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Conformational and Solid-State Studies of Diphenyl 1-Hydroxy-1-phenylethylphosphonate

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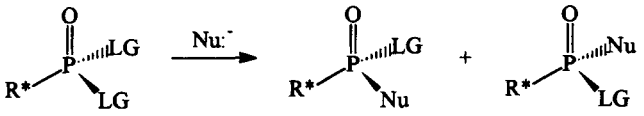
ABSTRACT

The crystal structure of the title compound, diphenyl 1-hydroxy-1-phenylethylphosphonate (1), was determined by the single-crystal X-ray diffraction method. The crystallographic data for 1 are as follow: $C_{20}H_{19}O_4P$, M_r = 354.34, monoclinic, $P2_1/n$, a = 9.787(1) Å, b = 20.235(1) Å, c = 9.797(1) Å, β = 106.18(3)°, V = 1863.3(4) Å^3, Z = 4, D_{calc} = *1.26 g/cm^3*, *λ(Mo-Kα) = 0.71073 Å*, *μ = 1.6 cm^{-1}*, *F(000) = 744*, *R = 0.018*, *and* R_w = *0.032 for 2258 observed reflections. The solid-state structure in a dimeric packing mode exhibits intermolecular hydrogen bonding of the type P=O···H–O. Infrared solution studies (CCl_4) indicate that upon high dilution (10^{-4} M) the dimers completely dissociate to give conformers with and without intramolecular hydrogen bonds. Theoretical studies (PM3) were undertaken to determine the energy profile about the P–C torsional angle, which exhibited low energy barriers to rotation with no clear minimum energy conformation.* © *1996 John Wiley & Sons, Inc.*

INTRODUCTION

Regulation of chiral centers during the synthesis of biologically important molecules [1] is a challenging task. The application of asymmetric induction is often used in this regard [1]. Whereas carbon-based chiral auxiliaries have long been used to induce chirality into carbon atoms [2], the long-range goal of the current investigation is to induce asymmetry at prochiral phosphorus [3]. The general concept is outlined in Equation 1 in which preferential formation of one diastereomer is desired. Only sparse examples of this type of asymmetric induction have been noted in the literature [4,5].



R* = Chiral Group LG = Leaving Group
Nu:⁻ = Allyl or Alkyl Group (1)

Several investigations of the stereochemical outcome of nucleophilic displacement at phosphorus have been conducted in our laboratory that primarily utilized phosphorus heterocyclic substrates [6]. Our present research involves the investigation of nucleophilic displacement at acyclic, prochiral phosphorus directly bonded to a chiral center. Preliminary results employing norbornyl-substituted phosphonates have shown promise [3]. Presented here is an initial study to determine the potential for facial

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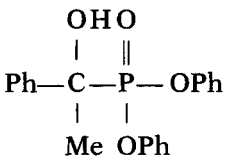
stereochemical differentiation in diphenyl 1-hydroxy-1-phenylethylphosphonate (1).



Similar phosphonate esters showed strong interactions between the P=O and the hydroxyl substituent that resulted in marked selectivity of the population of individual conformations [7]. These interactions are achieved via intramolecular hydrogen bonding, a donor–acceptor O → P effect (dipole–dipole), and the chelation of a metal ion (dipole–ion) [7b], which are anticipated to impede the rotation about the P–C bond of 1.

RESULTS AND DISCUSSION

Structural Studies

The ORTEP diagram for 1 is given in Figure 1. A listing of bond lengths (Å) and bond angles (°) are shown in Table 1. The packing diagram for 1 is displayed in Figure 2. The fractional coordinates are given in Table 2 along with the equivalent isotropic displacement parameter (B_{eq}) for each refined heavy atom. The torsional angles for 1 are listed in Table 3.

The P=O and P–O bond lengths determined for 1 of 1.461(2), 1.573(3), and 1.581(3) Å agree with the literature averages reported for phosphonates [8]. Recent X-ray diffraction studies of several acyclic phosphonates gave a P–C bond length range of 1.809(3)–1.85(2) Å [9], indicating that the 1.826(3) Å P–C bond length for 1 is typical.

