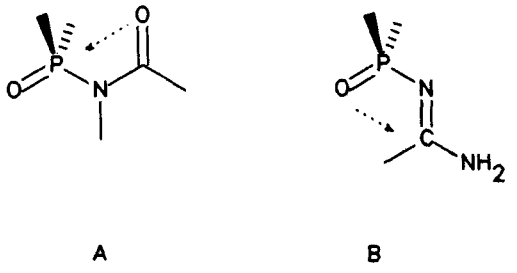
The crystal and molecular structure of dimethyl 2-hydroxy-3-benzoylpropylphosphonate (**1**) has been determined. $P2_1/c$, a = 11.989(3), b = 12.990(3), c = 8.601(3) Å; V = 1339.1(7) Å^3. Molecular parameters indicate strong intramolecular interactions between the hydroxyl oxygen and the phosphorus atom. The hydrogen bonding involves the phosphoryl group as a donor, and occurs intermolecularly, yielding a dimeric arrangement of the molecules. The acid-catalyzed dehydration of **1**, and the base-promoted elimination of the tosylate derivative, yielded the same (E) dimethyl 3-benzoyl-prop-2-en-ylphosphonate as the exclusive product.

Key words: 2-Hydroxy-3-benzoylalkylphosphonic ester, Crystal and molecular structure, Intramolecular interactions, Acid and base-catalyzed elimination.

INTRODUCTION

The phosphoryl, as well as the carbonyl group, represent functionalities that offer both, the electrophilic (phosphorus or carbon), and the nucleophilic (oxygen) centres; the biphilicity being largely responsible for the diverse reactivity of phosphoryl and carbonyl substrates. In systems containing both functional groups present, skeletal restrains usually make only one type of the intramolecular donor-acceptor interactions possible, reflecting relative nucleophilicity/electrophilicity of the respective centres. X-ray diffraction studies demonstrated that bifunctional derivatives such as phosphoric-carboxylic imides, $(RO)_2P(O)NHC(O)R$,[1] or N-phosphorylated urea, $(PhO)_2P(O)NHC(O)NMePh$,[2] attain an orientation that allows maximum of non-bonded interactions between carbonyl oxygen and phosphorus atom (Figure 1, A). On the other hand, in N-diethoxyphosphorylformamidine, $(EtO)_2P(O)$—$N{=}C(NH_2)H$, the arrangement of the molecular core is quite different, leading to a short contact between the phosphoryl oxygen and the formamidine carbon (Figure 1, B).[3]

In this work we report on yet another type of organophosphorus derivative, dimethyl 2-hydroxy-3-benzoylpropylphosphonate, $(MeO)_2P(O)$—CH_2—CH-(OH)—



A B

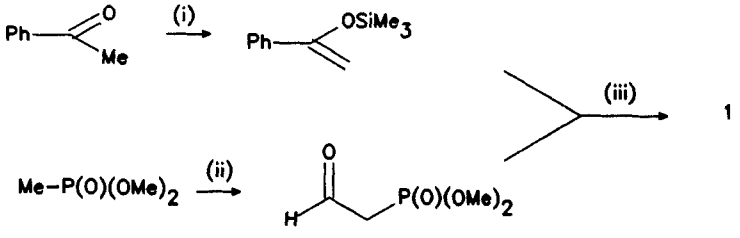
FIGURE 1 Intramolecular interactions in bifunctional systems.

CH_2—C(O)Ph (**1**), a system in which an additional nucleophilic group (hydroxyl) is present in an equidistant relationship with respect to the carbonyl and the phosphoryl group. Our earlier solution studies of **1** demonstrated strong preference of the 2-hydroxy substituent to interact with the phosphoryl rather than with the carbonyl group.[4] Since that time we were able to prepare **1** as a crystalline material, thus it was possible to compare the conformational behaviour of this compound in solution with its solid state structure.

RESULTS AND DISCUSSION

In our previous synthesis, **1** was prepared in five steps from ethyl acetoacetate and dimethyl methylphosphonate.[4] We now report a much simpler, three-step synthesis of **1** (total yield of pure product 67%), as shown in Scheme 1.

Conformational analysis of **1** showed that as far as the rotation about the C_1—C_2 bond is concerned, there is a strong preference for one out of three possible



(i) Me_3SiCl, DMF, Et_3N,

(ii) (a) BuLi, THF, −60°C
(b) DMF, −60°C
(c) 3M HCl, room temp.

