Crystal and Molecular Structure of Organophosphorus Insecticides. 5. Fospirate

Russell G. Baughman and Robert A. Jacobson*

The crystal and molecular structure of fospirate [dimethyl 3,5,6-trichloro-2-pyridyl phosphate, $(H_3CO)_2P(O)OC_5NHCl_3$, monoclinic, $P2_1/c$, $a = 12.267$ (5), $b = 8.685$ (1), $c = 14.102$ (6) Å, $\beta = 126.62$ (3)°, $Z = 4$, Mo Kα radiation] has been determined by three-dimensional x-ray analysis. The structure was solved by conventional Patterson and Fourier techniques to a final discrepancy index $R = 0.062$ for 1104 observed reflections ($F_o > 2.5\sigma(F_o)$). The phosphorus–meta hydrogen distance of 5.79 Å is within the range of literature values cited for the intramolecular active site-separation distance for insect acetylcholinesterase (AChE), yet is well outside that for mammalian AChE. CNDO molecular orbital calculations are presented to correlate the solid state structure to a probable in vivo model.

The crystal-structure investigation of fospirate, $(H_3CO)_2P(O)OC_5NHCl_3$, was undertaken as a part of a study of various organophosphorus (OP) insecticides being carried on at this Laboratory (Baughman and Jacobson, 1975; Gifkins and Jacobson, 1977; Rohrbaugh and Jacobson, 1976; Baughman and Jacobson, 1976; Baughman et al., 1977). The purpose of such a program is to better understand the relationship between structure and mechanism(s) relative to an insecticide's toxicity/activity. Since ronnel, bromophos, and Ruelene (the first, fourth, and fifth references, respectively above) are all phenoxy OP's, it now seems logical to investigate some heteronuclear ring systems in order to note any conformational similarities and/or dissimilarities which might result.

In the case of acetylcholinesterase (AChE) inhibition, one would ideally like to know the three-dimensional structure of the active sites, or that of a small range of possible low-energy conformations. The complexity of this enzyme virtually prohibits direct elucidation of its structure. However, accurate structural determinations of smaller molecules such as the organophosphorus (OP) and/or carbamate insecticides, which strongly interact with the active site(s) of AChE, would allow not only inferences to be made with regards to the topography of AChE but also yield valuable molecular insight into the insecticides themselves. [Structural investigations of the carbamates are concurrently being performed (Takusagawa and Jacobson, 1977)]. Such information could lead to the construction of insecticides which would better conform structurally as well as chemically to the most favorable (minimum energy) orientation of AChE.

EXPERIMENTAL SECTION

Crystal Data. From a 99+% pure sample of the title compound, a rectangular prismatic crystal with approximate dimensions 0.20 × 0.23 × 0.30 mm was selected and mounted on the end of a glass fiber using Elmer's Glue-All. The crystal was then mounted on a four-circle diffractometer, and three ω-oscillation photographs were taken at various χ and ϕ settings and verified that the crystal was indeed single.

From these photographs 15 independent reflections were selected and their coordinates were input into an automatic indexing program (Jacobson, 1976). The reduced cell scalars which resulted indicated monoclinic symmetry, which was confirmed by inspection of ω-oscillation photographs taken about each of the three axes in turn. Only the b axis showed a mirror plane. Observed layer line spacings agreed, within experimental error, with those predicted for this cell by the indexing program.

The lattice constants were obtained from a least-squares refinement based on the precise $\pm 2\theta$ ($|2\theta| > 30°$) measurements of 25 strong independent reflections. At 27 °C using Mo Kα ($\lambda = 0.70954$ Å) they are $a = 12.267$ (5), $b = 8.685$ (1), $c = 14.102$ (6) Å, and $\beta = 126.62$ (3)°. The observed density of 1.67(2) g cm^{-3} determined by the flotation method is in good agreement with the calculated value of 1.688 g cm^{-3} for four molecules with a molecular weight of 306.46 g mol^{-1} in a unit cell having a volume of 1205.83 Å^3.

Collection and Reduction of X-Ray Intensity Data. The data were collected at 27 °C with graphite monochromated Mo Kα radiation on an automated four-circle diffractometer designed and built in the Ames Laboratory and previously described by Rohrbaugh and Jacobson (1974). All data within a 2θ sphere of 45° [$(\sin\theta)/\lambda = 0.539$ Å^{-1}] in the hkl and $\bar{h}kl$ octants were measured using an ω-stepscan technique.

