576 *J. Agric. Food Chem.*, Vol. 26, No. 3, 1978

Baughman, Jorgensen, Jacobson

appear that benomyl is stable in that solvent (Chiba, 1977a). The results of this study make it possible to correct for the degradation which has taken place in the solvents tested, with the possible exception of methanol.

Chiba (1977a) has used *n*-butyl isocyanate extensively in his spectrophotometric method for the analysis of benomyl. For example, benomyl standard solutions have been stabilized with 1000 ppm BIC in chloroform. The results of this study make it possible to determine the extent of stabilization. As an example consider a solution originally containing 10 ppm benomyl (3.43×10^{-5} mol/L) in chloroform. To reform benomyl from the MBC present, one portion of a chloroform solution containing 100 000 ppm BIC is added to nine portions of this sample. The resultant BIC concentration is 10 000 ppm (0.101 mol/L). The value of $X = 1.92 \times 10^{-8}$, the moles of benomyl decomposed per liter, is obtained from:

$$K = 5.65 \times 10^{-5} = \frac{X(X - 0.101)}{3.43 \times 10^{-5} - X} \simeq$$

$$\frac{0.101X}{3.43 \times 10^{-5}} \tag{9}$$

Thus, 99.944% of intact benomyl remains in this solution.

Without the aid of BIC, it is difficult to retain intact benomyl in the solutions if concentrations of benomyl are low. For example, when benomyl solutions are prepared at 1 ppm and 0.1 ppm in chloroform, the percentage of benomyl remaining at equilibrium is calculated to be only 5.5 and 0.6%, respectively.

For the extraction of benomyl from different samples, ethyl acetate (Pease and Holt, 1971), benzene (Rouchaud and Decallonne, 1974), and chloroform (Peterson and Edgington, 1969, 1971) were used. Although the workers, who used ethyl acetate and benzene, did not intend to recover intact benomyl in their extracts and further treated

the extracts with other chemicals, it is of value to know the exact status of solutes in the extract at the time of further chemical treatment.

As a result of this study, the behavior of benomyl in organic solvents has been well elucidated, particularly regarding the reversible reaction of benomyl to MBC + BIC. With the better understanding obtained from this study about the rate of degradation of benomyl in organic solvents and with the knowledge of the significant effect of temperature on the degradation (Chiba, 1977b), more accurate and comprehensive analysis of benomyl and MBC can be achieved by using Chiba's spectrophotometric method (1977a).

LITERATURE CITED

Austin, D. J., Lord, K. A., Williams, I. H., *Pestic. Sci.* **7**, 211 (1976).
Baude, F. J., Gardiner, J. A., Han, J. C. Y., *J. Agric. Food Chem.* **21**, 1084 (1973).
Calmon, J. P., Sayag, D. R., *J. Agric. Food Chem.* **24**, 426 (1976).
Chiba, M., *J. Agric. Food Chem.* **25**, 368 (1977a).
Chiba, M., *Bull. Environ. Contam. Toxicol.* **18**, 285 (1977b).
Chiba, M., Doornbos, F., *Bull. Environ. Contam. Toxicol.* **11**, 273 (1974).
Clemons, G. P., Sisler, H. D., *Phytopathology* **59**, 705 (1969).
Pease, H. L., Holt, R. F., *J. Assoc. Off. Anal. Chem.* **54**, 1399 (1971).
Peterson, C. A., Edgington, L. V., *J. Agric. Food Chem.* **17**, 898 (1969).
Peterson, C. A., Edgington, L. V., *Phytopathology* **60**, 475 (1970).
Peterson, C. A., Edgington, L. V., *Phytopathology* **61**, 91 (1971).
Rouchaud, J. P., Decallonne, J. R., *J. Agric. Food Chem.* **22**, 259 (1974).

Crystal and Molecular Structure of Organophosphorus Insecticides. 10. Chlorpyrifos

Russell G. Baughman, Sharon K. Jorgensen, and Robert A. Jacobson*

The crystal and molecular structure of chlorpyrifos {*O,O*-diethyl *O*-3,5,6-trichloro-2-pyridyl thiophosphate, $(H_5C_2O)_2P(S)OC_5NHCl_3$, monoclinic, $C2/c$, $a = 22.06$ (1), $b = 9.485$ (2), $c = 15.990$ (6) Å, $\beta = 114.63$ (4)°, $Z = 8$, 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 $R = 0.066$ for 1421 observed reflections ($|F_o| > 2.5\sigma(F_o)$). The phosphorus–meta hydrogen distance of 5.78 Å is within the range of literature values cited for insect acetylcholinesterase (AChE), yet is well outside that for mammalian AChE. CNDO molecular orbital charge density calculations and van der Waals arguments are presented to correlate the solid state structure to a probable in vivo model.