(iii) $TiCl_4$, CH_2Cl_2, 78°C

SCHEME 1

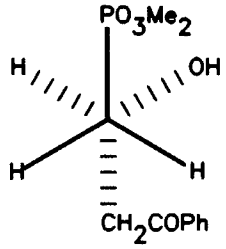


FIGURE 2 Preferred conformer of 1 in solution.

staggered conformations (54.4 ± 2.1% in five solvents) (Figure 2). The preferred rotamer can be explained by two factors: steric repulsion between the largest groups at the C_1—C_2 bond (PO_3Me_2 and CH_2COPh), and the attractive interactions between the hydroxyl function and the phosphoryl centre. Conformational analysis with respect to the rotation about the C_2—C_3 bond revealed, on the other hand, no preference for any particular conformation, yielding a statistical distribution of all three staggered rotamers. These results indicate that the intramolecular attraction in a 1-phosphoryl-2-hydroxy-3-keto substituted propane system involves the hydroxyl and the phosphoryl functions without a significant participation of the carbonyl group. The nature of those interactions is, however, not clear. The intramolecular hydrogen bonding (—O—H ··· O=P) seems a most obvious reason, but other studies of phosphonic derivatives[5] and sulfoxides[6] pointed at the importance of n(p) → d donor-acceptor interactions of the oxygen non-bonding electrons with the vacant 3d orbital of phosphorus or sulfur.

The perspective view of **1**, as determined by diffraction, together with atomic nomenclature, is given in Figure 3, while Table I lists selected molecular parameters, most relevant to the discussion.

Examination of the molecular parameters gives clear evidence for a full correspondence between the solution and the solid state structure of **1**. The P_1—C_1—C_2—C_3 moiety attains an almost ideal antiperiplanar orientation, and the HO—C_2—C_1—P_1 torsion angle is even smaller than the theoretical value for the ideal *gauche* orientation. The non-bonded distance between the OH group oxygen and the phos-

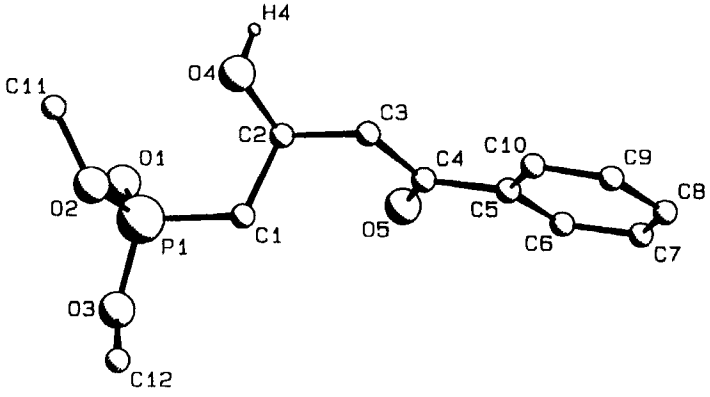


FIGURE 3 A perspective view of **1** with atomic numbering.

TABLE I

Selected molecular parameters for **1**

Intramolecular bond distances (Å)	
Bond	**Distance**
P_1—O_1	1.471(1)
P_1—C_1	1.80
C_1—C_2	1.54
C_2—O_4	1.43
C_2—C_3	1.53
C_3—C_4	1.51
Intramolecular bond angles (°)	
Bonds	**Angle**
O_1—P_1—O_3	109.6
O_2—P_1—O_3	102.7
C_1—P_1—O_3	106.4
O_1—P_1—O_2	115.1
O_1—P_1—C_1	114.5
O_2—P_1—C_1	107.5
P_1—C_1—C_2	112.3
C_1—C_2—C_3	110.9
C_2—C_3—C_4	113.5
C_1—C_2—O_4	107.7
C_3—C_2—O_4	109.5
Torsion angles (°) and non-bonded distance (Å)	
P_1—C_1—C_2—O_4	56.1(1)
C_4—C_3—C_2—O_4	-164.0(1)
C_1—C_2—C_3—C_4	76.3(2)
P_1—C_1—C_2—C_3	177.1(1)
P_1···O_4	3.022(0.001)

phorus atom is less than the sum of the respective van der Waals radii (3.30 Å), allowing to consider that section of the molecule as an "early stage" of the decomposition of an alkoxide intermediate in the Horner-Wadsworth-Emmons olefination.[7] As a consequence of the shift of the structure toward a trigonal bipyramide geometry, the bond angles at phosphorus are smaller for the quasi axial-equatorial arrangement (O_1—P_1—O_3, O_2—P_1—O_3, C_1—P_1—O_3, av. 106.2 ± 3.4°), and larger for the quasi equatorial-equatorial arrangement (O_1—P_1—O_2, O_1—P_1—C_1, O_2—P_1—C_1, av. 112.4 ± 4.2°). In conclusion, **1** represents another example in