Bond angles about the phosphorus suggest a distortion toward a trigonal pyramidal environment, away from tetragonal, with the phosphoryl oxygen (O3) occupying the apical position and O5, O2, and C24 the trigonal base [9b,10]. The angles involving P=O range from 114.2(1) to 115.6(2)°, while the bond angles not involving the P=O oxygen atom range from 101.1(1) to 106.1(2)° (see Table 2).

The two diastereotopic phenoxy O–C bond lengths are not significantly different, 1.392(4) and 1.406(4) Å for O5–C18 and O2–C12, respectively [11]. Both values are within the normal range for phenoxy O–C bond lengths for phosphorus esters [12,13a,14]. Interestingly, these values are not significantly different from the average value of 1.401(10) Å reported for carbonyl esters (C_{ar}–OC(O)C) [8].

The bond angles 123.5(2) and 125.1(2)° for P–O–Ph are closer to 120° than an idealized sp^3 angle of 109.5°. It appears that this angle is independent of the hybridization of the carbon atom attached to the oxygen in phosphorus esters [9d,f,14–16].

The torsional angles about the P1–C24 bond confirm a nearly staggered atomic arrangement with the *ipso* carbon (C6) *anti* to the phosphoryl oxygen (O3)

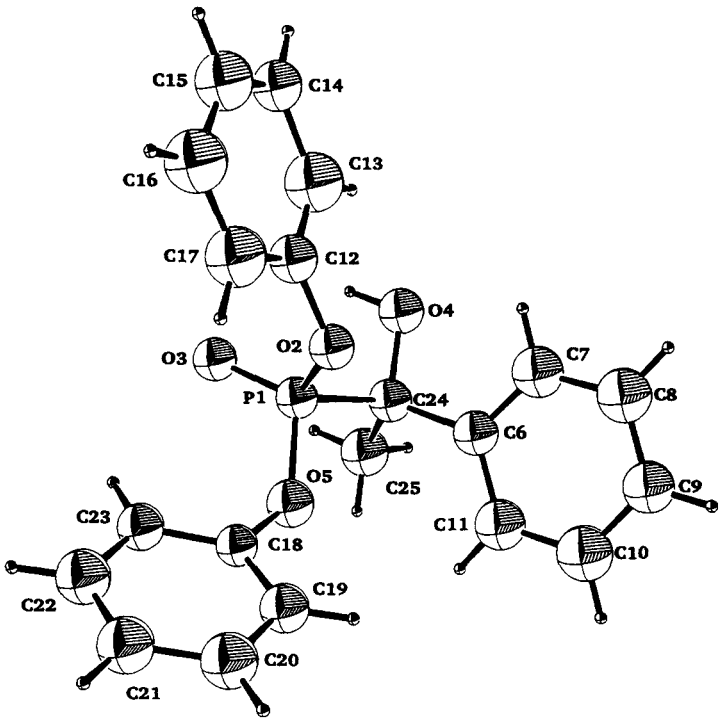


FIGURE 1 The ORTEP (30% thermal ellipsoids) diagram for 1.

TABLE 1 Selected Bond Lengths (Å)[a] and Bond Angles (°)[a] for **1**

			Bond Lengths		
Atoms	*Distance*	*Atoms*	*Distance*	*Atoms*	*Distance*
P1–O2	1.573(3)	P1–O(3)	1.461(2)	P1–O5	1.581(3)
P1–C24	1.826(3)	O2–C12	1.406(4)	O4–C24	1.430(4)
O5–C18	1.392(4)	C6–C11	1.391(5)	C6–C24	1.490(5)
C24–C25	1.540(6)				
			Bond Angles		
Atoms	*Angle*	*Atoms*	*Angle*	*Atoms*	*Angle*
P1–O2–C12	123.5(2)	P1–O5–C18	125.1(2)	P1–C24–O4	104.2(2)
P1–C24–C6	112.0(2)	P1–C24–C25	108.4(3)	O2–P1–O5	103.4(1)
O2–P1–C24	106.1(2)	O2–P1–O3	114.2(1)	O3–P1–O5	115.6(2)
O3–P1–C24	114.9(2)	O5–P1–C24	101.1(1)	O2–C12–C13	118.2(4)
O2–C12–C17	117.5(4)	O5–C18–C19	114.8(3)	O5–C18–C23	123.0(3)
O4–C24–C6	108.2(3)	O4–C24–C25	109.6(3)	C6–C24–C25	114.0(3)
C11–C6–C24	121.8(3)				

[a]Estimated standard deviations in the least significant digits are given in parentheses.

