

Crystal and Molecular Structure of Carbamate Insecticides. 3. Methomyl

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The crystal and molecular structure of methomyl (*S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate) has been determined by three-dimensional x-ray analysis. It crystallizes in the monoclinic space group $P2_1/n$ with cell dimensions $a = 13.996$ (6), $b = 9.678$ (3), $c = 6.096$ (2) Å, and $\beta = 91.45$ (4)°. The structure was solved by the heavy-atom technique and refined by full-matrix least-squares procedures to a final discrepancy factor $R = 0.054$ for 888 observed reflections. The molecule is approximately planar, and the moieties are weakly hydrogen bonded to one another along the b direction. The C–O single bond length was found to be somewhat lengthened (1.371 Å) relative to the equivalent distance found in carboxylic acids. Comparison of the general features of the carbamate group in methomyl, aldicarb, and MesuroI suggest a possible correlation of both C–O single bond distance and angle opposite the doubly bonded oxygen with LD₅₀ values. Results of CNDO molecular orbital calculations are also given for these three carbamate insecticides.

The crystal structure investigation of methomyl (*S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate) was undertaken as part of a series of structural investigations of carbamate insecticides. The purpose of such a program is to better correlate variations in structural parameters with an insecticide's toxicity/activity. Previously MesuroI (Takusagawa and Jacobson, 1977a) and aldicarb (Takusagawa and Jacobson, 1977b) have been structurally characterized. Since the acute oral LD₅₀ of aldicarb, methomyl, and MesuroI to rats are reported to be 0.93, 20, and 133 mg/kg (Health Effects Research Laboratory, 1976), respectively, we felt that a three-dimensional x-ray analysis of methomyl would complement our two previous structural investigations of carbamate insecticides and allow comparisons to be drawn for these three molecules.

EXPERIMENTAL SECTION

Crystal Data. C₅H₁₀N₂O₂S, mol wt = 166.15, monoclinic, $P2_1/n$, $a = 13.996$ (6), $b = 9.678$ (3), $c = 6.096$ (2) Å, $\beta = 91.45$ (4)°, $\rho_c = 1.306$ g/cm³, $Z = 4$, $\mu = 3.56$ cm⁻¹ for Mo K α , mp = 78–79 °C.

A crystal of approximate dimensions 0.2 × 0.2 × 0.1 mm along the a , b , and c crystal axes, respectively, was obtained after recrystallization of the sample from benzene solution and was placed in a thin-walled Lindeman glass capillary and mounted so that the b axis was along the ϕ axis of the four-circle diffractometer. Initial ω -oscillation Polaroid photographs were taken, and these photographs verified that the crystal selected was indeed single. From these photographs 14 reflections were accurately located on the diffractometer and their coordinates were then input into our automatic indexing program (Jacobson, 1976). The reduced cell and reduced cell scalars that resulted from this program indicated monoclinic symmetry. Subsequent ω -oscillation Polaroid pictures taken around each of the three cell axes in turn verified the $2/m$ Laue symmetry as well as the reciprocal lattice spacings predicted by the program.

Accurate unit cell parameters and their estimated standard deviations were obtained by a least-squares fit (Williams, 1964) to the 2θ values of 15 independent high-angle reflections measured on a previously aligned four-circle diffractometer.

Data were collected at room temperature using an automated four-circle diffractometer designed and built in the Ames Laboratory and previously described by

Rohrbaugh and Jacobson (1974). The diffractometer is interfaced to a PDP-15 computer in a real-time mode and is equipped with a scintillation counter. Graphite reflective-beam monochromated Mo K α radiation ($\lambda = 0.70954$ Å) was used for data collection. Within a 2θ sphere of 50° ($\sin \theta/\lambda = 0.595$ Å⁻¹), all data in the hkl , $hk\bar{l}$, $h\bar{k}l$, and $h\bar{k}\bar{l}$ octants were measured using a modified peak height measurement technique (Gifkins and Jacobson, 1976). Of the 3201 reflections examined, 2749 had positive peak intensity.

The following systematic absences were observed; $h0l$ when $h + l = 2n + 1$ and $0k0$ when $k = 2n + 1$. These absences are consistent only with the space group $P2_1/n$.

As a general check on electronic and crystal stability, the intensities of three standard reflections were remeasured every 75 reflections. They did not vary to any significant degree during the entire period of data collection.

