

Crystal and Molecular Structure of Organophosphorus Insecticides. 6. Amidithion

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The crystal and molecular structure of amidithion (*O,O*-dimethyl *S*-(*N*-2-methoxyethylcarbamoylmethyl) phosphorodithioate), $(\text{CH}_3\text{O})_2\text{P}(\text{S})\text{SCH}_2\text{C}(\text{O})\text{NHC}_2\text{H}_4\text{OCH}_3$, has been determined by three-dimensional x-ray analysis. The compound crystallizes in the monoclinic space group $P2_1/c$ with $a = 10.975$ (3), $b = 9.335$ (2), $c = 13.702$ (4) Å, and $\beta = 102.84$ (4)° with $Z = 4$. Graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.70954$ Å) was used for measurement of diffraction data. The structure was solved via direct methods and refined by a full-matrix least-squares procedure to a final discrepancy index of $R = \Sigma||F_o| - |F_c|| / \Sigma|F_o| = 0.066$. The atoms with greatest residual positive charge, as determined by a CNDO molecular orbital calculation are, in addition to the phosphorus, the carbonyl carbon and the amide hydrogen. The distance from phosphorus to either atom, 3.91 (1) or 4.24 (2) Å, respectively, is significantly shorter than the accepted anionic-esteratic site separation in mammalian acetylcholinesterase and may account for the lower toxicity of amidithion as compared with azinphosmethyl. The partial charge on phosphorus was found to be similar to that in azinphos-methyl, +1.063 vs. +1.041 e, respectively. Intramolecular interactions appeared to be slight.

As discussed in previous crystal structure analyses of organophosphorus insecticides (Baughman and Jacobson, 1975; Gifkins and Jacobson, 1976; Rohrbaugh et al., 1976), the ubiquitous or specific effectiveness of a particular insecticide may depend on its ability to accommodate a range of esteratic-anionic site separations in various acetylcholinesterase (AChE) enzymes. In addition, the effectiveness may also be related to the relative charge densities on the corresponding sites of the insecticide (Rohrbaugh et al., 1976). In order to substantiate or refute these conjectures, sufficient data must be obtained for a number of organophosphorus insecticides with varying degrees of effectiveness as reflected by insect and mammalian toxicities.

The structure of azinphos-methyl (Rohrbaugh et al., 1976), with a mammalian toxicity of $\text{LD}_{50} = 16$ mg/kg, exhibits a solid-state esteratic-anionic site separation, as measured by the phosphorus to oxo carbon distance, of 4.83 Å, and partial charge densities (via a CNDO calculation) of +1.041 and +0.325 e at these atoms, respectively. It was felt that it would be of interest to compare such parameters with those obtained for insecticides exhibiting less toxicity in mammalian systems in order to deduce correlations, if any, between those parameters and insecticide effectiveness. Therefore, a crystal of amidithion (*O,O*-dimethyl *S*-(*N*-2-methoxyethylcarbamoylmethyl) phosphorodithioate), $(\text{CH}_3\text{O})_2\text{P}(\text{S})\text{SCH}_2\text{C}(\text{O})\text{NHC}_2\text{H}_4\text{OCH}_3$, with an LD_{50} of 420 mg/kg (Pesticides and Toxic Substances Effects Laboratory, 1973), was chosen for three-dimensional x-ray analysis.

EXPERIMENTAL SECTION

Crystal Data. A sample of amidithion was kindly supplied by the Pesticide and Toxic Substances Effects Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, N.C. A nearly cylindrical crystal of dimensions $0.15 \times 0.15 \times 0.25$ mm was mounted in a 0.2 mm thin-walled Lindemann glass capillary and subsequently attached to a standard goniometer head. From four preliminary ω -oscillation photographs taken on an automated four-circle x-ray diffractometer at various χ and ϕ settings, 14 independent reflections were selected and their coordinates were input to an automatic indexing algorithm (Jacobson, 1976).

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The resulting reduced cell and reduced cell scalars indicated $2/m$ (monoclinic) symmetry. The monoclinic crystal system was confirmed by inspection of axial ω -oscillation photographs, which displayed a mirror plane with respect to only the b^* reciprocal lattice axis. Observed layer line spacings were within experimental error to those predicted for this cell. A least-squares refinement of the lattice constants (Takusagawa, 1975) based on the precise $\pm 2\theta$ measurements of 12 strong independent reflections on a previously aligned four-circle diffractometer (Mo $K\alpha$ graphite-monochromated radiation, $\lambda = 0.70954$ Å) yielded $a = 10.975$ (3), $b = 9.335$ (2), $c = 13.702$ (4) Å, and $\beta = 102.84$ (4)°.

