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X-Ray Crystallographic Studies of Contact Fungicide Cholothalonil

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Abstract
Chlorothalonil (2,4,5,6-tetrachloroisophthalonitrile) is a polychlorinated aromatic mainly used as a broad spectrum, contact fungicide. A rational approach to test these fungicides is to know the three dimensional structure of these compounds and macromolecular receptor sites as well as their molecular complex .The structures of these compounds can be obtained by X-ray diffraction method in crystalline form and they will invariably be similar to their structure in solutions. The activity of fungicides is intimately related to its chemical structure. Knowledge about the chemical structure of a chemical is useful for the synthesis of new compounds with more specific actions and fewer adverse reactions, to increase/decrease the duration of action of the original drug or to get a more potent compound, to restrict the action to a specific system of the body and to reduce the adverse reactions, toxicity and other disadvantages associated. We can understand the basic chemical groups responsible for drug action. Recently it has been observed that some of the fungicides are losing their effects. So analogous compounds can be designed as substitute, if their structures are known
Index Terms— Fungicide, ORTEP, Thermal ellipsoid

1 INTRODUCTION

A chemical or physical agent used to kill or control fungal pathogens is called fungicide. A systemic fungicide is defined as systemic fungi toxic compound that controls a fungus pathogen remote from the point of application. These active compounds are absorbed by the roots of plant and get acropetally trans located within it through the xylem to the leaves travelling peripherically accumulates at the edges and tips., thus providing protection as well as eradicating already established infection. A chemical or physical agent used to kill or control fungal pathogens is called fungicide. A systemic fungicide is defined as systemic fungi toxic compound that controls a fungus pathogen remote from the point of application.

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In the search for a more effective approach to plant disease control, the emphasis shifted to the exploitation of the biological properties of new fungicides, This new approach can be defined as being on a profound knowledge, at the physiology, biochemical and molecular levels, of the modes of action of exiting fungicides and the mechanisms of resistance to them in fungi. Such knowledge provides a ration guideline, not only in the development of new compounds, but also in strategies for judicious and sustained use of established fungicides (Fuchs, etal., 1983). The approach to disease control, thus, embraces the techniques and strategies to avoid or delay the development of field resistance to fungcides, based on investigation into the mechanism of resistance.

2 FUTURE OF DISEASE CONTROL AND RESEARCH PURPOSE

In the search for a more effective approach to plant disease control, the emphasis shifted to the exploitation of the biological properties of new fungicides, this new approach can be defined as being on a profound knowledge, at the physiology, biochemical and molecular levels, of the modes of action of exiting fungicides and the mechanisms of resistance to them in fungi. Such knowledge provides a ration guideline, not only in the development of new compounds, but also in strategies for judicious and sustained use of established fungicides. The approach to disease control, thus, embraces the techniques and strategies to avoid or delay the development of field resistance to fungcides, based on investigation into the mechanism of resistance. Chlorothalonil containing products are sold under the names Bravo, Echo, and Daconil. It was first registered for use in

the US in 1966 and in 1997; it was the third most used fungicide in the US, with some 12 millions used in agriculture alone in a year.

3 RESULTS

In Chlorothalonil-The structure obtained is almost accurate, In Benzene ring distance between C(1)-C(2) is 1.391(2), C(2)-C(3) is 1.389(3), C(3)-C(4) is 1.398(2) , C(4)-C(5) is 1.391(2), C(5)-C(6) is 1.392(2) and C(1)-C(6) is 1.393(2) and the theoretical Bond Lengths between C=C and C-C are 1.34 and 1.54 respectively showing the regular behaviour of benzene ring.The averaged C-Cl and C≡N bond length is 1.7108(16) and1.135(2) respectively, theoretically it comes to be1.77 and 1.16 respectively. These bond lengths are very-very close to theoretical values. By the torsion angles data we can see that the arrangement of atoms are symmetric and we can say that there is no or very small disagreement between the arrangements of atoms in the molecule of Chlorothalonil.