As a general check on electronic and crystal stability, the intensities of three standard reflections were remeasured every 75 reflections. These standard reflections were not observed to vary significantly throughout the entire period of data collection (~2 days). Hence, a decomposition correction was unnecessary. A total of 2424 reflections were recorded in this manner. Examination of the data revealed the following systematic absences: $h0l$ when $l = 2n + 1$ and $0k0$ when $k = 2n + 1$. These absences uniquely determine the space group as $P2_1/c$.

The intensity data were corrected for Lorentz and polarization effects and, since $\mu = 8.84$ cm^{-1}, absorption corrections were not made; maximum and minimum transmission factors were 0.838 and 0.767, respectively. The estimated variance in each intensity was calculated by:

$$\sigma_I^2 = C_T + 2C_B + (0.03C_T)^2 + (0.03C_B)^2$$

where C_T and C_B represent the total and background counts, respectively, and the factor 0.03 represents an estimate of nonstatistical errors. The estimated deviations in the structure factors were calculated by the finite difference method (Lawton and Jacobson, 1968). Equivalent data were averaged and 1114 reflections with $F_o > 2.5\sigma(F_o)$ were retained for use in subsequent calculations. During later work it was discovered that ten large reflections suffered from secondary extinction effects; these were eliminated from the final stages of refinement.

Solution and Refinement. The position of a chlorine was obtained from an analysis of a standard three-dimensional Patterson function. The remaining atoms were found by successive structure factor (Busing et al., 1962) and electron density map calculations (Hubbard et al.,

---

Contribution from the Ames Laboratory–ERDA and Department of Chemistry, Iowa State University, Ames, Iowa 50011.

Table I. Final Atomic Positional[a] and Thermal[b] Parameters for Fospirate

Atom	Fractional Coordinates x	y	z	Atomic temperature factors β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(1)	0.0378 (3)[c]	0.2057 (3)	0.1357 (2)	21.8 (4)	14.5 (4)	13.5 (3)	0.1 (3)	11.2 (3)	−0.3 (2)
Cl(2)	−0.3799 (2)	0.5855 (4)	−0.0065 (2)	11.4 (3)	32.4 (6)	15.4 (3)	−0.6 (3)	8.0 (2)	0.2 (3)
Cl(3)	−0.1786 (2)	0.8647 (3)	0.0668 (2)	17.2 (3)	18.3 (4)	14.1 (3)	3.5 (3)	9.7 (3)	2.9 (2)
P	0.3017 (2)	0.6126 (2)	0.2664 (2)	10.4 (3)	18.3 (4)	9.0 (2)	0.5 (3)	6.3 (2)	0.4 (2)
O(1)	0.1800 (5)	0.4959 (6)	0.1782 (4)	11.7 (7)	17.0 (9)	12.0 (5)	−1.3 (6)	7.6 (5)	−1.8 (6)
O(2)	0.3051 (6)	0.6550 (6)	0.3684 (5)	14.4 (7)	22 (1)	9.1 (5)	1.9 (7)	6.9 (5)	0.6 (6)
O(3)	0.4225 (5)	0.5200 (7)	0.2878 (5)	12.7 (7)	24 (1)	14.3 (6)	2.3 (7)	9.3 (6)	0.5 (7)
O(4)	0.2924 (6)	0.7460 (6)	0.1888 (5)	18.8 (9)	19 (1)	13.6 (6)	−1.9 (8)	11.8 (6)	0.1 (7)
N	0.0046 (6)	0.6569 (7)	0.1253 (5)	10.8 (9)	13 (1)	10.0 (6)	−0.4 (7)	6.2 (6)	−0.1 (6)
C(1)	0.0491 (7)	0.5162 (9)	0.1392 (6)	10.9 (9)	18 (1)	6.7 (6)	−1.6 (9)	5.6 (6)	−0.1 (7)
C(2)	−0.0281 (8)	0.3863 (8)	0.1149 (7)	16 (1)	13 (1)	8.7 (7)	−2 (1)	7.8 (8)	−1.1 (7)
C(3)	−0.1634 (8)	0.407 (1)	0.0696 (7)	14 (1)	19 (2)	9.2 (8)	−4 (1)	7.6 (8)	−2.2 (8)
C(4)	−0.2126 (8)	0.556 (1)	0.0519 (6)	12 (1)	20 (1)	9.0 (7)	−3 (1)	6.6 (7)	−0.9 (8)
C(5)	−0.1247 (9)	0.6770 (9)	0.0813 (7)	14 (1)	15 (1)	8.0 (7)	2 (1)	6.8 (7)	2.9 (7)
C(6)	0.457 (1)	0.371 (1)	0.3415 (9)	17 (1)	32 (2)	16 (1)	10 (1)	9 (1)	7 (1)
C(7)	0.254 (1)	0.900 (1)	0.1966 (8)	22 (2)	15 (1)	15 (1)	−1 (1)	11 (1)	1 (1)
H(1)	−0.2210[c]	0.3216	0.0509	4.5					
C(6)H(1)	0.3744	0.3034	0.2975	4.5					
C(6)H(2)	0.4898	0.3808	0.4255	4.5					
C(6)H(3)	0.5296	0.3244	0.3392	4.5					
C(7)H(1)	0.3326	0.9711	0.2282	4.5					
C(7)H(2)	0.2265	0.9002	0.2507	4.5					
C(7)H(3)	0.1758	0.9352	0.1162	4.5					