The crystal structure investigation of chlorpyrifos 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, 1976; Rohrbaugh and Jacobson, 1976; Baughman and Jacobson, 1976; Baughman and Jacobson, 1977;

Rohrbaugh and Jacobson, 1977; Baughman et al., 1978; Baughman and Jacobson, 1978). The purpose of such a program is to better understand the relationship between structure and mechanism(s) relative to an insecticide's toxicity–activity. Ronnel, bromophos, Crufomate, and ronnel oxon (the first, fourth, sixth, and eighth references, respectively, above) are all *phenoxy* OP's. The study of heteronuclear ring systems was begun with azinphosmethyl and fospirate (third and fifth references) in order to note any conformational similarities and/or dissimi-

Ames Laboratory-DOE and Department of Chemistry, Iowa State University, Ames, Iowa 50011.

larities resulting from the replacement of one or more ring carbons with nitrogen. Chlorpyrifos offers an example of an insecticide in the latter category, and, since it is the
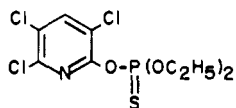
diethoxy *thio*phosphate analogue of fospirate, the possibility also exists to study structural vagaries due to replacement of an oxygen atom with a sulfur and methyl with ethyl groups.

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, 1977a,b,c)]. 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 × 0.20 × 0.10 mm was selected and mounted on the end of a glass fiber using Elmer's Glue-All. Subsequent experimental work was essentially as described previously (Baughman and Jacobson, 1975).

The lattice constants were obtained from a least-squares refinement based on the precise $\pm 2\theta$ ($20° < |2\theta| < 30°$) measurements of 20 strong independent reflections. At 27 °C using Mo Kα ($\lambda = 0.70954$ Å) they are $a = 22.06$ (1), $b = 9.485$ (2), $c = 15.990$ (6) Å, and $\beta = 114.63$ (4)°. The observed density of 1.49 (2) g cm^{-3} determined by the flotation method is in good agreement with the calculated value of 1.532 g cm^{-3} for four molecules with a molecular weight of 350.52 g mol^{-1} in a unit cell having a volume of 3041.3 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 50° {$(\sin \theta)/\lambda = 0.596$ Å^{-1}} in the hkl, $\bar{h}kl$, $hk\bar{l}$, and $\bar{h}k\bar{l}$ 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 (~4 days). Hence a decomposition correction was unnecessary. A total of 5687 reflections were recorded in this manner. Examination of the data revealed the following systematic absences: hkl when $h + k = 2n + 1$ and $h0l$ when $l = 2n + 1$ ($h = 2n + 1$). These absences coupled with a statistical indication of a center of symmetry implied $C2/c$ as the space group.

The intensity data were corrected for Lorentz and polarization effects, and, since $\mu = 8.39$ cm^{-1}, absorption corrections were not made; maximum and minimum

transmission factors were 0.92 and 0.85, 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 the 1426 reflections with $|F_o| > 2.5\sigma(F_o)$ were retained for use in subsequent calculations. During later work it was discovered that five 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., 1971). These atomic positions were subsequently refined by a full-matrix least-squares procedure (Busing et al., 1962), minimizing the function $\Sigma \omega(|F_o| - |F_c|)^2$, where $\omega = 1/\sigma_F{}^2$. This refinement yielded a conventional discrepancy factor of $R = \Sigma ||F_o| - |F_c||/\Sigma|F_o| = 0.125$. At this stage of the refinement all 18 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)]. Methyl hydrogens were inserted in approximately tetrahedral positions using the precise positions of the methyl carbon and the corresponding methoxy oxygen. Each set of methyl hydrogens was rotated by 60° about the corresponding O–Me bond; all 12 methyl hydrogens were assigned half-occupancy. As a result a "doughnut" of hydrogens was approximated. 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 $R = 0.066$. 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 parameters are listed in Table I, while the associated thermal parameters can be found in the supplementary material (see Supplementary Material paragraph at the end of the article). 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 given in the supplementary material.