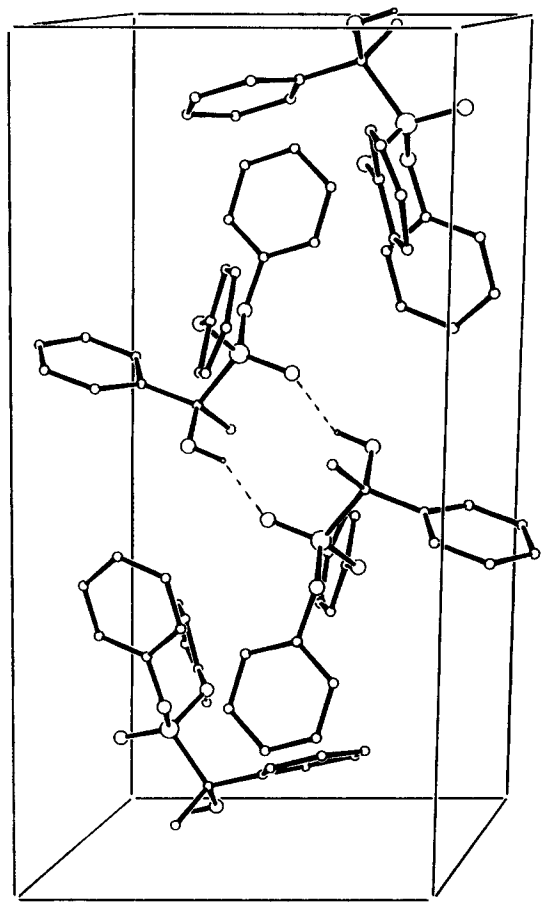


FIGURE 2 The packing diagram for **1** depicting the intermolecular hydrogen bonding.

TABLE 2 Fractional Coordinates and Equivalent Isotropic Displacement Parameters (Å²) for **1**

Atom	*x*[b]	*y*[b]	*z*[b]	*B*(*eq*)[a,b]
P1	0.1285(1)	0.10597(5)	0.1075(1)	5.31(2)
O2	0.2000(2)	0.1475(1)	0.0103(2)	5.63(7)
O3	−0.0183(2)	0.0865(1)	0.0384(2)	5.76(6)
O4	0.2396(2)	−0.0036(1)	0.0558(3)	6.34(6)
O5	0.1507(2)	0.1504(1)	0.2448(3)	6.35(6)
C6	0.4000(4)	0.0603(2)	0.2315(3)	5.49(7)
C7	0.4908(3)	0.0594(2)	0.1453(4)	7.4(1)
C8	0.6320(5)	0.0796(3)	0.1950(5)	9.4(1)
C9	0.6818(5)	0.1025(3)	0.3322(6)	9.9(1)
C10	0.5932(4)	0.1068(3)	0.4167(4)	9.4(2)
C11	0.4537(4)	0.0849(2)	0.3686(4)	7.4(1)
C12	0.1384(3)	0.1566(2)	−0.1362(4)	6.2(1)
C13	0.1382(4)	0.1059(3)	−0.2223(4)	9.9(1)
C14	0.0791(5)	0.1153(3)	−0.3690(7)	8.0(2)
C15	0.0336(5)	0.1731(3)	−0.4155(5)	9.2(2)
C16	0.0300(6)	0.2281(3)	−0.3292(4)	9.7(2)
C17	0.0886(6)	0.2191(2)	−0.1819(5)	9.2(1)
C18	0.1056(4)	0.2156(2)	0.2458(3)	4.51(8)
C19	0.2082(4)	0.2587(2)	0.3165(5)	6.3(1)
C20	0.1708(5)	0.3229(2)	0.3307(5)	7.6(1)
C21	0.0347(4)	0.3442(2)	0.2742(5)	7.8(1)
C22	−0.0685(3)	0.2993(2)	0.2046(5)	7.7(1)
C23	−0.0323(4)	0.2348(2)	0.1879(5)	6.0(1)
C24	0.2498(4)	0.0376(2)	0.1768(3)	5.79(9)
C25	0.1943(5)	−0.0001(2)	0.2871(5)	8.3(1)

[a]$B_{eq} = 4/3[a^2\beta(1,1) + b^2\beta(2,2) + c^2\beta(3,3) + ab(\cos\gamma)\beta(1,2) + ac(\cos\beta)\beta(1,3) + bc(\cos\alpha)\beta(2,3)]$.
[b]Estimated standard deviations in the least significant digits are given in parentheses.