The intensity data were corrected for Lorentz and polarization effects, but absorption and extinction corrections were not deemed necessary. The maximum and minimum transition factors were estimated to be 0.966 and 0.933, 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 are the total and the 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). Of the 2681 reflections, 1820 were considered observed ($>3\sigma_I$). Equivalent data were averaged, and the discrepancy factor between equivalent data was 0.029.

Structure Determination and Refinement. The position of the sulfur atom was obtained from analysis of a sharpened three-dimensional Patterson map. The remaining nonhydrogen atoms were found by successive structure factor and electron density map calculations. The atomic positional and isotropic thermal parameters were first refined by a block-diagonal least-squares procedure (Sakurai, 1967), minimizing the function $\sum w(|F_o| - |F_c|)^2$, where $w = 1/\sigma_F^2$, to a conventional discrepancy factor, $R = \sum ||F_o| - |F_c|| / \sum |F_o|$, of 0.155. Anisotropic thermal parameters were then introduced into the refinement, and all the hydrogen atoms were found in a difference electron density map calculated using data with $\sin \theta/\lambda < 0.45$.

Finally, the structural parameters of all atoms including isotropic hydrogen atoms were refined by a full-matrix least-squares procedure (Busing et al., 1962). In this

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Table I. Final Positional and Thermal Parameters^a and Their Estimated Standard Deviations^b

Atom	x	y	z	B _{iso}
C (1)	4676 (5)	2961 (7)	-5675 (8)	
S (2)	3893 (1)	3427 (1)	-3479 (2)	
C (3)	3780 (3)	1889 (4)	-2020 (6)	
C (4)	4263 (4)	576 (5)	-2669 (9)	
N (5)	3266 (3)	1785 (3)	-338 (5)	
O (6)	2814 (2)	3092 (3)	142 (4)	
C (7)	2197 (3)	3014 (5)	1850 (6)	
O (8)	1792 (2)	4061 (3)	2344 (4)	
N (9)	2104 (3)	1781 (4)	2803 (6)	
C (10)	1512 (4)	1627 (6)	4694 (8)	
H (1)	474 (4)	367 (6)	-675 (8)	7.2
H (2)	527 (5)	275 (6)	-519 (9)	7.2
H (3)	438 (4)	230 (5)	-660 (9)	7.2
H (4)	487 (4)	65 (6)	-273 (8)	6.5
H (5)	414 (3)	-19 (5)	-158 (7)	6.5
H (6)	393 (3)	18 (5)	-411 (8)	6.5
H (7)	247 (3)	118 (5)	225 (7)	5.5
H (8)	155 (3)	81 (5)	526 (8)	6.4
H (9)	88 (4)	202 (5)	450 (8)	6.4
H (10)	185 (4)	217 (5)	587 (8)	6.4

Atom	β ₁₁	β ₂₂	β ₃₃	β ₁₂	β ₁₃	β ₂₃
C (1)	106 (4)	289 (11)	403 (17)	-1 (5)	59 (7)	-6 (9)
S (2)	94 (1)	180 (2)	395 (4)	-3 (1)	54 (1)	2 (2)
C (3)	76 (3)	168 (6)	333 (12)	-6 (3)	18 (5)	-33 (7)
C (4)	99 (4)	177 (7)	500 (17)	5 (4)	73 (7)	-71 (8)
N (5)	90 (2)	148 (5)	402 (11)	11 (3)	57 (4)	-20 (6)
O (6)	94 (2)	139 (4)	403 (9)	10 (2)	74 (4)	1 (4)
C (7)	75 (3)	157 (6)	324 (12)	-4 (3)	22 (5)	-12 (7)
O (8)	89 (2)	141 (4)	464 (10)	19 (2)	60 (4)	-13 (5)
N (9)	80 (2)	137 (5)	424 (12)	-2 (3)	53 (4)	13 (6)
C (10)	95 (3)	175 (7)	477 (16)	12 (4)	73 (6)	48 (9)

^a All nonhydrogen atom parameters are multiplied by 10⁴; all hydrogen positional parameters by 10³. Anisotropic thermal factors are of the form of $\exp\{-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{23}kl + 2\beta_{13}hl)\}$. ^b In this and succeeding tables, estimated standard deviations are given in parentheses for the least significant figures and include the error in the lattice constants.

