

Crystal and Molecular Structure of Organophosphorus Insecticides.

17. Leptophos Oxon

Stacy M. Baker and Russell G. Baughman*

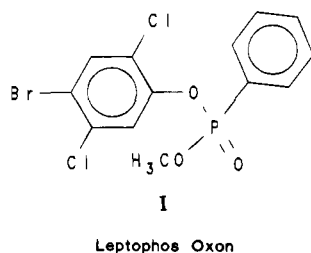
Division of Science, Northeast Missouri State University, Kirksville, Missouri 63501

The crystal structure of the organophosphorus insecticide leptophos oxon has been determined by three-dimensional X-ray diffraction analysis. The space group for leptophos oxon is *Pbca* with $a = 8.903(2)$, $b = 16.172(5)$, and $c = 21.202(6)$ Å, and eight molecules in the unit cell. The structure was solved by direct methods and refined by full-matrix least squares to a final discrepancy index of $R = 0.052$ with 1312 observed reflections [$F_o > 4.0\sigma(F_o)$]. For comparison purposes, the charge densities for the phosphorus atom in leptophos and the oxon were calculated with an AM1 Hamiltonian to be 2.575 and 2.689, respectively. Leptophos was calculated to have a lipid solubility of $\log P = 5.72$; the oxon, $\log P = 7.00$. Due to an interaction between the doubly bonded O and a ring H, the phosphorus in leptophos oxon participates in a third six-membered ring, fixing it closer to the plane of the tetrasubstituted aromatic ring.

Keywords: *Organophosphorus insecticide; acetylcholinesterase inhibition; leptophos oxon; X-ray structure; crystal structure*

INTRODUCTION

The crystal and molecular structure of leptophos oxon (I) was undertaken as part of an ongoing investigation of organophosphate (OP) insecticides (Baughman and Jacobson, 1975, 1976, 1977, 1978; Baughman *et al.*, 1978a,b; Baughman and Yu, 1982; Baughman, 1989; Baughman and Allen, 1995; Beckman and Jacobson, 1979; Gifkins and Jacobson, 1976, 1980; Lapp and Jacobson, 1980a,b; Rohrbaugh and Jacobson, 1976, 1977, 1978). By obtaining precise three-dimensional



structural information, one can compare the bond angles and distances, as well as the atomic charge densities for a series of OPs. This comparison should give insight into the ability of the $P \cdot \cdot \delta(+)$ regions in the insecticides to compete for the $\delta(-) \cdot \cdot \delta(-)$ active site in acetylcholinesterase (AChE), and thus into their relative toxicities.

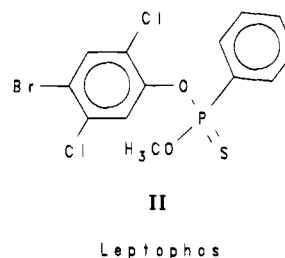
EXPERIMENTAL PROCEDURES

Crystal Data and Collection/Reduction of X-ray Intensity Data. The crystal data and information regarding the collection and reduction of the X-ray intensities for leptophos oxon is listed in Table 1.

Solution and Refinement of Structure. The structure of leptophos oxon was solved by SHELXTL PC (Siemens Analytical X-ray Instruments, Inc., 1990) and SHELXL-93 (Sheldrick, 1993), refining on F^2 , which yielded a conventional discrepancy factor of $R = 0.052$. The determined structure of the oxon is pictured in Figure 1 (Siemens Analytical X-ray Instruments, 1990). Fractional coordinates and thermal parameters are

listed in Table 2; bond lengths and angles, in Tables 3 and 4, respectively; selected torsional angles, in Table 5.

The structure of leptophos (II) was redetermined to a conventional discrepancy factor of $R = 0.035$, with no significant deviations from the determination by Lapp and Jacobson (1980b). For convenience in making



comparisons between the two OPs, the redetermined structure of leptophos is pictured in Figure 2 (Johnson, 1971); bond lengths and angles are listed in Tables 3 and 4, respectively (Busing *et al.*, 1964); selected torsional angles, in Table 5.