TABLE 3 Torsional Angles (°)[a] for 1

Atoms	*Angle*	*Atoms*	*Angle*	*Atoms*	*Angle*
O3–P1–O2–C12	−9.6(3)	O5–P1–O2–C12	−136.1(3)	C24–P1–O2–C12	118.6(3)
O2–P1–O5–C18	56.4(3)	O3–P1–O5–C18	−69.2(3)	C24–P1–O5–C18	166.0(3)
O3–P1–C24–C25	−59.6(3)	O5–P1–C24–C25	65.7(3)	O2–P1–C24–O4	−70.1(2)
O2–P1–C24–C6	46.7(2)	O2–P1–C24–C25	173.3(2)	O3–P1–C24–O4	57.1(3)
O3–P1–C24–C6	173.8(2)	O5–P1–C24–O4	−177.7(2)	O5–P1–C24–C6	61.0(2)
P1–O2–C12–C13	−73.3(4)	P1–O2–C12–C17	110.0(4)	P1–O5–C18–C19	−128.4(3)
P1–O5–C18–C23	55.3(5)	C11–C6–C24–P1	84.3(4)	C7–C6–C24–P1	−93.7(4)

[a]Estimated standard deviations in the least significant digits are given in parentheses.

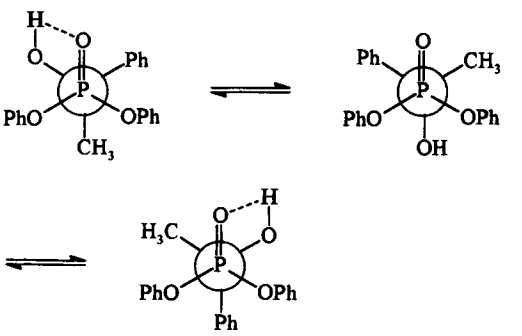
at 175.0(1)°. The hydroxyl oxygen is *gauche* to the phosphoryl oxygen [O3–P1–C24–O4 57.1(3)°], which places these atoms in a position favorable for intramolecular P=O···H–O–C hydrogen bonding.

Hydrogen-Bonding Study

Apart from depicting the unit cell, Figure 2 also displays the intermolecular P=O···H–O hydrogen bonds that exist in the solid state of 1. The strong intermolecular hydrogen bonds of 2.691(2) Å between the phosphoryl oxygen atoms and the hydroxyl oxygen atoms [O3···O4(−*x*,−*y*,−*z*)] form centrosymmetric dimers in which one molecule of (R) configuration is associated with one of (S) configuration [15]. The possibility also exists that the OH group participates in two hydrogen bonds (a fork bond) [9d,16,17] given the relatively close intramolecular O3···O4 contact of 3.097(2) Å.

A search of X-ray crystallographic data revealed nearly 150 examples of P=O···H–O–C hydrogen bonding since 1962 with only a few involving *α* hydroxyphosphonates [9d,e,13b,16,17]. All the *α* hydroxyphosphonates exhibit intermolecular hydrogen bonding, while several were found to exhibit both intra- and intermolecular hydrogen bonding [9d,16,17]. The crystallographic results from 1 most closely parallel those from dimethyl *α*-chloromethyl-*α*-hydroxybenzylphosphonate (2) by Hudson et al. [9e].