Table II. Bond Lengths and Angles for Methomyl

Bond Length, Å		Bond Angle, deg	
C(1)-S(2)	1.809 (5)	C(1)-S(2)-C(3)	103.2 (2)
S(2)-C(3)	1.744 (4)	S(2)-C(3)-C(4)	122.8 (3)
C(3)-C(4)	1.498 (6)	S(2)-C(3)-N(5)	122.6 (3)
C(3)-N(5)	1.271 (5)	C(4)-C(3)-N(5)	114.5 (4)
N(5)-O(6)	1.448 (4)	C(3)-N(5)-O(6)	110.7 (3)
O(6)-C(7)	1.371 (5)	N(5)-O(6)-C(7)	113.1 (3)
C(7)-O(8)	1.203 (5)	O(6)-C(7)-O(8)	116.9 (4)
C(7)-N(9)	1.335 (5)	O(6)-C(7)-N(9)	116.8 (4)
N(9)-C(10)	1.443 (6)	O(8)-C(7)-N(9)	126.3 (4)
C(1)-H(1)	0.96 (5)	C(7)-N(9)-C(10)	120.3 (4)
C(1)-H(2)	0.89 (6)	S(2)-C(1)-H(1)	113 (3)
C(1)-H(3)	0.94 (5)	S(2)-C(1)-H(1)	112 (3)
C(4)-H(4)	0.85 (5)	S(2)-C(1)-H(3)	110 (4)
C(4)-H(5)	1.01 (5)	C(3)-C(4)-H(4)	113 (4)
C(4)-H(6)	1.06 (5)	C(3)-C(4)-H(5)	111 (3)
N(9)-H(7)	0.85 (5)	C(3)-C(4)-H(6)	109 (3)
C(10)-H(8)	0.87 (5)	N(9)-C(10)-H(8)	112 (3)
C(10)-H(9)	0.97 (6)	N(9)-C(10)-H(9)	114 (3)
C(10)-H(10)	1.00 (5)	N(9)-C(10)-H(10)	105 (3)
N(9)-N(5)	2.544 (5)	C(7)-N(9)-H(7)	111 (3)
O(6)-S(2)	2.726 (3)	C(10)-N(9)-H(7)	128 (3)
H(7)-N(5)	2.04 (4)	N(9)-H(7)-N(5)	118 (4)
N(9)-O(8) ^a	3.054 (5)	N(9)-H(7)-O(8) ^a	147 (5)
H(7)-O(8) ^a	2.31 (5)	H(7)-O(8)-C(7) ^a	125 (2)
		N(9)-O(8)-C(7) ^a	119.2 (3)

^a Via symmetry operation (1/2 - x, -1/2 + y, 1/2 - z).

refinement, the isotropic thermal parameters of hydrogen atoms were fixed to be those of the atoms to which the hydrogen is bonded. The final discrepancy factor was 0.054, while the weighted discrepancy factor, $R_w = (\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2)^{1/2}$, was 0.064. The atomic scattering factors for the nonhydrogen atoms were those of Hanson et al. (1960), while for the hydrogen atoms, those of Stewart

et al. (1965) were used. The final positional and thermal parameters are listed in Table I.

RESULTS AND DISCUSSION

Stereoscopic illustrations (Johnson, 1971) of the molecule and the crystal structure are given in Figures 1 and 2, respectively. The bond lengths and angles are listed in