DESCRIPTION OF STRUCTURE AND DISCUSSION

The structures of leptophos and leptophos oxon are noticeably different about their relative phosphorus atoms. In leptophos, the C6-C1-O1-P torsional angle is 84.4° , whereas the corresponding torsional angle in the oxon is 37.9° . The phosphorus in leptophos oxon is closer to the plane of the tetrasubstituted aromatic ring (-0.865 Å vs 1.273 Å in leptophos) due to the H6A $\cdot \cdot$ O3 interaction, as shown in Figure 1. The attraction between O3 and H6A also results in the formation of a third six-membered ring (see Tables 3 and 4 for distances and angles) in the oxon. While the extra ring is not as stable as the other two, it does decrease the amount of rotational freedom about the P-O1 and O1-C1 bonds, which may contribute to the decrease in mammalian toxicity of the oxon as compared to leptophos ($LD_{50} = 118$ and $LD_{50} = 42$, respectively). This formation of an extra six-membered ring is also observed

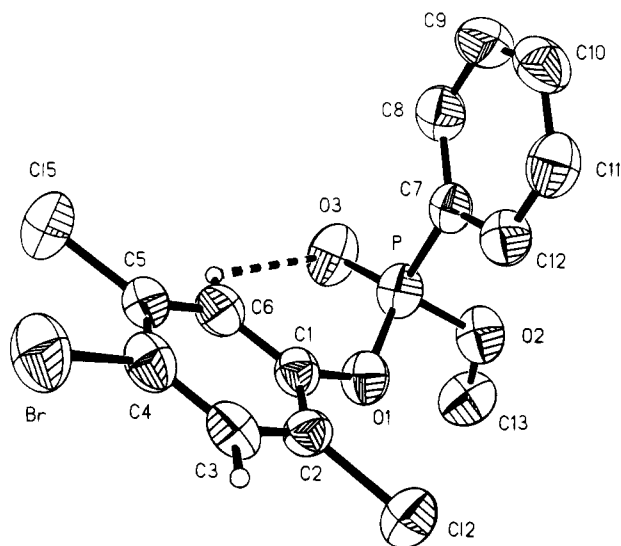


Figure 1. Leptophos oxon molecule showing 50% probability ellipsoids for the non-hydrogen atoms.

Table 1. Crystal and Collection/Reduction Data

compound	leptophos oxon
empirical formula	$C_{13}H_{10}BrCl_2O_3P$
formula weight	395.99
temperature (K)	293(2)
wavelength (Å)	0.71073
crystal system	orthorhombic
space group	$Pbca$
unit cell dimensions	
<i>a</i> (Å)	8.903(2)
<i>b</i> (Å)	16.172(5)
<i>c</i> (Å)	21.202(6)
volume (Å ³)	3053(2)
<i>Z</i>	8
density (calculated) (Mg/m ³)	1.723
crystal size (mm)	0.25 × 0.44 × 0.46
absorption coefficient (mm ⁻¹)	3.150
<i>T</i> _{min}	0.235
<i>T</i> _{max}	0.455
<i>F</i> (000)	1568
θ range for data collection (deg)	1.92 to 25.01
index ranges	$0 \leq h \leq 10$ $-19 \leq k$ ≤ 19 $-25 \leq l \leq 25$
reflections collected	10265
independent reflections	2695 ($R(\text{int}) = 0.1192$)
refinement method	on F^2
(full-matrix least squares)	
data/restraints/parameters	2695/0/181
goodness-of-fit on F^2	1.018
final <i>R</i> indices	$R1 = 0.0518$ [$I > 2\sigma(I)$] $wR2 = 0.0841$
<i>R</i> indices (all data)	$R1 = 0.1441$ $wR2 = 0.1112$
largest difference peak and hole (e Å ⁻³)	0.450 and -0.358

in the crystal structure of crufomate (Baughman *et al.*, 1978a), where the C6–C1–O1–P torsional angle is -53.8° . However, an intramolecular ring involving an H \cdots O interaction is *not* observed in ronnel oxon (Baughman and Jacobson, 1978). Therefore, the presence of this type of interaction should not be assumed in other oxons yet to be studied.