A strong, broad ν_{OH} stretching frequency centered at 3300 cm^{-1} is observed in the solid-state IR (KBr) spectrum of 1. The CCl_4 solution infrared spectrum of 1 (10^{-2} *M*) has moderate OH bands at 3600 and 3570 cm^{-1} and a very strong band at 3310 cm^{-1}. These results are nearly identical to 3320, 3576, and 3600 cm^{-1} found by Shagidullin and Trutneva [18a] for diethyl 1-methyl-1-hydroxyethylphosphonate. Upon dilution (10^{-3} *M*), the intensity of the 3310 cm^{-1} band weakens relative to the other two bands, and further dilution (10^{-4} *M*) results in the complete disappearance of the 3310 cm^{-1} band. These results indicate that the dimeric form (ν_{OH} = 3310 cm^{-1}) does not remain intact in dilute solutions. Although the exact assignments of the two high-energy bands cannot be made, neither band can be attributed to an intermolecular hydrogen bond since the bands are concentration independent. By analogy to previous work [18,19,20], the suggested assignments correspond to one free OH (3600 cm^{-1}) and one intramolecularly hydrogen-bonded OH (3570 cm^{-1}). This would imply that a conformational equilibrium exists in dilute CCl_4 solutions as shown (Equation 2).



(2)

Conformational Studies

The minimum energy conformation about the P–C bond will greatly influence the effectiveness of chelation or hydrogen bonding. Likewise, the placement of the methyl group vs. the phenyl group may influence the predominate face of attack by the nucleophile. Thus, in order to garner information about the minimum energy conformation and the rotational barriers about the P1–C24 bond, the conformational energy profile of the torsional angle O3–P1–C24–O4 was determined using semiempirical calculations at the PM3 level. For each point of the profile, the structure was fully optimized. Figure 3 graphically displays the results from these PM3 calculations for 1.

Several features emerge from the conformational energy profile of 1. First, the location of the least stable conformation (~240°) coincides with an eclipsed interaction of the relatively bulky phenyl

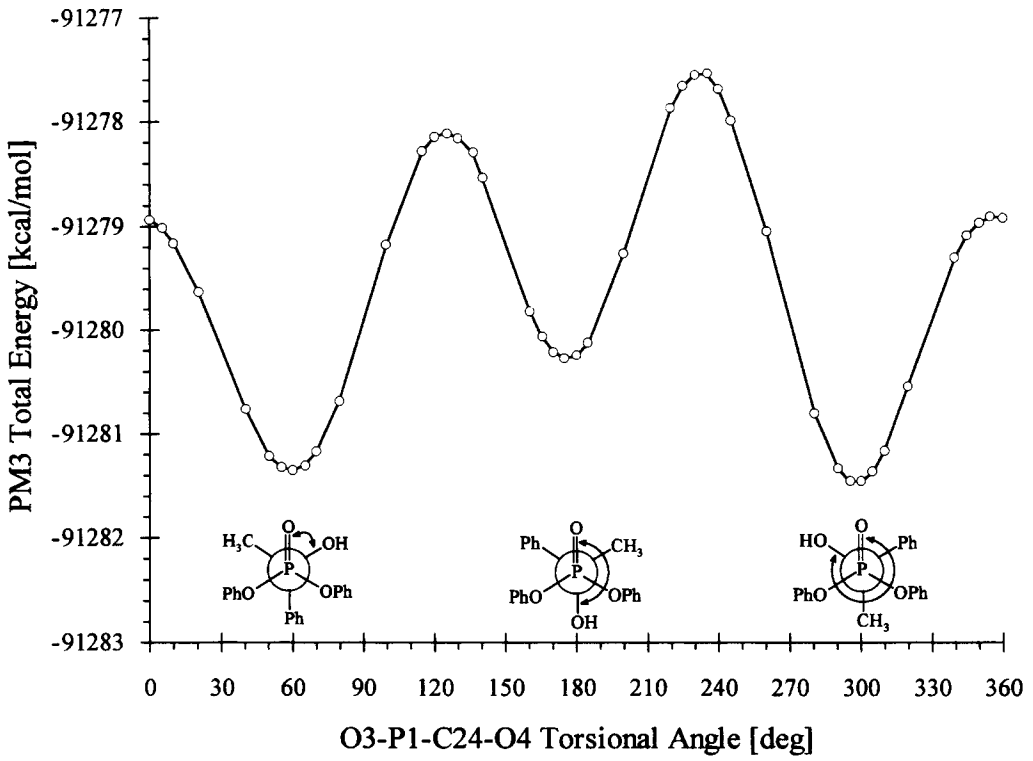


FIGURE 3 The rotational energy profile (PM3) about the P1–C24 bond (O3–P1–C24–O4 torsional angle) of **1**. Each point was fully geometry optimized using a geometric restraint of 400 kcal/mol at the given torsional angle (°) followed by calculating the total energy (kcal/mol) at the PM3 level. The crystallographic torsional angle was determined to be 57.1(3)°.