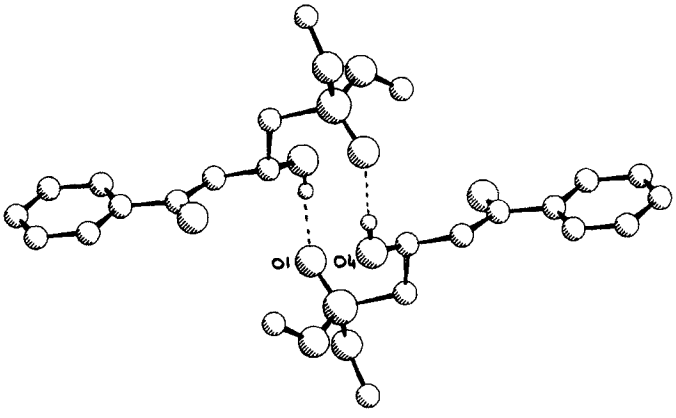


FIGURE 4 Intermolecular hydrogen bonding in **1**.

which intramolecular interactions correspond to model A (Figure 1). Molecular structure of **1** gives no evidence for any intra- (or inter-)molecular interactions involving the carbonyl group.

Figure 4 shows the hydrogen bonding operating in crystalline **1** and yielding dimeric species with a pair of the —O—H ··· O=P *inter*molecular hydrogen bonds (O ··· O = 2.718(2) Å; O—H ··· O = 169(2)°). Since the hydroxyl hydrogen (H_4) is bonded to the phosphoryl oxygen (O_1) of *another* molecule of **1**, the hydrogen bonding effect cannot be responsible for the close approach of the C_2—OH group to the phosphoryl centre of *the same* molecule. We conclude therefore that the four-center n(p) → d electronic interactions between oxygen and phosphorus are important not only from the reactivity point of view, but also play a role in the conformational preferences in those systems.

Figure 5 shows the packing arrangement of the molecules in the unit cell. The hydrogen bonded dimers pack in a zig zag fashion which is stabilized by $\pi \cdots \pi$ interactions between adjacent phenyl rings. The phenyl rings are offset from a perfectly stacked face-to-face arrangement, as is commonly seen in crystalline ar-

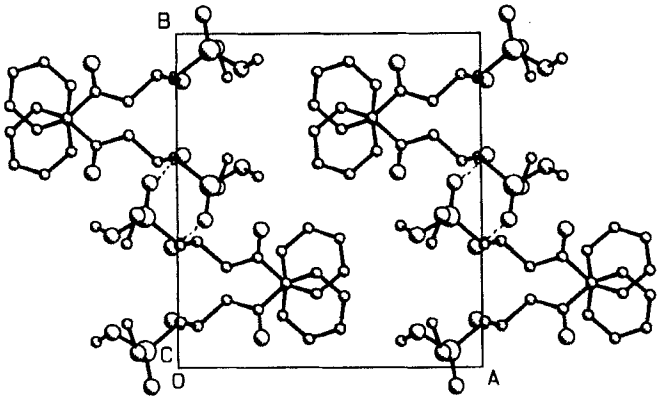
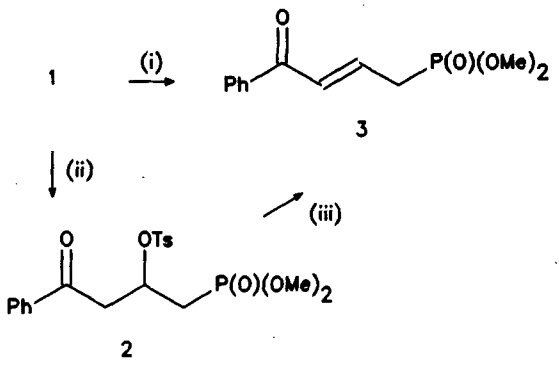


FIGURE 5 Packing diagram for **1**.