[a] The positional parameters for all atoms are represented in fractional unit cell coordinates. [b] The β_{ij} are defined by: $T = \exp\{-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})\}$. If only the β_{11} column is listed, this corresponds to an isotropic temperature factor. All hydrogen isotropic temperature factors have been set equal to 4.5. Nonhydrogen thermal parameters are ($\times 10^3$). [c] In this and succeeding tables estimated standard deviations are given in parenthesis for the least significant figures and include the error in the lattice constants. Since the hydrogens were not refined, no standard deviations are given.

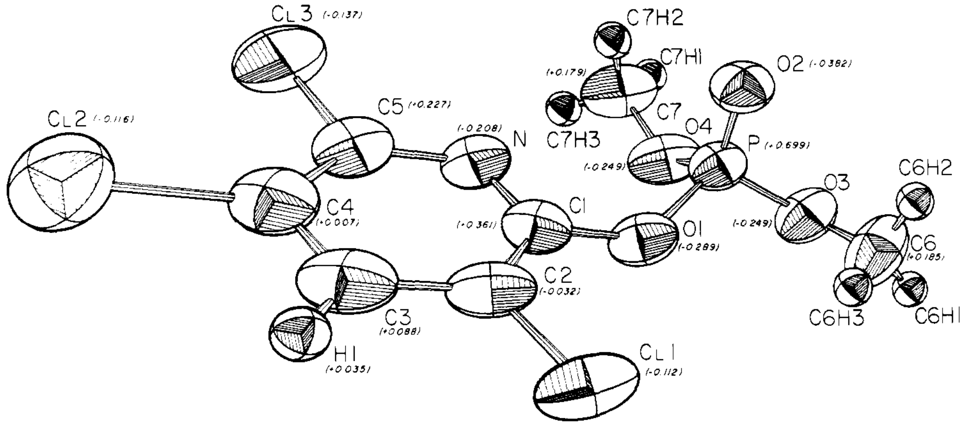

Figure 1. The fospirate molecule showing 50% probability ellipsoids; 30% for hydrogens. The numbers in parentheses refer to partial charge densities from a CNDO/2 calculation.

1971). These atomic positions were subsequently refined by a full-matrix least-squares procedure (Busing et al., 1962) minimizing the function $\sum w(|F_o| - |F_c|)^2$, where $w = 1/\sigma_F^2$. This refinement yielded a conventional discrepancy factor of $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.125$. At this stage of the refinement all 16 nonhydrogen atoms had been refined using isotropic thermal parameters. The scattering factors used were those of Hanson et al. (1960), modified for the real and imaginary parts of anomalous dispersion (Templeton, 1962). The scattering factors for hydrogen were those of Stewart et al. (1965).

Analysis of an electron density difference map did not reveal either the ring or the methyl hydrogens. Consequently, the ring hydrogen atom position was fixed at 0.95 Å from the corresponding carbon (C(3)). The methyl hydrogens were inserted in approximately tetrahedral positions using the precise positions of the corresponding methyl carbon and the methoxy oxygen. The methyl C–H distances were set equal to 1.0 Å; all isotropic hydrogen temperature factors were set equal to 4.5 Å^2.

Subsequent anisotropic least-squares refinement without varying the hydrogen parameters converged to $R = 0.062$. Since this procedure yielded slightly different nonhydrogen atom positions, all of the hydrogen positions were recalculated. Further refinement cycles did not significantly alter any atomic parameters and the discrepancy factor did not change.

The final positional and thermal parameters are listed in Table I. Standard deviations were calculated from the inverse matrix of the final least-squares cycle. Bond lengths and angles are listed in Table II and Table III, respectively (Busing et al., 1964). Dihedral angles and least-square planes are listed in Table IV.