DESCRIPTION OF STRUCTURE AND DISCUSSION

The pyridoxyl group in chlorpyrifos, shown in Figure 1 (Johnson, 1971), is essentially planar. For the most part, packing in the fospirate crystal can be regarded as primarily van der Waals in nature as all close intermolecular interactions are greater than or comparable to the sum of the van der Waals radii (cf. Table II). Consequently the molecular configuration is unlikely to be a function of crystal packing.

Table I. Final Atomic Positional[a] Parameters for Chlorpyrifos

Atom	x	y	z
Cl(1)	0.4939 (1)[b]	-0.1379 (2)	0.6295 (2)
Cl(2)	0.3266 (1)	0.2230 (3)	0.3841 (1)
Cl(3)	0.4195 (1)	0.4722 (2)	0.5010 (2)
S	0.6679 (1)	0.2277 (2)	0.6677 (1)
P	0.6304 (1)	0.2115 (2)	0.7546 (1)
O(1)	0.5620 (2)	0.1222 (5)	0.7177 (3)
O(2)	0.6697 (2)	0.1269 (5)	0.8449 (3)
O(3)	0.6160 (3)	0.3471 (6)	0.7958 (3)
N	0.4924 (3)	0.2773 (7)	0.6095 (4)
C(1)	0.5080 (3)	0.147 (1)	0.6370 (5)
C(2)	0.4711 (4)	0.0316 (8)	0.5908 (5)
C(3)	0.4147 (4)	0.055 (1)	0.5116 (5)
C(4)	0.3971 (3)	0.193 (1)	0.4829 (5)
C(5)	0.4377 (4)	0.3000 (9)	0.5338 (5)
C(6)	0.620 (1)	0.483 (2)	0.766 (1)
C(7)	0.621 (1)	0.585 (2)	0.797 (1)
C(8)	0.6971 (5)	-0.009 (1)	0.8437 (6)
C(9)	0.7284 (5)	-0.065 (1)	0.9355 (7)
H(1)	0.388	-0.022	0.477
C6H(1)	0.573	0.492	0.715
C6H(2)	0.654	0.480	0.738
C8H(1)	0.732	-0.004	0.813
C8H(2)	0.660	-0.076	0.811

[a] The positional parameters for all atoms are represented in fractional unit cell coordinates. [b] In this and succeeding tables estimated standard deviations are given in parentheses for the least significant figures; later tables include the error in the lattice constants. Since the hydrogen positions were not refined, no standard deviations are given. Positions for the methyl hydrogens are not given as they were approximated.

The unusually elongated C(6) and C(7) thermal ellipsoids (cf. Figure 1) suggests some disordering of these atoms. Therefore an attempt was made to account for such disorder via a least-squares refinement replacing each carbon with two carbons having an assigned occupancy of one-half and being displaced initially by ~0.8 Å along the major axis of each ellipsoid. This procedure reduced R by
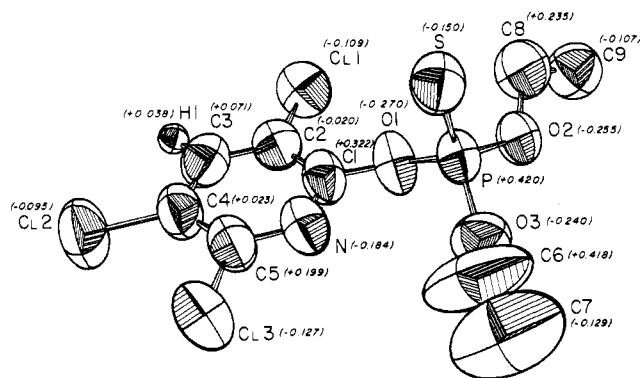

Figure 1. The chlorpyrifos molecule showing 50% probability ellipsoids; 30% for hydrogens. The numbers in parentheses refer to partial charge densities from a CNDO II calculation.

only 0.006 but did account for the distance and angle discrepancies involving O(3), C(6), and C(7) (cf. Tables II and III). That is, instead of short O(3)–C(1) and C(6)–C(7) bonds connecting the centers of the ellipsoids, the "left" half of C(6) is actually bonded to the "right" half of C(7) and vice versa, with O(3) remaining essentially fixed and intact; intermediate conformations also would occur. As the distances and angles in the remaining (and chemically significant) portion of the molecule were essentially unchanged throughout either refinement, only the time and lattice-averaged model will be reported here.