Collection and Reduction of X-Ray Intensity Data.

Data were collected at room temperature on an automated four-circle diffractometer designed and built in this Laboratory (Rohrbaugh and Jacobson, 1974). The diffractometer is interfaced to a PDP-15 computer in a time-sharing mode and is equipped with a scintillation counter. Graphite-monochromated Mo $K\alpha$ radiation was used for data collection.

All data (2209 reflections) within a 2θ sphere of 45° ($\sin \theta / \lambda = 0.539 \text{ \AA}^{-1}$) in the hkl and $\bar{h}k\bar{l}$ octants were measured via an ω -scan data collection mode, using a takeoff angle of 4.5° .

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 data collection period. Examination of the data revealed systematic absences of the $h0l$ reflections for $l = 2n + 1$ and $0k0$ reflections for $k = 2n + 1$, thus uniquely defining the space group as $P2_1/c$.

The intensity data were corrected for Lorentz-polarization effects and, since the minimum and maximum transmission factors differed by less than 5% for $\mu = 0.49 \text{ cm}^{-1}$, no absorption correction was made. 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 count and background count, 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 zone data were averaged and only those re-

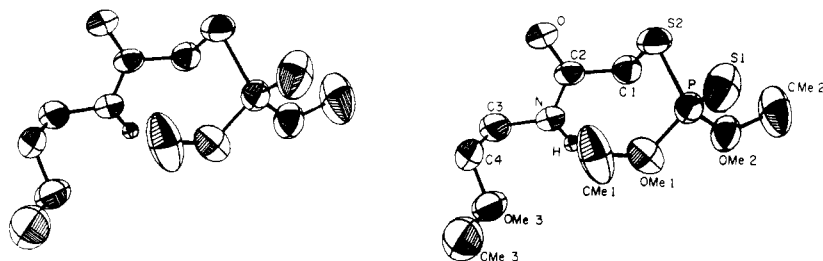


Figure 1. Stereographic view of amidithion with hydrogen atoms omitted. In this and succeeding drawings 50% probability ellipsoids are depicted.

flections for which $|F_o| > 2\sigma_{F_o}$ were retained for structural refinement. There were consequently 1512 independent reflections used in subsequent calculations.

Solution and Refinement of Structure. The program MULTAN (Main et al., 1971) was used to assign phases to the 300 largest E values. The E map (Hubbard et al., 1971) resulting from the solution set corresponding to the best figure of merit unambiguously revealed the positions of 12 nonhydrogen atoms. The remaining atoms were found by successive structure factor (Busing et al., 1962) and electron density map calculations. Methyl hydrogen ambiguities were resolved by refining two sets of methyl hydrogens for each methyl carbon. The sets were displaced by 60° and were each assigned half-occupancy.

In addition to positional parameters for all atoms, the anisotropic thermal parameters for all nonhydrogen atoms were refined by a full-matrix least-squares procedure (Busing et al., 1962), minimizing the function $\sum \omega(|F_o| - |F_c|)^2$ where $\omega = 1/\sigma_F^2$, to a conventional discrepancy factor of $R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.071$. Analysis of the weights (ω) was performed via a requirement that $\omega(|F_o| - |F_c|)^2$ should be a constant function of $|F_o|$ and $(\sin \theta)/\lambda$ (Cruickshank and Pilling, 1961). Accordingly, inspection of the weighting scheme indicated that the reflections at very low as well as very high $(\sin \theta)/\lambda$ values were somewhat overweighted, and the weights were subsequently adjusted. Seven strong, low angle reflections exhibited secondary extinction effects and were removed from the data set. Successive iterations of refinement on the 1505 remaining reflections produced convergence to $R = 0.066$ and $R_w = 0.077$, where $R_w = [\sum \omega(|F_o| - |F_c|)^2 / \sum \omega |F_o|^2]^{1/2}$. The scattering factors used for nonhydrogen atoms were those of Hanson et al. (1960), modified for the real and imaginary parts of anomalous dispersion (Templeton, 1962). The hydrogen scattering factors were those of Stewart et al. (1965).