The change from P=S to P=O and the formation of an additional ring in leptophos oxon cause significant ($>3\sigma$) differences in the values of some of the bond angles about the phosphorus atom, most notable being those containing the double bonds. The S=P–O1 and S=P–O2 angles in leptophos are $116.6(1)^\circ$ and $114.8(1)^\circ$, respectively, whereas the values of the corresponding O3=P–O1 and O3=P–O2 angles are reversed

Table 2. Final Unit Cell Positions ($\times 10^4$) Displacement Parameters [$\text{\AA}^2 \times 10^3$] for Leptophos Oxon

atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq) ^a	<i>d</i> ^b
Br	2601(1)	2321(1)	3610(1)	73(1)	-0.094
Cl(2)	5481(2)	4470(1)	2008(1)	63(1)	0.027
Cl(5)	1483(2)	1344(1)	2328(1)	73(1)	0.050
P	2970(2)	3532(1)	406(1)	51(1)	-0.865
O(1)	4135(4)	3516(2)	992(2)	52(1)	-0.023
O(2)	3831(5)	4119(2)	-49(2)	58(1)	-0.777
O(3)	2591(5)	2715(2)	163(2)	67(1)	-0.366
C(1)	3782(7)	3205(4)	1581(3)	44(2)	-0.005
C(2)	4339(6)	3611(4)	2100(3)	44(2)	0.002
C(3)	3995(7)	3324(4)	2701(3)	49(2)	0.004
C(4)	3102(7)	2642(4)	2781(3)	52(2)	-0.007
C(5)	2553(7)	2223(3)	2255(3)	50(2)	0.004
C(6)	2900(7)	2513(4)	1656(3)	50(2)	0.002
C(7)	1624(8)	4810(4)	1065(3)	53(2)	-3.060
C(8)	1406(7)	4128(4)	667(3)	42(2)	-2.566
C(9)	-36(9)	3915(4)	473(3)	58(2)	-3.406
C(10)	-1230(9)	4391(5)	675(3)	69(2)	-4.725
C(11)	-1016(9)	5063(5)	1055(3)	64(2)	-5.211
C(12)	398(9)	5271(4)	1249(3)	61(2)	-4.386
C(13)	5184(8)	3865(4)	-368(3)	73(2)	0.451

^a *U*(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor. ^b Distance from a least-squares plane defined by C1–C6.

Table 3. Selected Interatomic Distances (Å)

bond	distance	
	leptophos oxon	leptophos
Br–C4	1.886(6)	1.897(4)
Cl2–C2	1.733(6)	1.723(4)
Cl5–C5	1.718(6)	1.737(4)
P–O3 ^a	1.459(4)	1.910(2)
P–O1	1.618(4)	1.610(3)
P–O2	1.556(4)	1.578(3)
P–C7	1.781(6)	1.790(4)
O1–C1	1.384(6)	1.404(4)
O2–C13	1.441(7)	1.417(6)
C1–C2	1.374(8)	1.381(5)
C1–C6	1.377(8)	1.375(5)
C2–C3	1.389(8)	1.397(5)
C3–C4	1.371(8)	1.373(5)
C4–C5	1.392(8)	1.375(5)
C5–C6	1.389(8)	1.379(5)
C7–C8	1.391(8)	1.382(5)
C7–C12	1.403(8)	1.394(5)
C8–C9	1.381(8)	1.395(5)
C9–C10	1.366(9)	1.376(7)
C10–C11	1.366(9)	1.372(6)
C11–C12	1.377(8)	1.394(6)
O3 \cdots H6A	2.530	

^a Corresponds to the S atom in leptophos.

($113.9(2)^\circ$ and $116.6(2)^\circ$, respectively) in the oxon. The S=P–C7 angle is $116.7(2)^\circ$ in leptophos, whereas the corresponding O3=P–C7 angle is $114.7(3)^\circ$ in the oxon. The O2–P–C7 angle decreases from $106.6(2)^\circ$ in leptophos to $104.4(3)^\circ$ in leptophos oxon.