DESCRIPTION OF STRUCTURE AND DISCUSSION

The pyridoxyl group in fospirate, shown in Figures 1 and 2 (Johnson, 1971), is essentially planar (cf. Table IV, plane II). For the most part, packing in the fospirate crystal can be regarded as either weakly coulombic or van der Waals in nature. The former is a manifestation of the charge

Table II. Selected Interatomic Distances (Å) for Fospirate

Bonding Distances		Non-Bonding Distances			
		Interaction	Via	Obsd distance	Total van der Waal distance (Pauling, 1960)
C(1)-C(2)	1.38 (1)	Cl(1)···O(1)	Intramolecular	2.917 (5)	3.20
C(2)-C(3)	1.39 (1)	Cl(2)···Cl(3)	Intramolecular	3.161 (4)	3.60
C(3)-C(4)	1.39 (1)	$C(6)H_3$···O(2)	Intramolecular	3.24 (1)	3.4
C(4)-C(5)	1.38 (1)	$C(7)H_3$···O(2)	Intramolecular	3.00 (1)	3.4
C(5)-N	1.33 (1)				
N-C(1)	1.30 (1)				
		N···O(2)	Intramolecular	3.204 (8)	2.9
C(1)-O(1)	1.364 (9)	N···O(4)	Intramolecular	3.177 (8)	2.9
C(2)-Cl(1)	1.709 (8)	N···$C(7)H_3$	Intramolecular	3.34 (1)	3.5
C(3)-H(1)	0.950 (8)				
C(4)-Cl(2)	1.714 (8)	H(1)···O(2)	2_1	2.419 (5), 2.32[a]	2.6
C(5)-Cl(3)	1.725 (8)	Cl(2)···Cl(2)	{center of inversion + one cell in *x* and *y*}	3.400 (5)	3.60
		$C(6)H_3$···O(4)	2_1 + one cell in *x*	3.52 (1)	3.4
P-O(1)	1.609 (5)				
P=O(2)	1.461 (6)				
P-O(3)	1.549 (6)				
P-O(4)	1.551 (6)				
O(3)-C(6)	1.43 (1)				
O(4)-C(7)	1.44 (1)				

[a] Using a C(6)-*proton* distance of 1.08 Å (Sutton, 1958).

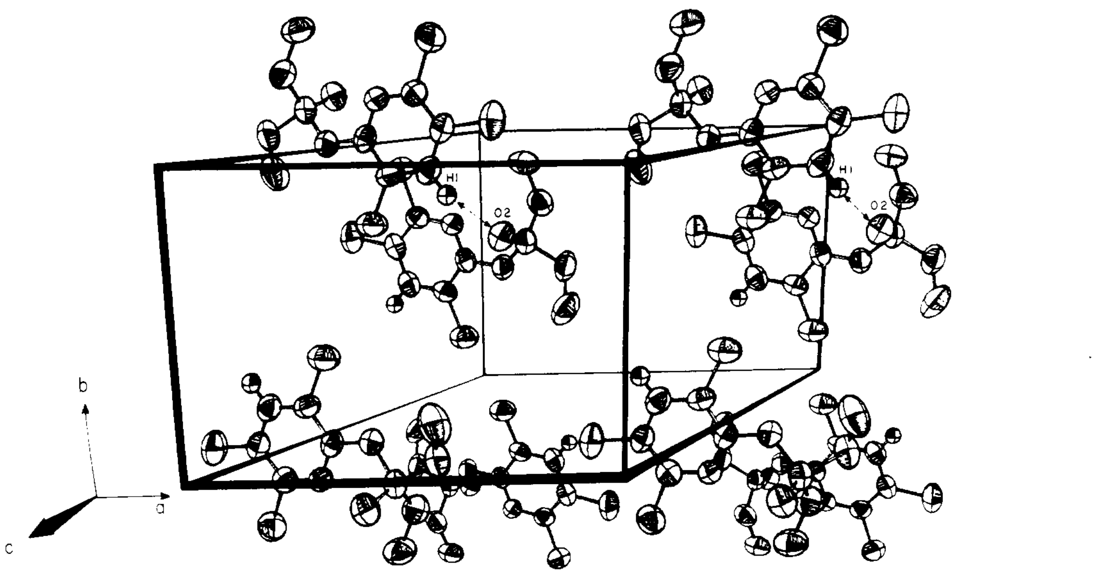

Figure 2. View of two adjacent unit cells illustrating packing in the *a* and *b* directions.

density distribution within each individual molecule and hence corroborates one's "chemical intuition" of atoms with δ(+) and δ(−) charges. The H(1)···O(2) interaction related via the twofold screw operation serves as such an example (Figure 2 and Tables II and III), while on the other hand, the N···$C(7)H_3$ and $C(6)H_3$···O(4) interactions appear to be van der Waals in character (Figure 2 and Table II).