group and phosphoryl oxygen atom [21]. Second, the location of the global minimum at ~300° does not agree with the torsional angle found in the crystal structure of 57.1(3)°; however, both the small energy difference between the two minima (60 and 300°) of ~0.12 kcal/mol and the low barrier for interconversion between the two conformations (~2.5 kcal/mol) suggest that both conformations will be equally populated in the gas phase. Third, the least stable staggered conformation (~180°) corresponds to the conformer in which the phenyl and methyl groups are *gauche* to the phosphoryl oxygen atom. As with the other rotamers, steric interactions between the bulky substituents and the phosphoryl oxygen atom appear to influence greatly the energy of the system.

In the present PM3 study, no significant deviation from 20° in the O4–C24–C6–C7 torsional angle was encountered throughout the rotation around the P–C bond. The NMR resonance of the ortho protons (δ 7.75–7.71) is shifted downfield from the other aromatic protons [22]. These two observations indicated that the rotation of the α-phenyl group may be restricted. Recent studies of β hydroxyphosphonates have calculated (PM3) rotational energy barriers of ~12 kcal/mol about the C_α–C_{ipso} bond (rotation of the phenyl group) [22]. Additional PM3 rotational energy profiles for 180° rotation of the C24–C6 bond were determined for two conformations about the P–C bond and are shown in Figure 4.

Both conformations about the P–C bond gave nearly the same rotational energy profile for the O4–C24–C6–C7 torsional angle, which indicates that changes in the conformation of the P–C bond have little influence on the rotation of the phenyl group. Vassilev and Dimitrov [22] attributed the restricted rotation of the phenyl ring to steric controls imposed by bulky β substituents. However, in **1** no restricted rotation could be discerned from the calculations. The low-energy barriers to rotation may be ascribed to the small steric influence of the methyl substituent and the relatively long P–C bond.

Space-filling models [23] were employed to investigate if the two faces of the phosphorus center opposite the phenoxy leaving groups show potential for blocking nucleophilic access to the phosphorus. Using the coordinates from the crystal structure of **1**, the faces opposite each phenoxy group were viewed down each P–O bond. From this view, it appears that the phosphorus center is not sufficiently blocked by the methyl group. Although chelation or intramolecular hydrogen bonding may restrict rotation of the P1–C24 bond, the lack of both a definitive low-energy conformer and a blocked face strongly suggests that the methyl group does not pro-