Other angles that differ significantly ($>3\sigma$) include the P–O1–C1 angle which increases from $121.5(2)^\circ$ in leptophos to $123.6(4)^\circ$ in leptophos oxon, O1–P–C7 which increases from $99.9(2)^\circ$ in leptophos to $105.8(3)^\circ$ in leptophos oxon, and the P–O2–C13 angle which decreases slightly from $123.3(3)^\circ$ in leptophos to $121.9(4)^\circ$ in leptophos oxon. It is interesting to note that while the P–O1–C1 angles in ronnel oxon (no H \cdots O interaction), leptophos oxon and crufomate (both with H \cdots O interactions) are $\leq 2\sigma$ of being equal ($123.2(2)$, $123.6(4)$, and $122.8(3)^\circ$, respectively), the O3=P–O1 type angles in leptophos oxon and crufomate are equal but $\sim 5\sigma$ greater than that for ronnel oxon ($113.9(2)$, $113.7(2)$, and $112.9(2)^\circ$, respectively).

Table 4. Bond Angles (Degrees)

angle	degrees	
	leptophos oxon	leptophos
O3 ^a -P-O1	113.9(2)	116.6(1)
O3 ^a -P-O2	116.6(2)	114.8(1)
O3 ^a -P-C7	114.7(3)	116.7(2)
O1-P-O2	99.8(2)	99.9(2)
O1-P-C7	105.8(3)	99.9(2)
O2-P-C7	104.4(3)	106.6(2)
P-O1-C1	123.6(4)	121.5(2)
P-O2-C13	121.9(4)	123.3(3)
O1-C1-C2	117.9(6)	119.3(4)
O1-C1-C6	121.9(6)	120.2(4)
C2-C1-C6	120.2(6)	120.4(4)
C12-C2-C1	120.3(5)	121.7(3)
C12-C2-C3	120.0(5)	118.9(3)
C1-C2-C3	119.7(6)	119.4(4)
C2-C3-C4	120.6(6)	119.8(4)
Br-C4-C3	118.3(5)	118.0(3)
Br-C4-C5	121.9(5)	121.8(3)
C3-C4-C5	119.8(6)	120.2(4)
C15-C5-C4	121.7(5)	120.9(3)
C15-C5-C6	119.0(5)	118.7(3)
C4-C5-C6	119.3(6)	120.4(4)
C1-C6-C5	120.4(6)	119.8(4)
P-C7-C8	119.8(5)	119.4(3)
P-C7-C12	120.2(5)	120.4(3)
C8-C7-C12	120.0(6)	120.0(4)
C7-C8-C9	118.7(6)	119.8(4)
C8-C9-C10	121.3(7)	119.7(4)
C9-C10-C11	120.1(7)	121.0(4)
C10-C11-C12	120.8(6)	119.7(5)
C7-C12-C13	119.1(7)	119.7(4)
P-O3 ^a ·H6A	87.6	
O3 ^a ·H6A-C6	126.4	

^a Corresponds to the S atom in leptophos.

Table 5. Torsional Angles [Signs per Klyne and Prelog (1960)]

	leptophos oxon	leptophos ^a	crufomate ^b
C6-C1-O1-P	37.9	84.4	-53.8
C1-O1-P-O2	167.2	-69.3	-178.9
C1-O1-P=O3	-67.9	55.1	57.1
O2-P-C7-C12	-69.0	-66.3	52.2
O3=P-C7-C12	162.1	163.8	-179.4
O1-P-O3 ^a ·H6A	39.5	-55.7	-20.5
O1-P-O2-C13	71.2	24.5	-67.6

^a The O3 atom in leptophos oxon corresponds to the S atom in leptophos. ^b The O3, O2, C7, C12, and C13 atoms in leptophos oxon correspond, respectively, to the O2, O3, N, C13, and C12 atoms in crufomate.

Significant differences occur in the lengths of the P-O2 and O2-C13 bonds, with leptophos containing the longer P-O2 bond and shorter O2-C13 bond (*cf.* Table 3). This is the result of the O3 atom in leptophos oxon possessing a higher electronegativity than the sulfur atom in leptophos, thus drawing the O2 atom closer to the phosphorus, and lengthening the O2-C13 bond. The S=P bond in leptophos is 1.910(2) Å, whereas the respective O3=P bond in the oxon is 1.459(4) Å. These correspond very closely with ronnel at 1.903(2) Å (Baughman and Jacobson, 1975) and its oxon at 1.450(3) Å.