(i) TsOH, benzene, reflux

(ii) TsCl, pyridine, 15 – 20°C

(iii) Bu^tOK/Bu^tOH, room temp.

SCHEME 2

omatic hydrocarbons.[8] The distance from the overlapping atom, C(6) to the plane of its neighbouring phenyl ring is 3.65(4) Å.

The molecule of **1**, as a secondary alcohol with two methylene groups, each substituted by a strongly electron-withdrawing group, should be susceptible to the dehydration reaction. Regioselectivity of the dehydration would, in turn, indicate the preference of the olefinic bond to be located in the α,β-relation to either of the two functional groups. Substrate **1** was subjected to the acid-catalyzed dehydration, and (after conversion to the tosylate derivative) to the base-promoted elimination. In both cases (E) dimethyl 3-benzoyl-prop-2-enylphosphonate (**3**) was formed as the exclusive product (Scheme 2). Since both eliminations give products usually determined by the relative stability of the isomeric alkenes,[9] exclusive formation of **3** confirms our earlier observation[10] of only weakly stabilizing effect of a phosphoryl substituent on an adjacent olefinic bond.

EXPERIMENTAL

Solvents and commercially available reagents were purified by conventional methods immediately before use. NMR spectra were recorded on a Bruker AC 300 NMR spectrometer at a probe temperature 30°C, and chemical shift values are given relative to TMS (^1H) and 85% H_3PO_4 (^{31}P).

Preparation of 1-phenyl-1-trimethylsilyloxyethylene was accomplished by some modification of the procedure given for silylation of 2-methylcyclohexanone[11] (adding reagents with cooling in an ice bath and carrying the reaction out at room temp. for 2 h, followed by reflux for 20 h). (79%), b.p. 60–62°C/2 mbar (lit.[12] b.p. 89–91°C/16 mbar); δ_H ($CDCl_3$) 0.27 (9H, s), 4.42 (1H, d, J_{HH} 1.7 Hz), 4.91 (1H, d, J_{HH} 1.7 Hz), 7.30 (2H, m), 7.59 (2H, m), 7.95 (1H, m).

Dimethyl 2-oxoethylphosphonate was prepared according to the literature procedure[13] (78%), b.p. 87–89°C/1.33 mbar (lit.[13] b.p. 106–110°C/17 mbar); δ_H ($CDCl_3$) 3.04 (2H, dd, J_{HP} 22.1, J_{HH} 3.1 Hz), 3.72 (6H, d, J_{HP} 11.0 Hz), 9.60 (1H, t, J_{HH} 3.1 Hz); δ_P 22.2.

Preparation of **1** was carried out following the procedure given for the condensation of 1-trimethylsilyloxy-1-cycloxehene with benzaldehyde.[12] (86%), purified by washing with cold ether; m.p. 75–76°C; δ_H ($CDCl_3$) 2.10 (1H, ddd, J_{HP} 17.9, J_{HH} 15.3, 7.4 Hz), 2.20 (1H, ddd, J_{HP} 18.3, J_{HH} 15.3, 5.6 Hz), 3.30 (2H, d, J_{HH} 5.2 Hz), 3.76 (3H, d, J_{HP} 11.0 Hz), 3.80 (3H, d, J_{HP} 10.9 Hz), 4.61 (1H, m), 7.45 (2H, t, J_{HH} 6.3 Hz), 7.56 (1H, t, J_{HH} 6.3 Hz), 7.94 (2H, d, J_{HH} 6.3 Hz); δ_P 32.0. Anal. Calcd for $C_{12}H_{17}O_5P$: C, 52.90; H, 6.24. Found: C, 52.01; H, 6.15%.

Preparation of dimethyl 2-tosyloxy-3-benzoylpropylphosphonate (**2**). **1** was treated with tosyl chloride in pyridine at room temperature for 26 h and at 65°C for 5 h. **2** (60%), oil, purified by column chromatography (silica gel, ethyl acetate-chloroform, 2:1); δ_H ($CDCl_3$): 2.16 (3H, s), 2.33–2.70 (2H, m), 3.37 (2H, d, J_{HH} 2.3 Hz), 3.74 (6H, d, J_{HP} 11.0 Hz), 5.25 (1H, m), 7.15 (2H, d, J_{HH} 8.0 Hz), 7.30–7.50 (3H, m), 8.10 (2H, d, J_{HH} 6.4 Hz), 8.35 (2H, d, J_{HH} 8.0 Hz); δ_P 26.7.