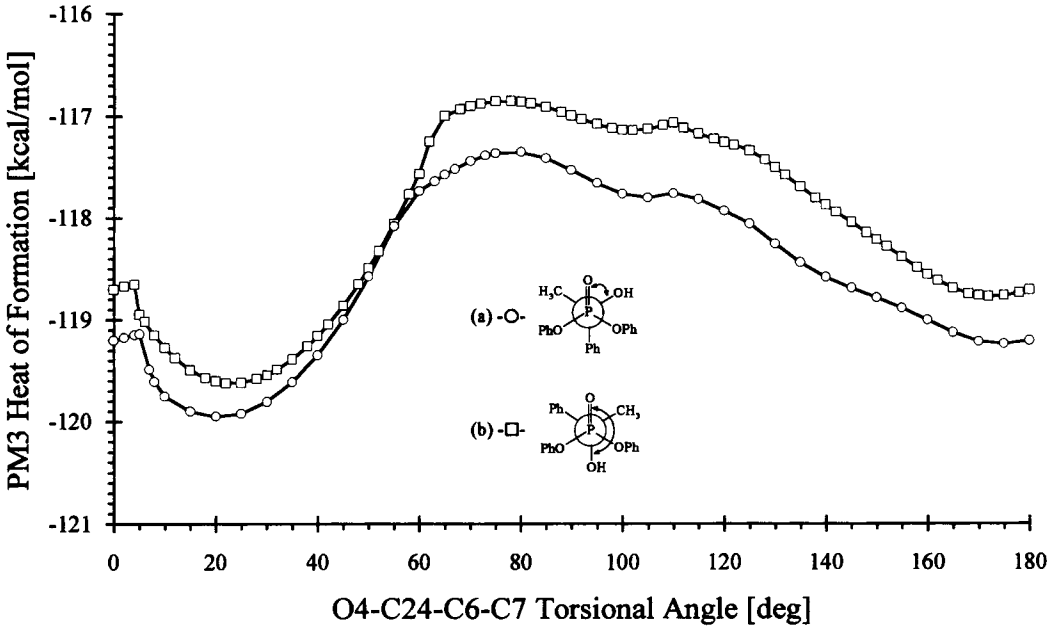


FIGURE 4 Rotational energy profile (PM3) about the C_{α}–C_{ipso} bond (O4–C24–C6–C7) for **1**. Each point was fully geometry optimized using a geometric restraint of 400 kcal/mol at the given torsional angle (°) followed by calculating the heat of formation (kcal/mol) at the PM3 level. Two initial conformations about the P–C bond (O3–P1–C24–C25) were used: (a) −60°[-○-] and (b) 60° [-□-].

vide the necessary steric bias to give facial stereochemical differentiation.

Additional space-filling models were also used to investigate diphenyl 1-hydroxy-2,2-dimethyl-1-phenylpropylphosphonate (**3**). Again, the molecule was viewed down the P–O bonds of the potential diastereotopic leaving groups. This model seems to indicate that the bulkier *t*-butyl group of **3** may block access to the phosphorus more than the methyl group of **1**, but conformational studies of **3** indicate free rotation about the P–C bond with no definitive low-energy conformer.

CONCLUSION

The X-ray crystal structure of **1** closely parallels the results from the crystal structure of **2** by Hudson et al. [9e]. Strong intermolecular hydrogen bonds form centrosymmetric dimers of the form P=O···H–O in which one molecule of (R) configuration is associated with one of (S) configuration. Although intermolecular hydrogen bonding is present in the solid state of **1**, the fact that the dimeric form is broken upon dilution in CCl_4 strongly suggests that metal chelation or intramolecular hydrogen bonding could be used to insure a locked conformation about the P1–C24 bond [7].

The PM3 level calculations indicate that both **1** and **3** lack an explicit low-energy conformation about the P–C bond and have low barriers to rotation. These results may be attributed to the relatively long P–C bond [1.812(2) Å] compared with the average C–C bond length of 1.530(15) [8]. The long P–C bond does not allow for significant interaction between the groups on the phosphorus atom and the *a* substituents, thus reducing both steric and torsional strain.

Preliminary modeling studies indicate that the methyl substituent does not possess the necessary steric bias to block nucleophilic access to the phosphorus opposite the leaving group. Although more rigorous calculations are needed, modeling results from **3** suggest that an increase in the size of the *a* substituent may hinder access to the phosphorus.

EXPERIMENTAL

Synthesis

General. The reaction was carried out in flame-dried glassware under a nitrogen atmosphere. ^1H NMR spectra were taken at 300 MHZ; ^{13}C NMR spectra were taken at 75 MHZ; ^{31}P NMR (121 MHZ) chemical shifts are relative to 85% phosphoric acid (H_3PO_4, external standard) on a GE OMEGA 300 MHz NMR spectrometer. ^1H and ^{13}C NMR δ values were referenced to TMS or $CDCl_3$. Infrared spectra were recorded on a Mattson GL-4020 FT-IR using a variable path length cell (NaCl). All solvents and re-

agents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and were purified and dried by standard literature methods. The elemental analysis was performed by Midwest Microlab of Indianapolis, IN.

Diphenyl 1-hydroxy-1-phenylethylphosphonate (1)