The final positional and thermal parameters are listed in Table I. The standard deviations were calculated from the inverse matrix of the final least-squares cycle.

DESCRIPTION AND DISCUSSION

A stereographic view of amidithion depicting 50% probability ellipsoids is provided in Figure 1 (Johnson, 1971) and interatomic distances and angles (Busing et al., 1964) are listed in Table II. Intramolecular bond distances and angles are in good agreement with those reported previously in the literature.

As has been observed in prior crystal structure analyses of organophosphorus insecticides (Baughman and Jacobson, 1975; Gifkins and Jacobson, 1976; Rohrbaugh et al., 1976), the geometry about the phosphorus can be described as a distorted tetrahedron. In particular, the angles involving the doubly bonded sulfur, S(1), with the methoxy oxygens are both approximately 9° greater than tetrahedral, while the (methoxy oxygen)–phosphorus–(methoxy oxygen) angle is reduced to $95.4(2)^\circ$. These

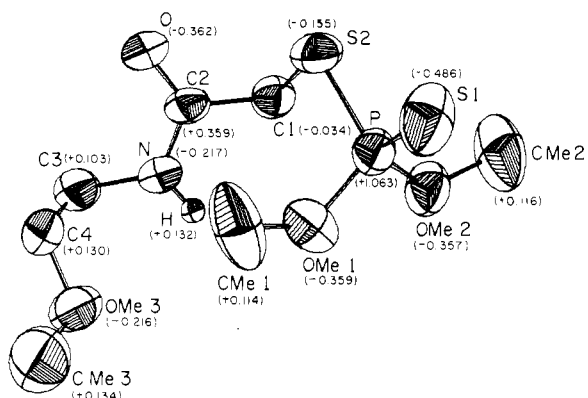


Figure 2. Partial charge densities obtained from CNDO/2 molecular orbital calculations for amidithion.

results parallel those found in the analyses cited above and in particular are in good agreement with the results for azinphos-methyl (Rohrbaugh et al., 1976) where the latter angle was found to be $94.3(7)^\circ$.

Results of a CNDO/2 molecular orbital calculation (Segal, 1970) indicate two of the most probable positive centers in addition to the phosphorus are C(2) and H (cf. Figure 2). The solid state P–C(2) and P–H distances are 3.91 (1) and 4.24 (2) Å, respectively. It should also be noted that the P–C(3) and P–C(4) distances are 5.696 (6) and 5.805 (7) Å, respectively, although these are less likely candidates for enzyme binding. The P–C(2) and P–H distances are both significantly shorter than the corresponding solid-state separation observed in azinphos-methyl (4.83 (2) Å). When autotoxicosis through inhibition of acetylcholinesterase (AChE) by organophosphorus insecticides is considered, it is useful to recall that the nitrogen to carbonyl carbon distance in acetylcholine is estimated at 4.7 Å (Chothia and Pauling, 1969), when the molecule is in a proper configuration to react with bovine erythrocyte AChE. From a series of experiments carried out by Hollingworth et al., (1967), however, it was concluded that the distance between the anionic and esteratic centers of fly head AChE may be as much as 1 Å greater than that in the mammalian enzyme. In amidithion the primary positive center separations appear to be too small for most efficient binding to the enzyme. Therefore on the basis of configurations found in the solid state, it would appear that amidithion would be less effective than azinphos-methyl in the mammalian systems, assuming that in vivo transport properties are similar and that the inhibition of AChE is the primary toxic mode. Examination of the mammalian LD_{50} 's for azinphos-methyl and amidithion supports this hypothesis, i.e., LD_{50} (azinphos-methyl) = 16, LD_{50} (amidithion) = 420 mg/kg. However, we recognize that this distance argument would also suggest that the amidithion molecule would be significantly less effective in insect systems, unless the enzyme inter-