The C(1)–O(1) bond in chlorpyrifos is significantly (>3σ) 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 5σ longer than the other two. These observations, which when coupled with a CNDO II molecular orbital calculation 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 former effect is the likely cause of the C(1)–O(1)–P angle being greater than tetrahedral (cf. Table

Table II. Selected Interatomic Distances (A) for Chlorpyrifos

Bonding distances		Interaction	Via	Obsd distance	Total van der Waals distance (Pauling, 1960)
C(1)–C(2)	1.38 (1)				
C(2)–C(3)	1.37 (1)				
C(3)–C(4)	1.39 (1)	P⋯H(1)	Intramolecular	5.78 (2)	(3.1)
C(4)–C(5)	1.37 (1)	Cl(2)⋯Cl(3)	Intramolecular	3.175 (6)	3.6
C(5)–N	1.32 (1)	P⋯N	Intramolecular	3.02 (1)	3.4
N–C(1)	1.308 (9)	P⋯Cl(1)	Intramolecular	4.364 (3)	3.7
		P⋯C(1)	Intramolecular	2.64 (1)	3.6[b]
		P⋯C(3)	Intramolecular	4.953 (8)	(3.6)[b]
C(1)–O(1)	1.364 (9)	P⋯C(4)	Intramolecular	5.172 (7)	(3.6)[b]
C(2)–Cl(1)	1.721 (8)	P⋯C(5)	Intramolecular	4.328 (7)	(3.6)[b]
C(3)–H(1)	0.950 (8)				
C(4)–Cl(2)	1.717 (9)				
C(5)–Cl(3)	1.711 (8)	S⋯C(9)H₃	2₁ + 1 cell in x and z – 1 in y	3.87 (1)	3.85
		Cl(2)⋯O(2)	n-glide + 1 cell in y – 1 in x	3.548 (6)	3.20
P–O(1)	1.611 (5)	Cl(2)⋯C8H(1)	n-glide + 1 cell in y – 1 in x	3.286 (4)	3.0
P=S	1.898 (4)	Cl(2)⋯C(8)	n-glide + 1 cell in y – 1 in x	3.79 (1)	3.5[b]
P–O(2)	1.562 (5)	Cl(3)⋯C(9)H₃	n-glide + 1 cell in y – 1 in x	3.99 (1)	3.8
P–O(3)	1.538 (6)[a]	Cl(1)⋯C(7)H₃	2-fold + 1 cell in x and z –1 in y	4.15 (2)	3.8
O(2)–C(8)	1.426 (9)	S⋯C8H(1)	2₁ + 1 cell in x and z – 1 in y	3.300 (2)	3.05
O(3)–C(6)	1.39 (2)[a]	Cl(2)⋯C(7)H₃	Center + 1 cell in x and z – 1 in y	3.97 (2)	3.8
C(6)–C(7)	1.08 (2)[a]				
C(8)–C(9)	1.44 (1)				
C(6)–C6H(1)	1.00 (2)				
C(6)–C6H(2)	1.00 (2)				
C(8)–C8H(1)	1.00 (1)				
C(8)–C8H(2)	1.00 (2)				

[a] Due to disorder; see text. [b] Bondi, 1964.

Crystal and Molecular Structure of Chlorpyrifos

J. Agric. Food Chem., Vol. 26, No. 3, 1978   **579**

Table III. Bond Angles (Degrees) for Chlorpyrifos

C(1)-C(2)-C(3)	118.0 (7)
C(2)-C(3)-C(4)	118.6 (7)
C(3)-C(4)-C(5)	118.5 (7)
C(4)-C(5)-N	122.9 (7)
C(5)-N-C(1)	118.2 (7)
N-C(1)-C(2)	123.7 (6)
O(1)-C(1)-N	119.0 (7)
O(1)-C(1)-C(2)	117.2 (8)
Cl(1)-C(2)-C(1)	122.0 (6)
Cl(1)-C(2)-C(3)	120.0 (7)
H(1)-C(3)-C(2)	120.5 (9)
H(1)-C(3)-C(4)	120.9 (8)
Cl(2)-C(4)-C(3)	118.9 (7)
Cl(2)-C(4)-C(5)	122.6 (7)
Cl(3)-C(5)-C(4)	120.8 (6)
Cl(3)-C(5)-N	116.4 (6)
C(1)-O(1)-P	124.8 (5)
O(1)-P-S	113.7 (2)
O(1)-P-O(2)	98.2 (3)
O(1)-P-O(3)	105.6 (3)
S-P-O(2)	118.4 (2)
S-P-O(3)	118.5 (3)
O(2)-P-O(3)	99.6 (3)
P-O(2)-C(8)	121.8 (5)
P-O(3)-C(6)	125.1 (8)
O(2)-C(8)-C(9)	110.2 (8)
O(3)-C(6)-C(7)	132 (2)[a]

[a] Due to disordering; see text.