The C(1)–O(1) bond in fospirate is significantly (~7σ) shorter than the two methoxy C–O bonds (cf. Table II), while the P–O(1) bond is the longest of the three P–O bonds, being at least 6σ longer than the other two. These observations, which are in agreement with CNDO/2 molecular orbital calculations of the Pople and Beveridge (1970) type, are consistent with a bonding formulation in which there is a weak π overlap of the p_z orbital on the oxygen with the ring system which simultaneously weakens the O–P bond. The later effect should enhance phosphorylation (Clark et al., 1964). Such variations in bond lengths have been noted earlier as the bond lengths corresponding to P–O(1) and C(1)–O(1) in fospirate, ronnel (Baughman and Jacobson, 1975), Coroxon (Gifkins and Jacobson, 1977), and bromophos (Baughman and Jacobson, 1976) are all within 3σ of being identical. The angles of the type S═P–O or O═P–O in these compounds are all greater than the tetrahedral angle of 109.47°. In fospirate the angle between the normal to the ring and the P–O(2) vector is 19.9°, which is only ~ 1.5° greater than the angle between the normals to the O(1)–O(3)–O(4) plane and the ring (cf. Table IV).

As with ronnel, bromophos, and Ruelene (Baughman et al., 1977), the phosphorus in fospirate is opposite the Cl(1) side of a plane which is perpendicular to the ring and contains the C(1)–O(1) bond. The position of the phosphorus appears to be dictated by the interactions of O(2), $C(7)H_3$, and O(4) with N as well as the phosphate group with Cl(1). Both O(2) and O(4) are essentially equidistant (~3.2 Å) from the nitrogen (cf. Table II). This is only 0.3

Table III. Bond Angles (Degrees) for Fospirate

C(1)-C(2)-C(3)	117.5 (7)
C(2)-C(3)-C(4)	118.6 (7)
C(3)-C(4)-C(5)	118.5 (7)
C(4)-C(5)-N	123.0 (7)
C(5)-N-C(1)	118.0 (6)
N-C(1)-C(2)	124.5 (7)
O(1)-C(1)-N	117.9 (6)
O(1)-C(1)-C(2)	117.6 (7)
Cl(1)-C(2)-C(1)	121.6 (6)
Cl(1)-C(2)-C(3)	120.9 (6)
H(1)-C(3)-C(2)	120.7 (9)
H(1)-C(3)-C(4)	120.7 (8)
Cl(2)-C(4)-C(3)	119.5 (6)
Cl(2)-C(4)-C(5)	122.0 (7)
Cl(3)-C(5)-C(4)	120.5 (7)
Cl(3)-C(5)-N	116.5 (6)
C(1)-O(1)-P	123.8 (5)
O(1)-P-O(2)	112.8 (3)
O(1)-P-O(3)	99.3 (3)
O(1)-P-O(4)	106.3 (3)
O(2)-P-O(3)	118.5 (3)
O(2)-P-O(4)	117.0 (3)
O(3)-P-O(4)	100.6 (3)
P-O(3)-C(6)	121.1 (6)
P-O(4)-C(7)	121.9 (5)
P-O(2)· · ·H(1)[a]	149.5
P-O(4)· · ·C(6)[b]	127.9 (4)
C(7)-O(4)· · ·C(6)[b]	94.2 (5)
O(2)· · ·H(1)-C(3)[a]	140.7

[a] Through 2_1, using a C(3)-*proton* distance of 1.08 Å (Sutton, 1958). [b] Through 2_1, and one cell in *x*.

Å longer than the sum of the van der Waals radii. As a result, the N-C(1)-O(1)-P torsional angle is only 11.5° and O(2) is skewed away from the C(1)-O(1)-P plane toward the Cl(1) side of the ring (cf. Figure 1 and Table IV). The fact that the oxygens are symmetrically disposed seems to imply that the twofold screw related H(1)···O(2) interaction, which is the only significant intermolecular interaction involving either O(2) or O(4), is of little or no consequence in determining the position of the phosphorus, as the H(1)···O(2) distance of 2.3 Å would only indicate a weak hydrogen bond at best (cf. Tables II and III and Figure 2). The molecular configuration especially in the neighborhood of the phosphorus atom may therefore be somewhat immobilized primarily as a result of van der Waals restrictions to rotation about the C(1)-O(1) and O(1)-P bonds; the forces involved would not be expected to be as strong as those due to the intramolecular hydrogen bonds in bromophos (Baughman and Jacobson, 1976) and Ruelene (Baughman et al., 1977).