Table I. Final Atom Positional^a and Thermal^b Parameters

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S1	3568 (2)	6872 (2)	5143 (1)	161 (2)	248 (3)	126 (1)	-49 (2)	81 (1)	-61 (2)
S2	2360 (1)	5397 (1)	6835 (1)	140 (2)	108 (2)	143 (1)	15 (1)	62 (1)	-2 (1)
P	2678 (1)	7277 (1)	6159 (1)	95 (1)	128 (2)	80 (1)	-9 (1)	24 (1)	-14 (1)
OMe1	1399 (3)	8084 (4)	5847 (3)	121 (4)	215 (6)	87 (3)	36 (4)	22 (3)	18 (3)
OMe2	3277 (3)	8362 (4)	6996 (3)	118 (4)	169 (5)	99 (3)	-26 (4)	23 (3)	-33 (3)
OMe3	-2554 (4)	8192 (4)	5839 (3)	177 (5)	128 (5)	96 (3)	-21 (4)	-17 (3)	14 (3)
O	-211 (3)	4341 (3)	7064 (3)	129 (4)	95 (5)	119 (3)	-5 (3)	15 (3)	-1 (3)
N	-751 (4)	6612 (4)	7314 (3)	112 (4)	92 (5)	93 (3)	1 (4)	20 (3)	9 (3)
C1	1422 (5)	5985 (6)	7697 (4)	112 (5)	133 (7)	71 (3)	-3 (5)	13 (3)	11 (4)
C2	73 (4)	5574 (5)	7326 (3)	118 (5)	95 (6)	59 (3)	4 (5)	15 (3)	19 (3)
C3	-2100 (5)	6345 (6)	7027 (5)	107 (6)	131 (7)	133 (6)	5 (5)	39 (5)	25 (5)
C4	-2638 (6)	6723 (6)	5969 (5)	101 (6)	124 (7)	119 (5)	-15 (5)	6 (4)	-17 (5)
CMe1	428 (7)	7535 (15)	5047 (6)	113 (7)	504 (25)	77 (5)	-3 (11)	-2 (5)	30 (10)
CMe2	4563 (7)	8270 (14)	7499 (9)	130 (8)	370 (22)	143 (9)	-36 (11)	-8 (6)	-107 (12)
CMe3	-3123 (10)	8626 (12)	4856 (7)	217 (12)	290 (18)	109 (7)	-49 (12)	-27 (8)	50 (9)
H1C1	154 (4)	709 (6)	778 (4)						
H2C1	175 (4)	539 (5)	830 (4)						
H1C3	-250 (4)	703 (5)	756 (4)						
H2C3	-228 (4)	532 (6)	710 (3)						
H1C4	-338 (5)	643 (6)	587 (4)						
H2C4	-216 (5)	613 (6)	558 (3)						
H1Me1	-30 (14)	830 (14)	497 (11)						
H2Me1	10 (11)	652 (14)	539 (9)						
H3Me1	87 (12)	741 (13)	441 (9)						
H4Me1	70 (12)	678 (12)	452 (11)						
H5Me1	-50 (10)	762 (12)	539 (8)						
H6Me1	15 (13)	812 (13)	456 (10)						
H1Me2	479 (10)	938 (12)	760 (9)						
H2Me2	454 (11)	788 (15)	825 (11)						
H3Me2	505 (10)	761 (14)	719 (9)						
H4Me2	460 (10)	711 (12)	766 (8)						
H5Me2	461 (11)	881 (15)	807 (10)						
H6Me2	505 (10)	842 (13)	683 (8)						
H1Me3	-321 (10)	1014 (12)	489 (8)						
H2Me3	-426 (10)	810 (12)	487 (7)						
H3Me3	-238 (9)	801 (10)	437 (7)						
H4Me3	-328 (11)	788 (12)	425 (9)						
H5Me3	-387 (13)	903 (15)	499 (9)						
H6Me3	-283 (10)	927 (13)	459 (8)						
H	-47 (5)	747 (6)	747 (4)						

^a The positional parameters for all nonhydrogen atoms are presented in fractional unit cell coordinates ($\times 10^4$). Positional parameters for hydrogen atoms are ($\times 10^3$). Atoms H1Me1 through H6Me3 have been assigned half-multiplicity. ^b The β_{ij} are defined by: $T = \exp(-h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hkl\beta_{12} + 2hl\beta_{13} + 2kh\beta_{23})$ and are ($\times 10^4$). An isotropic thermal parameter of 2.5 was assigned for all hydrogen atoms. ^c In this and succeeding tables, estimated standard deviations are given in parentheses for the least significant figures.