As previously noted (Baughman and Jacobson, 1978), certain P··δ(+) distances may give insight into the toxicities of OPs, since it is theorized that the δ(+) P atom and δ(+) centers bind to the δ(-)··δ(-) portion of the active site in AChE. The charge densities of the P atom in leptophos and the oxon were calculated using an AM1 Hamiltonian to be 2.575 and 2.689, respectively (Hypercube, Inc., 1994); charges for all of the atoms in leptophos oxon, leptophos, and crufomate are provided

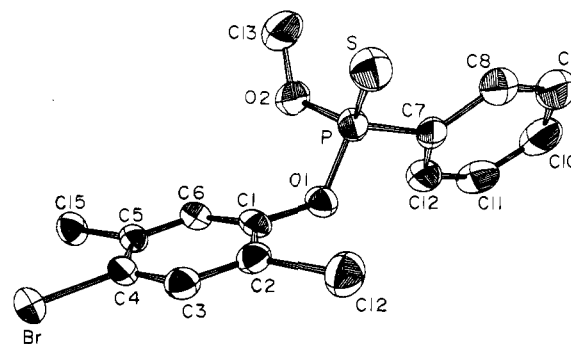


Figure 2. Leptophos molecule showing 50% probability ellipsoids for the non-hydrogen atoms.

in the supplementary material. The distances from the δ(+) P atoms to the tetrasubstituted δ(+) ring centers in leptophos and the oxon are 3.90 and 3.91 Å, respectively. Neither of these values, however, corresponds with the δ(-) active site separations for insect AChE, which are 5.0–5.5 (Hollingworth *et al.*, 1967) or 4.5–5.9 Å (O'Brien, 1963). Other potential binding sites are the two aryl hydrogens which are also δ(+); H3 = 0.161 and H6 = 0.158 in leptophos and H3 = 0.149 and H6A = 0.164 in the oxon (Hypercube, Inc., 1994). The P··H3 and P··H6A distances are 5.52 and 3.38 Å, respectively, in leptophos; 5.77 and 2.86 Å in the oxon. Therefore the most likely atoms in the insecticides to compete for the active site are the P··H3 atoms, since they are both electron deficient and at distances within the expected ranges.

Lipid solubilities of the insecticides may also contribute to their relative toxicities. An insecticide that is not lipophilic will not easily pass through a membrane and may not reach the synaptic nerve (Foye, 1981). Leptophos was calculated to have a lipid solubility of log *P* = 5.72; the oxon, log *P* = 7.00, with *P* being the partition coefficient between 1-octanol and water (Hypercube, Inc., 1994). One cannot expect, however, that all OPs with a P=O will have a higher lipid solubility, since crufomate has a lipid solubility of log *P* = 5.94.

ACKNOWLEDGMENT

We thank NMSU Computer Services for the computer time and K. R. Fountain and P. Xu for their assistance in the charge density and lipid solubility calculations.

Supplementary Material Available: Tables 2–4, listing hydrogen positions, anisotropic thermal parameters, and net atomic charges (3 pages), and Table 1, a listing of the observed and calculated structure factor amplitudes (6 pages). Ordering information is given on any current masthead page.

LITERATURE CITED

- Baughman, R. G. Further Details on the Crystal and Molecular Structure of the Organophosphorus Insecticide Chlorpyrifos Methyl. *J. Agric. Food Chem.* **1989**, *37*, 1505–1507.
- Baughman, R. G.; Allen, J. L. Structures of Organophosphorus Insecticides. Anzinphos Ethyl. *Acta Crystallogr.* **1995**, in press.
- Baughman, R. G.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 1. Ronnel. *J. Agric. Food Chem.* **1975**, *23*, 811–815.
- Baughman, R. G.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 4. Bromophos. *J. Agric. Food Chem.* **1976**, *24*, 1036–1041.
- Baughman, R. G.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 5. Fospirate. *J. Agric. Food Chem.* **1977**, *25*, 582–587.