To further substantiate such a view, a CNDO/2 molecular orbital calculation (after Pople and Beveridge, 1970) was carried out for fospirate in order to obtain information on the change in the potential energy surface as a function of incremental rotations about the C(1)-O(1) or O(1)-P bonds. In the case of rotation about the C(1)-O(1) bond, the C(1)-O(1)-P-O(2) torsional angle was maintained at 47.5° (i.e., the angle in the solid state) throughout the calculations. Similarly, the C(2)-C(1)-O(1)-P angle was kept at 11.6° during the set of calculations involving the rotation about the O(1)-P bond. Results of these calculations are shown in Figures 3 and 4, respectively. Since they represent plots of uncoupled degrees of freedom and because of the approximate nature of the calculations, it is not too surprising that the minima of each plot correspond to slightly different dihedral angles than are actually observed in the solid state. The minimum in Figure 3 coincides with a C(2)-C(1)-O(1)-P angle only ~12° greater than the observed angle of 11.6°. Figure 4 indicates a C(1)-O(1)-P-O(2) angle just ~8° less than 47.5°. It is also interesting to note that the depths of both potential wells are ~2.5 kcal mol^{-1} (1 au = 627.4 kcal mol^{-1}) and the energy minima on both plots occur at ~−202.5780 au, as expected.

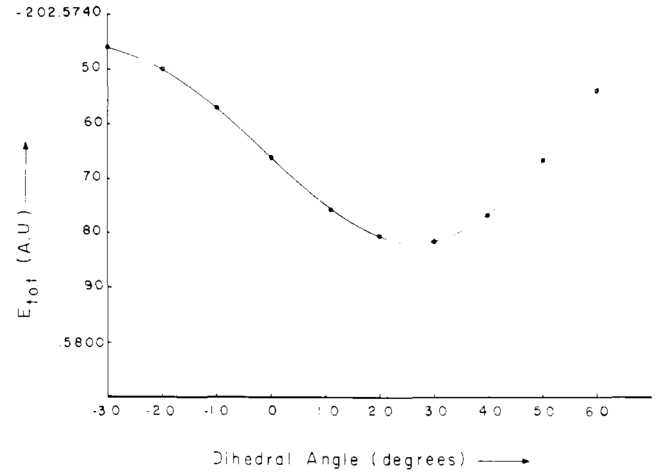

Figure 3. Total energy vs. C(2)-C(1)-O(1)-P dihedral angle from CNDO calculations.

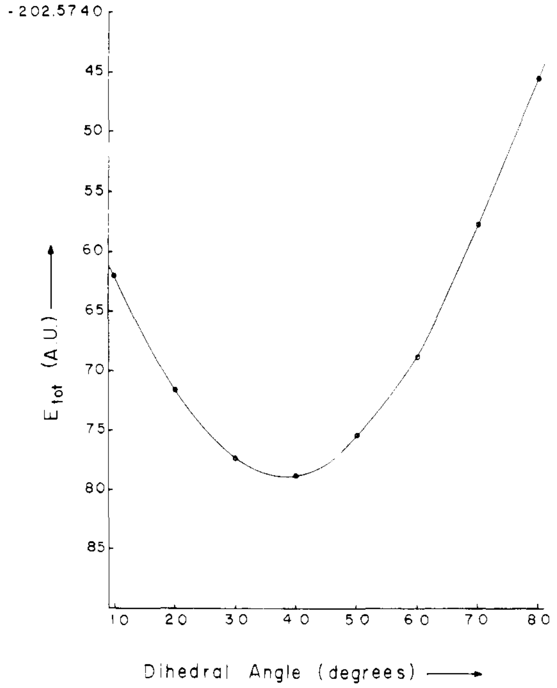

Figure 4. Total energy vs. C(1)-O(1)-P-O(2) dihedral angle from CNDO calculations.

As these results were obtained using CNDO methods, the absolute values of the energies and charges, as well as the differences in energies, are not as exact as with ab initio calculations. The later methods are usually unavailable for this size of a problem and are extremely cost prohibitive. Although admittedly approximate, the energies and charges obtained in this CNDO/2 calculation certainly give better than "order-of-magnitude" information expecially since d orbital contributions are included for the phosphorus and chlorine atoms.