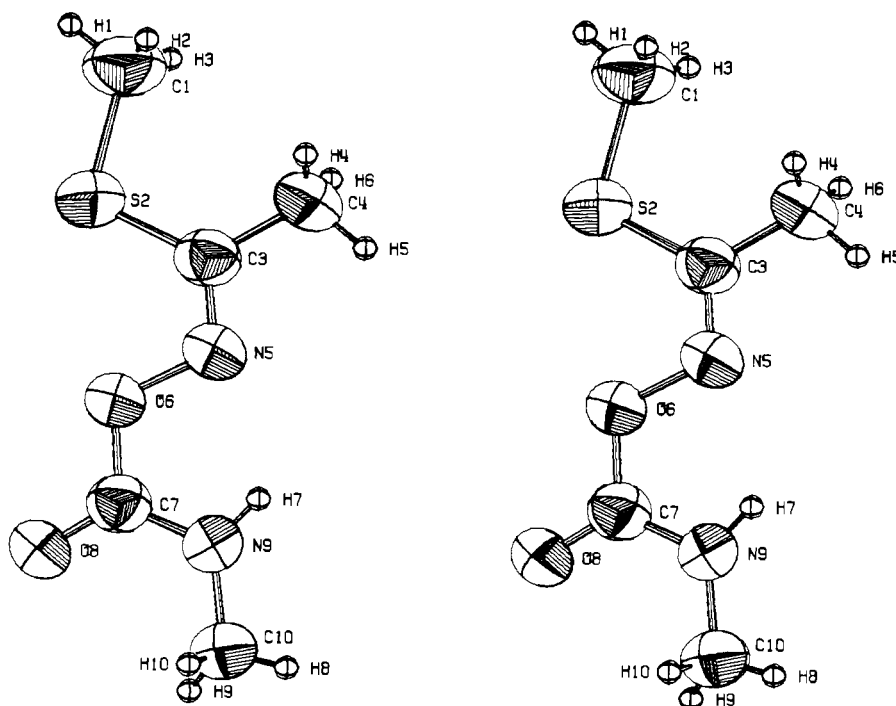


Figure 1. A stereoscopic illustration of methomyl molecule. The thermal ellipsoids of the nonhydrogen atoms are drawn at the 50% probability.

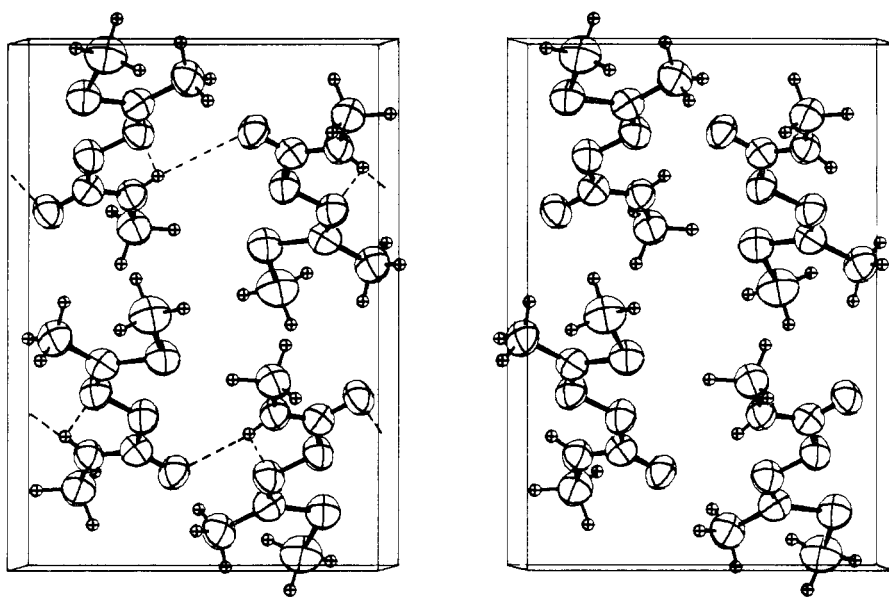


Figure 2. The crystal structure of methomyl as viewed down the *c* axis. The *b* axis is horizontal.

Table II while Table III presents the torsional angles and the least-squares planes along with deviations from these planes.

The molecule is approximately planar if the hydrogen atoms of the methyl groups are excluded. The sections composed of S(2), C(3), C(4), N(5), and O(6) (plane II, Table III) and O(6), C(7), O(8), and N(9) (plane III, Table III) are quite planar, deviating by at most 0.012 Å; the dihedral angle between these planes is 4.3° which can be compared with the 9.2° angle found in aldicarb. The O(6) and the S(2) atoms are *cis* to one another. The C(3)–N(5)–O(6) bond angle of 110.7° results in bringing O(6) somewhat close to S(2), 2.726 (3) Å, compared with a van der Waals contact of 3.2 Å. The difference between the S(2)–C(3) and S(2)–C(1) bond lengths and the somewhat shortened C(3)–C(4) distance could signify some π bond

delocalization among S(2), C(3), N(5), and to some extent C(4). The C(3)–N(5) distance of 1.271 (5) Å corresponds closely to the C–N distance in dimethylglyoxime (Merritt and Lanterman, 1952) for the nominal double bond.