III) while the later 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 chlorpyrifos, ronnel (Baughman and Jacobson, 1975), Coroxon (Gifkins and Jacobson, 1976), bromophos (Baughman and Jacobson, 1976) fospirate (Baughman and Jacobson, 1977), Crufomate (Baughman et al., 1978), and ronnel oxon (Baughman and Jacobson, 1978) are all nearly identical. The pyridoxy OP's (fospirate and chlorpyrifos), though, do display a C(1)–O(1) bond length ~4σ less than that for the phenoxy OP's, apparently a result of the replacement of a ring carbon with a more electronegative nitrogen.

Angles of the S=P–O or O=P–O type in these compounds are all greater than the tetrahedral angle of 109.47°, while angles of the O–P–O type are all smaller than tetrahedral. The internal ring angles in chlorpyrifos are identical with their counterparts in fospirate. Those with nitrogen at the vertex are less than 120°, but, when nitrogen is the terminal atom, they are greater than 120°; the two types of angles are significantly (~5σ) different from each other (cf. Table III). In chlorpyrifos the angle between the normal to the ring and the P=S vector is 34.1° which is in the range of 20 to 40° observed with most of the OP's studied. This general agreement in observed angles is probably just a consequence of the similarities of these somewhat immobilized ring-containing compounds but could prove to be a reaction variable with OP's having many rotation degrees of freedom.

As with ronnel, bromophos, Crufomate, fospirate, and ronnel oxon, the phosphorus in chlorpyrifos is opposite the Cl(1) side of a plane which is perpendicular to the ring and contains the C(1)–O(1) bond. Since each molecule interacts only weakly with all of the other molecules in the unit cell (cf. Table II), the configuration of chlorpyrifos in the solid state is primarily dictated by intramolecular forces. Consequently the position of the phosphorus is a result of the van der Waals barrier to rotation about the C(1)–O(1) bond which is afforded by Cl(1) and N. By not having any substituent on the nitrogen, the thiophosphate group is allowed to avoid Cl(1). As a result the P–

O(1)–C(1)–C(2) torsional angle is 145.90° which is ~23° smaller than the corresponding angle in fospirate, presumably due to the presence of the sulfur in chlorpyrifos vs. an oxygen in fospirate. The lack of a substituent on nitrogen may be the major cause of the disordered C(6)–C(7) ethyl group, though disordering was not noted in fospirate (the only other previously studied pyridoxy OP). This also allows the Cl(3)–C(5)–C(4) angle to be >5σ larger than the Cl(3)–C(5)–N angle. A minor factor which may contribute to the disordered ethyl group is the near total absence of intermolecular interactions involving C(7) as contrasted to C(9) where they are very much present (though weakly) (cf. Table II). The upshot of this is that the P⋯N distance turns out to be less than a van der Waals separation apart while P⋯Cl(1) is not (cf. Table II). The S⋯N, C(6)⋯N, and O(3)⋯N separations (3.62, 3.48, and 3.16 Å, respectively) are all just ~0.2 Å greater than the sum of the respective van der Waals radii, thus reflecting a slight stabilization of the phosphorus position on the N side of the ring.

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 chlorpyrifos. In addition to being "distance compatible", the atoms involved must also be "charge compatible" with AChE. As a first approximation to the OP active site (O'Brien, 1974), only two atoms will be considered here in accordance with the presence of two residues in Krupka's (1964) [possibly incorrect (O'Brien, 1974)] active site model of AChE. Analysis of the steric interactions of the remaining parts of both molecules, without knowing more about the structure(s) of AChE, would be futile.