On the basis of a restricted phosphorus position, comparison of some intramolecular distances with literature site-separation distances for AChE should give some insight into the toxicity/activity of fospirate. In addition to being "distance compatible", the two atoms involved must both have a net δ(+) charge to be in agreement with the AChE model of Krupka (1964). (Only two atoms are

Table IV. Dihedral Angles (Degrees) and Least-Squares Planes

Atom	Distance from plane, Å	Atom	Distance from plane, Å	Atom	Distance from plane, Å	Atom	Distance from plane, Å
Plane (I)[b] defined by carbons (1-5) and N: $(-0.37180)X + (0.00525)Y + (0.92830)Z - (1.70879) = 0$		Plane (II)[b] defined by all 11 pyridoxyl members: $(-0.36624)X + (-0.00126)Y + (0.93052)Z - (1.66461) = 0$				Plane (III)[b] defined by P, O(2), O(3), and C(6): $(0.61564)X + (0.54225)Y + (0.57179)Z - (5.75549) = 0$	
C(1)	−0.0106	C(1)	0.0048	O(1)	−0.0530	P	−0.2470
C(2)	0.0042	C(2)	0.0222	Cl(1)	0.0110	O(2)	0.1093
C(3)	0.0035	C(3)	0.0120	H(1)	0.0182	O(3)	0.2563
C(4)	−0.0054	C(4)	−0.0082	Cl(2)	−0.0525	C(6)	−0.1186
C(5)	−0.0003	C(5)	−0.0046	Cl(3)	0.0371		
N	0.0085	N	0.0132	O(3)	0.3494		
				O(4)	−0.4161		

Atom	Distance from plane, Å	Atom	Distance from plane, Å
Plane (IV)[b] defined by P, O(2), O(4), and C(7): $(0.78723)X + (0.19757)Y + (0.58415)Z - (4.03107) = 0$		Plane (V)[b] defined by P, O(1), O(2), and C(1): $(0.03262)X + (0.86730)Y + (-0.49671)Z - (2.97294) = 0$	
P	−0.0688	P	0.1914
O(2)	0.034	O(1)	−0.2162
O(4)	0.0710	O(2)	−0.0895
C(7)	−0.0371	C(1)	0.1143

Planes Defined By:	Dihedral angle of planes[a]
O(1)-O(3)-O(4); N-C(2)-C(4)	18.1 (3)
O(1)-O(3)-O(4); C(1)-C(3)-C(5)	18.5 (3)
O(1)-O(3)-O(4); O(1)-P-C(1)	47.3 (5)
O(1)-P-C(1); C(1)-C(3)-C(5)	11.6 (5)
O(1)-P-C(1); C(2)-C(4)-N	11.5 (5)
O(1)-P-C(1); P-O(2)-O(1)	47.5 (6)

[a] Angles correspond to the orientation shown in Figures 1 and 2, so that the phosphorus is directed toward the N side of the ring. [b] Planes are defined by $c_1X + c_2Y + c_3Z - d = 0$, where X, Y, and Z are Cartesian coordinates which are related to the triclinic cell coordinates (x, y, z) by the transformations: $X = xa \sin\gamma + zc\{(\cos\beta - \cos\alpha\cos\gamma)/\sin\gamma\} = xa + zc\cos\beta$, $Y = xa\cos\gamma + yb + zc\cos\alpha = yb$, $Z = zc\{1 - \cos^2\alpha - \cos^2\beta - \cos^2\gamma + 2\cos\alpha\cos\beta\cos\gamma)^{1/2}/\sin\gamma\} = zc\sin\beta$.

being considered here in accordance with the presence of two residues in the active site of AChE. Analysis of the steric interactions of the remaining parts of both molecules, without knowing more about the structure of AChE, would be futile.)

Using the CNDO/2 method, approximate values for the charge density distribution in fospirate can be computed; results are shown in Figure 1. Examination of this figure (and Table II) shows that P···H(1) (5.79 Å), P···C(3) (4.95 Å), P···C(4) (5.14 Å), and P···C(5) (4.27 Å) are the most important pairs in this regard. The small charge on C(4) of +0.007e would appear to rule out the P···C(4) pair as an important contributor to inhibition. The P···H(1) and P···C(3) distances fall outside of the mammalian AChE site-separation range of 4.3–4.7 Å (Hollingworth et al., 1967; O'Brien, 1963) and yet are close to or within the range for insect AChE given by Hollingworth et al. (1967) of 5.0–5.5 Å and O'Brien (1963) of 4.5–5.9 Å. It is even conceivable that since both H(1) and C(3) are $\delta(+)$ and are both "distance compatible" with AChE, the C(3)–H(1) pair might correspond to a *region* of $\delta(+)$ charge having P···$\delta(+)$ distances of from 4.95 to 5.79 Å. Considering charge, distance, steric factors, and overall reactivity, P···H(1) may be slightly favored as the reactive species toward insect AChE in fospirate. However, the P···C(5) pair, due to its shorter distance, may play a more important role in mammalian toxicity, unless significant conformational alterations in AChE or fospirate accompany any in vivo free-energy changes.