The H(7)–N(5) (intramolecular) and H(7)–O(8) (intermolecular) distances of 2.04 and 2.31 Å, respectively, along with N(9)–H(7)---N(5) and N(9)–H(7)---O(8) angles of 118 and 147° (cf. Table II) indicate the presence of a weak bifurcated hydrogen bond. Thus each molecule is weakly linked to a neighboring molecule by part of this hydrogen bond to form an infinite chain along the *b* direction in this crystal (Figure 2). Although the hydrogen bonding pattern in methomyl is similar to that found in aldicarb and Mesurol, the corresponding intermolecular N...O distance is longer (3.054 vs. 2.828 and 2.926 Å, respectively). Such a lengthening would be consistent with

Table III. Torsional Angles, Least-Squares Planes, and Planes, and Deviations

Torsional Angle, deg			
C(1)-S(2)-C(3)-N(5)	-179.1		
C(4)-C(3)-N(5)-O(6)	-178.9		
C(3)-N(5)-O(6)-C(7)	175.7		
N(5)-O(6)-C(7)-O(8)	-179.9		
O(6)-C(7)-N(9)-C(10)	176.4		
Least-Squares Planes ^a			
(I)	0.7569X + 0.2493Y + 0.6041Z = 3.7194		
(II)	0.7723X + 0.2504Y + 0.5838Z = 3.8425		
(III)	0.7328X + 0.2240Y + 0.6426Z = 3.6099		
Deviations, Å			
	I	II	III
C(1)	-0.074*	-0.022	-0.330
S(2)	-0.008*	0.0*	-0.197
C(3)	0.021*	0.007*	-0.092
C(4)	-0.015*	-0.012*	-0.128
N(5)	0.051*	0.004*	-0.002
O(6)	0.058*	-0.003*	0.0*
C(7)	-0.005*	-0.101	0.001*
O(8)	-0.005*	-0.115	0.0*
N(9)	-0.062*	-0.173	0.0*
C(10)	-0.052*	-0.200	0.079
H(1)	-0.22	-0.15	-0.52
H(2)	0.67	0.73	0.41
H(3)	-0.88	-0.82	-1.13
H(4)	0.62	0.64	0.49
H(5)	0.06	0.05	0.0
H(6)	-0.98	-0.97	-1.10
H(7)	-0.01	-0.11	0.04
H(8)	0.0	-0.16	0.16
H(9)	-0.70	-0.86	-0.56
H(10)	0.85	0.70	0.99

^a X, Y, and Z are coordinates in Å along the cartesian *a*, *b*, and *c** axes, respectively. The plane is determined by asterisked atoms.

the assumption of a bifurcated hydrogen bond and the consequent weakening of each interaction.

The most interesting feature of the structure is the conformation of the carbamate group. Numerous investigators, such as Kolbezen et al. (1954), have suggested that carbamate insecticides in their action effectively compete with acetylcholine for the active site on acetylcholinesterase and thus inhibit the hydrolysis of the toxic acetylcholine. Inspection of the bond distances and angles for this portion of the molecule (Table II) reveals the C(7)-O(6) (1.371 Å) bond is possibly lengthened ($\sim 2.5\sigma$) compared with the average of those usually found in esters (1.358 Å, Sutton (1965)). On the other hand, the C(7)-N(9) and C(7)-O(8) bond lengths are approximately the same as those found in most amides (Sutton, 1965) and in urea (Caron and Donahue, 1969) and in carboxylic acids (Takusagawa et al., 1971), respectively. Such distances along with the angles about C(7) suggest a structure for the carbamate group having a delocalized double bond

Table IV. Carbamate Bond Lengths and Angles, and LD₅₀ Values (Rats) for Aldicarb, Methomyl, and Mesurol

Compound	<i>a</i> , Å	<i>b</i> , Å	<i>c</i> , Å	α , deg	β , deg	γ , deg	δ , deg	LD ₅₀ , mg/kg
Aldicarb	1.414	1.228	1.319	113.1	112.9	118.5	128.6	0.93
Methomyl	1.371	1.203	1.335	113.1	116.9	116.8	126.3	20.0
Mesurol	1.369	1.200	1.328	118.9	123.4	109.5	127.3	133.0