Dehydration of **1**. **1** (0.20 g, 0.73 mmol) and p-toluenesulfonic acid monohydrate (0.005 g, 0.026 mmol) were dissolved in benzene (60 mL) and the solution was heated to reflux for 7 h with distilling benzene slowly off. The residue (quantitative yield) was kept under reduced pressure, dissolved in $CDCl_3$, and the solution was examined by NMR spectroscopy. ^{31}P NMR spectrum contained only one signal at δ_P 27.7. ^1H NMR spectrum allowed to identify the product as

TABLE II

Crystal data and structure refinement for **1**

Empirical formula	$C_{12}H_{17}O_5P$
Formula weight	272.23
Temperature	294(2) K
Space group	$P2_1/c$
Unit cell dimensions	a = 11.989(3) Å α = 90 ° b = 12.990(3) Å β = 91.34(3) ° c = 8.601(3) Å γ = 90 °
Volume	1339.1(7) $Å^3$
Z	4
Density (calculated)	1.350 Mg/m^3
Absorption coefficient	0.215 mm^{-1}
F(000)	576
Crystal size	0.30 x 0.30 x 0.28 mm
Theta range for data collection	1.70 to 29.97 °
Index ranges	-16<=h<=0, 0<=k<=18, -12<=l<=12
Reflections collected	4302
Independent reflections	3888 [R(int) = 0.0191]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3887 / 0 / 147
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0453, wR2 = 0.1334
R indices (all data)	R1 = 0.0814, wR2 = 0.1407
Largest diff. peak and hole	0.281 and -0.263 $e.Å^{-3}$
Absorption correction, (min, max, ave transmission)	91.72, 99.97, 95,79 %

(E) dimethyl 3-benzoyl-prop-2-enylphosphonate (**3**); δ_H ($CDCl_3$): 2.85 (2H, dd, J_{HP} 23.0, J_{HH} 7.3 Hz), 3.75 (6H, d, J_{HP} 10.9 Hz), 6.92 (1H, ddt, J_{HH} 15.4, J_{HP} 7.5, J_{HH} 7.5 Hz), 7.02 (1H, dt, J_{HH} 15.4, 4.3 Hz), 7.44 (2H, t, J_{HH} 7.5 Hz), 7.52 (1H, t, J_{HH} 7.5 Hz), 7.90 (2H, d, J_{HH} 7.5 Hz).

Elimination of **2**. **2** (0.50 g, 1.17 mmol) was dissolved in Bu^{t}OH (2.5 mL) and potassium tert-butoxide (0.17 g, 1.52 mmol) was added to the solution. The mixture was incubated at room temperature for 18 h, evaporated under reduced pressure, water (5 mL) was added, the pH of the solution was adjusted to 7 with trifluoroacetic acid, and extracted with chloroform (5 × 4 mL). After drying ($MgSO_4$) and evaporation, crude product was obtained as an oil, 0.220 g (73%). ^{31}P NMR spectrum showed again the presence of only one product (δ_P 27.8), and the ^{1}H NMR spectrum was identical to that of **3** described above.

X-ray intensity data for **1** were collected on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated MoKα radiation (λ = 0.7107 Å) and the ω-2θ technique. Accurate cell dimensions were obtained by least squares analysis of the setting angles of 24 reflections in the range $16 < \theta < 17°$. Data were collected with variable scan width and scan speed. Three reference reflections were monitored periodically for intensity and orientation control. The data were corrected for Lorentz polarization effects and an empirical absorption correction[14] was applied.

The structure was solved by direct methods using SHELXS-86[15] and refined using SHELXL93.[16] In the final refinement of **1**, the non-hydrogen atoms were treated anisotropically. The hydroxyl hydrogen was located in the difference map and refined isotropically. All other hydrogens were placed in calculated positions. Further details are given in Table II.

Fractional atomic coordinates, full tables of bond lengths and angles, anisotropic temperature factors and structure factors have been deposited.

ACKNOWLEDGEMENTS

Financial assistance of the University of Pretoria, University of Cape Town, and the Foundation for Research Development is gratefully acknowledged. We thank Professor R. L. Nassimbeni for helpful discussions.

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