It should be noted that even rotations about the C(1)–O(1) bond of ±40°, which, according to Figure 3, may possibly be achieved in vivo, would correspond to a maximum change in the P–H(1) distance, for example, of only ±0.03 Å, which is not likely to be critical with respect to the distances in AChE and to the I_{50} of the insecticide as pertains to the conformation which AChE or fospirate might have to distort to in order to react. However, such a rotation would cause the phosphorus to be in a slightly different position relative to the other ring substituents. This may be partially responsible, then, for changes in I_{50} and/or LD_{50} values as a result of subtle *steric* influences of the insecticide AChE. But, in order to make better comparisons and predictions, many heretofore unreported I_{50} and LD_{50} values will need to be investigated and tabulated. In addition, further similar CNDO calculations will need to be performed to obtain a better idea of the potential energy barriers which may be necessary to overcome in adduct formation.

ACKNOWLEDGMENT

The authors would like to thank D. Wendell Osborne, Dow Chemical Company, Midland, Mich., for kindly supplying a sample of the title compound.

Supplementary Material Available: A listing of the observed and calculated structure factor amplitudes (3 pages). Ordering information is given on any current masthead page.

LITERATURE CITED

Baughman, R. G., Eckey, D. A., Jacobson, R. A., *J. Agric. Food Chem.*, in preparation (1977).

Baughman, R. G., Jacobson, R. A., *J. Agric. Food Chem.* **23**, 811 (1975).

Baughman, R. G., Jacobson, R. A., *J. Agric. Food Chem.* **24**, 1036 (1976).

Busing, W. R., Martin, K. O., Levy, H. A., "ORFLS, A Fortran Crystallographic Least Squares Program", U.S. Atomic Energy Commission Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1962.

Busing, W. R., Martin, K. O., Levy, H. A., "ORFFE, A Fortran Crystallographic Function and Error Program", U.S. Atomic Energy Commission Report ORNL-TM-306, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1964.

Clark, V. M., Hutchinson, D. W., Kirby, A. I., Warren, S. G., *Angew. Chem.* **76**, 704 (1964).

Gifkins, M. R., Jacobson, R. A., *J. Agric. Food Chem.*, **24**, 232 (1976).

Hanson, H. P., Herman, F., Lea, J. D., Skillman, S., *Acta Crystallogr.* **17**, 1040 (1960).

Hollingworth, R. M., Fukuto, T. R., Metcalf, R. L., *J. Agric. Food Chem.* **15**, 235 (1967).

Hubbard, C. A., Quicksall, C. O., Jacobson, R. A., "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFPROJ, ALFFT, and FRIEDEL", U.S. Atomic Energy Commission Reprt IS-2625, Iowa State University and Institute for Atomic Research, Ames, Iowa, 1971.

Jacobson, R. A., *J. Appl. Crystallogr.* **9**, 115 (1976).

Johnson, C. A., "ORTEP-II: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations", U.S. Atomic Energy Commission Report ORNL-3794 (Second Revision with Supplemental Instructions), Oak Ridge National Laboratory, Oak Ridge, Tenn., 1971.

Krupka, R. M., *Can. J. Biochem.* **42**, 677 (1964).

Lawton, S. L., Jacobson, R. A., *Inorg. Chem.* **7**, 2124 (1968).

O'Brien, R. D., *J. Agric. Food Chem.* **11**, 163 (1963).

Pauling, L., "Nature of the Chemical Bond", Cornell University Press, Ithaca, N.Y., 1960.

Pople, J. A., Beveridge, D. L., "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.

Rohrbaugh, W. J., Jacobson, R. A., *Inorg. Chem.* **13**, 2535 (1974).

Rohrbaugh, W. J., Jacobson, R. A., *J. Agric. Food Chem.* **24**, 713 (1976).

Stewart, R. F., Davidson, E. R., Simpson, W. T., *J. Chem. Phys.* **42**, 3175 (1965).

Sutton, L. E., Ed., "Tables of Interatomic Distances and Configuration in Molecules and Ions", The Chemical Society, Burlington House, London, W.1., 1958.

Takusagawa, F., Jacobson, R. A., *J. Agric. Food Chem.* **25**, 577 (1977).

Templeton, D. H., in "International Tables for X-ray Crystallography", Vol. III, Table 3.3.2c, The Knoch Press, Birmingham, England, 1962, pp 215–216.

Received for review November 1, 1976. Accepted January 31, 1977. Prepared for the U.S. Energy Research and Development Administration under Contract No. W-7405-eng-82.