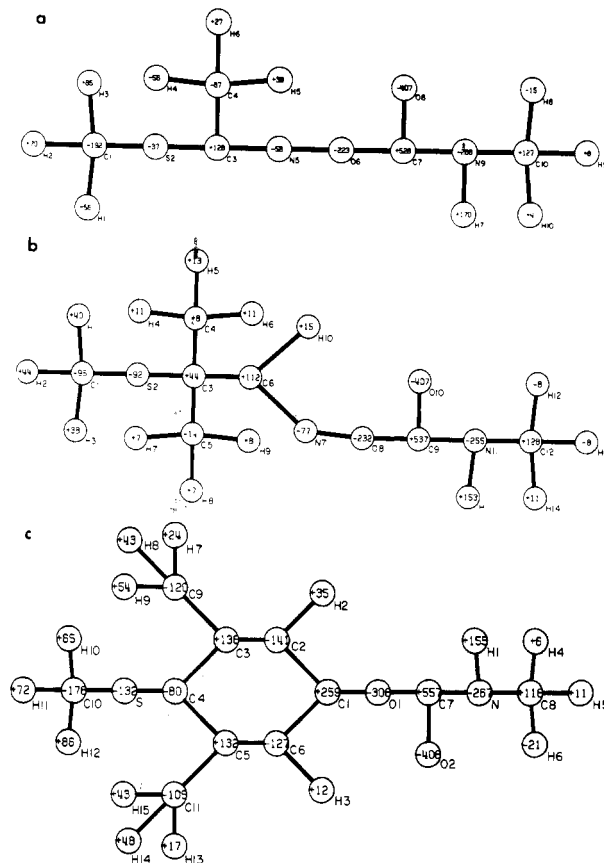


Figure 3. Results of CNDO calculations for (a) methomyl, (b) aldicarb, and (c) Mesurol.

involving O(8)-C(7)-N(9) and consequently slight electron withdrawal from O(6). Such observations correlate well with any theory that proposes ready disruption of the C(7)-O(6) bond in the course of a reaction with acetylcholinesterase.

The configuration found for the carbamate group is, in general, in good agreement with the two previous structure determinations of the carbamate insecticides Mesurol (Takusagawa and Jacobson, 1977a) and aldicarb (Takusagawa and Jacobson, 1977b) carried out in this laboratory. However, some variation in distances and angles are found as given in Table IV. Although admittedly it is not certain that the *in vivo* moiety is identical with that studied here, results in this table suggest that lower LD₅₀'s are associated with lengthened C-O single bonds and wider angles (γ) opposite the C=O group. Both would be consistent with a model in which an important component is the interaction of the carbamate with a serine hydroxyl group on acetylcholinesterase during which cleavage of the C-O single bond takes place, resulting in carbamylation of the enzyme. Charge density calculations were also carried out for methomyl, aldicarb, and Mesurol, and the

results are shown in Figure 3. A CNDO/2 molecular orbital calculation (Segal, 1970) was carried out, in each case using the positional parameters obtained in the x-ray study. The numbers associated with the partial charge densities in the figure are not intended to represent the absolute charge on each atom, since the CNDO calculation is an approximation. Comparisons, however, should be valid since the same approximation is used in each case.

In all cases there is a residual positive charge on the carbon of the carbamate group, as would be expected. Moreover, the value of this charge is approximately the same in all three molecules (0.53 to 0.56 e). Similarly, little variation is found in residual charge density on the nitrogen (-0.26 to -0.29 e) and doubly bonded oxygen (-0.41 e). The charge density on the singly bonded oxygen shows some variation (-0.22 to -0.31 e, the latter for Mesurol) and may be significant. The noncarbamate portions (i.e., those reacting with the acidic site group in AcChE) of these three molecules are quite different; hence, detailed comparisons are not possible. However, distances between partially positively charged sites can be noted. In aldicarb, the distance between the carbon in the carbamate group and C(6) or C(3) is 3.50 or 4.84 Å, respectively, while in methomyl the appropriate distances are C(7)-C(3), 3.45; C(7)-H(4), 5.25; C(7)-H(5), 4.66; and C(7)-H(6), 5.20 Å; and in Mesurol, C(7)-C(3), 4.36; C(7)-C(5), 4.65 Å. Moreover, distances less than 4.5 Å fall outside the ranges quoted for the acetylcholinesterase site separation distance (Hollingworth et al., 1967; O'Brien, 1963).

It is hoped that these structural and other similar fundamental investigations can lead to a better understanding of the role which carbamates play as insecticides and thus be instrumental in the design of molecules having optimal toxic and environmental properties.

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Supplementary Material Available: A listing of the observed and calculated structure factor amplitudes (5 pages). Ordering information is given on any current masthead page.

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