- Baughman, R. G.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 8. Ronnel Oxen. *J. Agric. Food Chem.* **1978**, *26*, 403–407.
- Baughman, R. G.; Yu, P. J. Crystal and Molecular Structure of Organophosphorus Insecticides. 14. Iodofenphos. *J. Agric. Food Chem.* **1982**, *30*, 293–295.
- Baughman, R. G.; Eckey, D. A.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 7. Crufomate. *J. Agric. Food Chem.* **1978a**, *26*, 398–403.
- Baughman, R. G.; Jorgensen, S. K.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 10. Chlorpyrifos. *J. Agric. Food Chem.* **1978b**, *26*, 576–580.
- Beckman, D. E.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 12. Dowco 214. *J. Agric. Food Chem.* **1979**, *27*, 712–715.
- Busing, W. R.; Martin, K. O.; Levy, H. A. ORFFE, A Fortran Crystallographic Function and Error Program. U.S. Atomic Energy Commission, Oak Ridge National Laboratory: Oak Ridge, TN, 1964; Report ORNL-TM-306.
- Foye, W. O. *Principles of Medicinal Chemistry*, 2nd ed.; Lea and Febiger: Philadelphia, PA, 1981; pp 60–62.
- Gifkins, M. R.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 2. Coroxon. *J. Agric. Food Chem.* **1976**, *24*, 232–236.
- Gifkins, M. R.; Jacobson, R. A. *O*-Ethyl-*O*-(4-Nitrophenyl) Benzene Phosphonothioate (EPN). *Cryst. Struct. Commun.* **1980**, *9*, 571–574.
- Hollingworth, R. M.; Fukuto, T. R.; Metcalf, R. L. Selectivity of Sumithion Compared with Methyl Parathion. Influence of Structures on Acetylcholinesterase Activity. *J. Agric. Food Chem.* **1967**, *15*, 235–241.
- Hypercube, Inc. HyperChem Molecular Visualization and Simulation (CHEMPLUS 1.0A, AM1 Hamiltonian), Waterloo, Ontario, Canada, 1994.
- Johnson, C. K. ORTEP: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations. U.S. Atomic Energy Commission, Oak Ridge National Laboratory: Oak Ridge, TN, 1971; Report ORNL-3794 (2nd revision with supplementary instructions).
- Klyne, W.; Prelog, V. Description of Steric Relationships Across Single Bonds. *Experientia* **1960**, *16*, 521–523.
- Lapp, R. L.; Jacobson, R. A. Crystal and Molecular Structures of Organophosphorus Insecticides. 13. *S*-Isopropyl *O*-Methyl *O*-(3,5,6-Trichloro-2-Pyridyl) Phosphoramidothioate and Dimethoate. *J. Agric. Food Chem.* **1980a**, *28*, 755–759.
- Lapp, R. L.; Jacobson, R. A. *O*-Methyl-*O*-(4-Bromo-2,5-Dichlorophenyl)Phenylphosphonothioate, C₁₃H₁₀BrCl₂O₂PS. *Cryst. Struct. Commun.* **1980b**, *9*, 65–69.
- O'Brien, R. D. Binding Organophosphates to Cholinesterase. *J. Agric. Food Chem.* **1963**, *11*, 163–166.
- Rohrbaugh, W. J.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 6. Amidithion. *J. Agric. Food Chem.* **1977**, *25*, 588–591.
- Rohrbaugh, W. J.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 9. Stirofos. *J. Agric. Food Chem.* **1978**, *26*, 1120–1124.
- Rohrbaugh, W. J.; Meyers, E. K.; Jacobson, R. A. Crystal and Molecular Structure of Organophosphorus Insecticides. 3. Azinphos-methyl. *J. Agric. Food Chem.* **1976**, *24*, 713–717.
- Sheldrick, G. M. SHELXL-93 Program for the Refinement of Crystal Structures, Institut für Anorganische Chemie, Universität Göttingen, Bundesrepublik, Deutschland, 1993.
- Siemens Analytical X-ray Instruments, Inc. SHELXTL PC, Madison, WI, 1990.

Received for review June 1, 1994. Accepted November 21, 1994.®

JF9402901

® Abstract published in *Advance ACS Abstracts*, January 1, 1995.