Using the CNDO II method of Pople and Beveridge (1970), approximate values for the charge density distribution in chlorpyrifos can be computed; results are shown in Figure 1. The use of this method is not as exact as with ab initio calculations which are extremely cost-prohibitive and are usually unavailable for this size of a problem. Although admittedly approximate, the charges obtained certainly give much better than "order of magnitude" information especially since d-orbital contributions are included for the phosphorus, sulfur, and chlorine atoms. Owing to the similarities of the OP's investigated, relative comparisons of, say, charge densities using the same CNDO II program for each molecule is a valid procedure even if the charge densities are not "absolute". It is for this reason that the CNDO results of ronnel oxon, Ruelene, fospirate, and chlorpyrifos may be compared. For example, the mammalian LD_{50}'s of chlorpyrifos and fospirate differ by a factor of 5 (~168 vs. 869 mg kg^{-1} (Osborne, 1976), respectively) while the charge densities on the phosphorus atoms are +0.420e and 0.699e, respectively. On the basis of these charges alone, the LD_{50} values might have been reversely predicted. This implies that, in addition to the charge on the phosphorus, many other variables (i.e., the charges on other atoms, steric interactions, etc.) need to be considered. But until the true (O'Brien, 1974) OP active sight is known, few good inferences can be made. However, the OP site separation distances should still be *comparable* to literature values for the *ACh* site–separation since (fortunately) the sizes of many OP's are similar to that of ACh. Therefore, this study now provides preliminary information which should prove to be of considerable value in deducing the true OP site.

Examination of Figure 1 and Table II shows that, in the case of chlorpyrifos, P⋯H(1) (5.78 Å), P⋯C(3) (4.95 Å),

P···C(4) (5.17 Å), and P···C(5) (4.33 Å) are interesting reaction pairs to consider. These distances are nearly identical with those in fospirate. The small charge on C(4) of +0.023e may possibly 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/or O'Brien (1963) of 4.5–5.9 Å. It is even conceivable that since both H(1) and C(3) are $\delta(+)$ and may both be "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 5.78 Å. Considering charge, distance, steric factors, and overall reactivity, P···H(1) may be *slightly* favored as a specific reactive species toward insect AChE in chlorpyrifos. The P···C(5) pair, due to its shorter separation, may play a more important role in mammalian toxicity, unless significant conformational alterations accompany an in vivo process.

It should be noted that even a rotation of the phosphorus about the C(1)–O(1) bond to the Cl(1) van der Waals limit would only decrease, say, the P···H(1) distance by only ~0.03 Å. This may possibly happen in vivo, even with the comparatively increased moment of inertia caused by the addition of C(7) and C(9), yet is not likely to be critical with respect to the distances in AChE and to the I_{50} of the insecticide. 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 with AChE. But, in order to make better comparisons and predictions, many heretofore unreported insect and mammalian I_{50} and LD_{50} values will need to be investigated and tabulated, especially for the isozymes of AChE.

ACKNOWLEDGMENT

Supplementary Material Available: A listing of the observed and calculated structure factor amplitdues (9 pages), thermal parameters, and dihedral angles and least-squares planes. Ordering information is given on any current masthead page.

LITERATURE CITED

Baughman, R. G., Jacobson, R. A., J. Agric. Food Chem. 23(4), 811 (1975).

Baughman, R. G., Jacobson, R. A., J. Agric. Food Chem. 24(5), 2036 (1976).

Baughman, R. G., Jacobson, R. A., J. Agric. Food Chem. 25(3), 582 (1977).

Baughman, R. G., Eckey, D. A., Jacobson, R. A., J. Agric. Food Chem. 26, 398 (1978).

Baughman, R. G., Jacobson, R. A., J. Agric. Food Chem. 26, 403 (1978).

Bondi, A., J. Phys. Chem. 68(3), 441 (1964).

Busing, W. R., Martin, K. O., Levy, H. A., "OR FLS, 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., "OR FFE, A Fortan Crystallographic Function and Error Program", U.S. Atomic Energy Commission Report ORNL-TM-306, Oak Ridge National Laboratory, Oak Ridge, Tenn., 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(2), 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(2), 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 Report 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., "OR TEP-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(2), 163 (1963).

O'Brien, R. D., Hetnarski, B., Tripathi, R. K., Hart, G. J., ACS Symp. Ser. No-2, 1–13 (1974).

Osborne, D. W., Dow Chemical Co., Midland, Mich., LD$_{50}$'s for chlorpyrifos and fospirate, private communication, 1976.

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(11), 2535 (1974).

Rohrbaugh, W. J., Jacobson, R. A., J. Agric. Food Chem. 24(4) 713 (1976).

Rohrbaugh, W. J., Jacobson, R. A., J. Agric. Food Chem. 25, 588 (1977).

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

Takusagawa, F., Jacobson, R. A., J. Agric. Food Chem. 25(2), 329 (1977a).

Takusagawa, F., Jacobson, R. A., J. Agric. Food Chem. 25(2), 333 (1977b).

Takusagawa, F., Jacobson, R. A., J. Agric. Food Chem. 25(3), 577 (1977c).

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.