To a 500 mL flask was added 25.0 g (208 mmol) of acetophenone, 58.5 g (250 mmol) of diphenyl phosphite, and 250 mL of benzene. To this solution ~0.2 g (~8 mmol) of NaH was added slowly. After 24 hours of stirring, the mixture was washed with water (3 × 50 mL), sat'd NaCl (3 × 50 mL), and again with water (1 × 50 mL), and dried over Na_2SO_4. The solvent was removed to give a clear oil, but after 4 days clear crystals developed. The crystals were recrystallized twice in benzene to give 22.6 g of 1 (32%), mp 123–125°C. ^{13}C NMR ($CDCl_3$) δ 150.63 (J_{PC} = 10.98 Hz) and 150.45 (J_{PC} = 10.98 Hz), 139.98 (s), 129.51 (s), 128.15 (J_{PC} = 2.44 Hz), 127.79 (J_{PC} = 3.66 Hz), 126.18 (J_{PC} = 4.89 Hz), 125.05 (s), 120.48 (J_{PC} = 3.66 Hz), 73.81 (J_{PC} = 159.92 Hz), 25.60 (J_{PC} = 6.10 Hz). ^1H NMR ($CDCl_3$) δ 7.75–7.71 (m, 2H), 7.43–7.08 (m, 9H), 7.05–6.91 (m, 4H), 4.09 (br s, 1H, OH), 1.97 (d, 3HJ_{PH} = 16.84 Hz). ^{13}P NMR ($CDCl_3$) δ 17.78. Anal. calcd. for $C_{20}H_{19}O_4P$: C, 67.79; H, 5.40. Found: C, 67.60; H, 5.36.

X-ray Crystal Structure Determination

The slow evaporation of solvent from a CH_2Cl_2 solution of 1 resulted in the formation of X-ray quality crystals. Measurements of the racemic crystals were made on an Enraf-Nonius CAD4 computer-controlled kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator. Data handling, reduction, and analysis were performed using MULTAN [24]. The data were collected using Mo*Ka* (0.71073 Å) radiation and the ω-2θ scan technique at 23(1) °C. The intensities of three reflections were checked every 120 minutes. Intense reflections were automatically attenuated with Zr foil; the attenuation factor was 18.1. An empirical absorption correction based on a series of psi scans was applied to the data. Experimental details are listed in Table 4. The structure was solved by direct methods using SHELX86 [25] with the remaining atoms located by difference Fourier synthesis. The structure was refined by full-matrix least-squares refinement to a final R and R_w of 0.018 and 0.032, respectively.

Semiempirical Calculations

Semiempirical calculations were performed using PM3 [26] with the HyperChem [23] software package. Each conformation of 1 was optimized with a restrained O–C–P=O [O3–P1–C24–O4] torsional angle (force constant = 400 kcal/mol). Optimization was continued until the heat of formation gradient was lower than 0.01 kcal $mol;^{-1}$ $Å;^{-1}$ for each conformer. The PM3 total energy was calculated after convergence. The starting point for each restrained optimization cycle was the optimized structure obtained from the closest torsion angle; at the 0° point, the crystal structure was used and only the torsional angle varied. Model 3 was built by replacing the methyl group from the optimized structure of 1 with an idealized *t*-butyl group. The conformational study of 3 was performed in the same manner as for *1* above.

Two initial conformations about the P–C bond were used to study the O4–C24–C6–C7 (O–C_a–C_{ipso}–C_{ortho}) torsional angle of 1: O3–P1–C24–C25 = −60 and 60°. The torsional angle was restrained in steps from 0 to 180° and the PM3 heat of formation was determined after convergence.

TABLE 4 Crystallographic Experimental Details for **1**

Crystal Data	
$C_{20}H_{19}O_4P$	Mo $K\alpha(\lambda$ = 0.71073 Å)
M_r = 354.34	D_{calc} = 1.26 g cm^{-3}
Monoclinic	Cell parameters from 25 reflections
$P2_1/n$	θ = 9.0–18.0°
a = 9.787(1)Å	μ = 1.6 cm^{-1}
b = 20.235(1)Å	rectangular
c = 9.797(1)Å	0.35 × 0.35 × 0.65
β = 106.18(3)°	colorless
V = 1863.3(4)Å^3	T = 296(1)K
Z = 4	
Intensity Measurements	
CAD-4 diffractometer	θ_{max} = 36.5°
ω-2θ scan technique	h = 0 → 11
Absorption correction: empirical via ψ scans (from 1,000 to 1.038 on I)	k = −24 → 0
	l = −11 → 11
	3 standard reflections checked every 120 minutes intensity loss: 2.29%
3660 measured reflections	
2258 observed reflection with $F_0^2 > 3.0\sigma(F_0^2)$	
Structure Solution and Refinement	
Refinement on F	226 parameters
R = 0.018	R_w = 0.032
$\Delta\rho_{max}$ = 0.82 e $Å^{-3}$	

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