Table II. Bond Distances (Å) and Angles (deg) for Amidithion

Distances			
P-S(1)	1.908 (2)	C(3)-C(4)	1.481 (9)
P-S(2)	2.050 (2)	C(4)-OMe(3)	1.388 (6)
P-OMe(1)	1.566 (4)	CMe(1)-OMe(1)	1.442 (8)
P-OMe(2)	1.562 (4)	CMe(2)-OMe(2)	1.429 (8)
S(2)-C(1)	1.816 (6)	CMe(3)-OMe(3)	1.412 (9)
C(1)-C(2)	1.504 (7)	P-C(2)	3.910 (10)
C(2)-O	1.228 (5)	P-H	4.24 (2)
C(2)-N	1.323 (6)	P-C(3)	5.696 (6)
C(3)-N	1.466 (7)	P-C(4)	5.805 (7)
Angles			
P-S(2)-C(1)	102.3 (2)	P-OMe(2)	121.7 (5)
S(1)-P-S(2)	109.0 (1)	C(4)-OMe(3)-CMe(3)	112.2 (6)
S(1)-P-OMe(1)	118.0 (2)	C(2)-N-C(3)	121.7 (4)
S(1)-P-OMe(2)	117.6 (2)	S(2)-C(1)-C(2)	111.2 (4)
S(2)-P-OMe(1)	107.6 (2)	C(1)-C(2)-O	120.9 (4)
S(2)-P-OMe(2)	108.0 (2)	O-C(2)-N	123.3 (5)
OMe(1)-P-OMe(2)	95.4 (2)	N-C(3)-C(4)	112.4 (5)
P-OMe(1)-CMe(1)	120.2 (6)	C(3)-C(4)-OMe(3)	109.7 (5)

action with the methylene carbons, C(3) or C(4), are more important than we have assumed. It is generally accepted that it is the oxidized phosphate form that inhibits the enzyme; however, the primary effect of such oxidation would be to enhance the charge on the phosphorus and

most likely cause only minor perturbations on the rest of the molecular configuration.

An examination of intramolecular interactions indicates that the orientation of the phosphate group relative to the rest of the molecule is not necessarily fixed. If one were

to allow free rotation about the C(1)–S(2) bond, the molecule could attain maximum positive center separations of approximately 4.7 Å for P–C(2) and 5.5 Å for P–H. However, the orientation of the planar segment of the organic moiety would change and its orientation relative to the phosphate group may be important. For example, if one calculates the angle between the normal to the plane of the ring system and the P=O or P=S bond in ronnel (Baughman and Jacobson, 1975), coroxon (Gifkins and Jacobson, 1976), and azinphos-methyl (Rohrbaugh et al., 1976), the following results are obtained: 23.7, 38.45, and 23.90°, respectively. In the first two cases in particular, intramolecular interactions tend to dictate these angles and therefore one can assume that they will not change greatly when the moieties are in solution. In amidithion, if one assumes bonding delocalization effects are operative, then C(1), C(2), O, N, and H should define a plane, and indeed the greatest deviation from the least-squares plane defined by these atoms is 0.003 Å. Moreover, for the solid-state configuration found, the angle between this plane and the one normal to the P=S(1) bond is 23.46°, well within the range found in previous studies. If the orientation of the phosphate group relative to the planar segment of the organic moiety is an important topographical factor in the binding of the insecticide to the enzyme, it may be reasonable to assume that the site separations found for amidithion in the solid state are valid parameters in the consideration of effectiveness.

As discussed previously (Rohrbaugh et al., 1976), there may also exist a relationship between effectiveness and the partial charge density on the phosphorus atom. The charge on the phosphorus atom of amidithion obtained from CNDO/2 molecular orbital calculations (Segal, 1970) is +1.063 e (cf. Figure 2). This value is approximately equivalent to that for azinphos-methyl, and consequently, no comparative argument for charge density on phosphorus vs. insecticide effectiveness can be made based on these parameters alone.

As noted above, amidithion is approximately 25 times less toxic in mammalian systems than is azinphos-methyl. A comparison of solid-state structural features has yielded some supportive evidence to the correlations between effectiveness and positive center separations, and to gross topographical features, particularly if one assumes a preferred orientation of the planar section of the organic moiety relative to the phosphate group. Such a comparison, however, has been inconclusive regarding the importance of partial charge densities. It appears that future structural work should include further investigations as to orientational effects and also the study of an insecticide with an LD₅₀ two orders of magnitude greater than azinphos-methyl.

Supplementary Material Available: A listing of the observed and calculated structure factor amplitudes (4 pages). Ordering information is given on any current masthead page.

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