4 DISCUSSION

The crystal structure consists of parallel sheets stacked along *a-axis*. The molecules overlap while running along the *a-axis*.

5 CONCLUSIONS

Cholrothalonil reduces fungal intracellular glutathione molecules to alternate forms which cannot participate in essential enzymatic reactions, ultimately leading to cell death.Thus we study the structure of variety of such compounds and correlate their structure with biological activity, so that more safer and effective fungicides at reasonable price can be developed.

6 METHODS

6.1 Experimental

The structures of these compounds can be obtained by X-ray diffraction method in crystalline form and they will invariably be similar to their structure in solutions. First grow the crystals of existing fungicides available and synthesize their derivatives in lab. The determination of structural perturbation in fungicide derivatives and comparison of the result of their molecular association with other receptor sites by X-Ray crystallography techniques will be done. In parallel with these structural studies, spectroscopic studies carried out on them. The goal is then to tie together the structural and spectroscopic studies to have more comprehensive account of the precise shape of these molecules, the non-covalent interaction which are likely to be involved in and the changes introduced in molecular geometry and electronic structure of these compounds as a result of their molecular association with other compounds. Thus we study the structure of variety of such compounds and correlate their structure with biological activity, so that more safer and effective
fungicides at reasonable price can be developed. Crystallization of hexaconazole was done by slow evaporation from a solution of methanol at 293°K temp.The crystals obtained were white and rectangular in shape. The density of crystal 1.334 Mg/m^3 is measured by floatation method the mixture of benzene and Bromoform .The unit cell parameters were determined by automatic computerized 4-circled Enraf-Nonius CAD-4 Diffractometer. The preliminary information about crystal is given in Table.1.

6.2 Data Collection and Structure Solution

X-Ray crystallographic data were collected at 296K with $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) using a Bruker Nonius SMART CAD diffractometer equipped with graphite monochromator. The SMART software was used for data collection and also for indexing the reflections and determining the unit cell parameters; the collected data were integrated using SAINT software. The structures were solved by direct methods and refined by full-matrix least-squares calculations using SHELXTL software. All the non-H atoms were refined in the anisotropic approximation against F^2 of all reflections. The H-atoms, except those attached to N and O were placed at their calculated positions and refined in the isotropic approximation; those attached to heteroatoms (N and O) were located in the difference Fourier maps, and refined with isotropic displacement coefficients. The data were collected at 296(2)K
The three dimensional intensity data were collected on a computerized automatic 4-circle CAD-4 Enraf-Nonious diffractometer using graphite filtered MoKα (Å) radiation's at SAIF Madras.. Temperature of crystal during data collection was 293°K. All the data were corrected for Lorentz and Polarization effect. Three standard reflection were measured where h various -12 to12, k varies from -11 to 13,l varies from -16 to10. The total number of reflections were 14496 out of which unique reflection were 2746. Each intensity measurement involved in a scan over the reflection peak, a back ground measurement at each end of the scan range and measurement of the peak height. The structure was solved using SHELXS- program for crystal structure solution.

6.3 Refinement

The positional co-ordinates, which were obtained from SHELXS 97 and isotropic temperature factors, were subjected to refinement by SHELXL refinement program. After so many cycles of refinement the R factors dropped to 0.0458. Further refinement of the structure was carried out with individuals so R factor reduced to 0.0354.

$-2P_1$^ 2[h^2a*^2U_{11}+----------+2hKa*bxU_{12} (1)

The hydrogen atoms were fixed at this stage by geometrical considerations and were not refined. Refinement of the structure was terminated after two more cycles when all the deviations in parameters became much smaller than the corresponding estimated standard derivations. The final R value was 0.0354 for all 14496 reflections collected. Reflections were measured where h various -12 to12, k varies from -11 to 13,l varies from -16 to10. The total number of reflections were 14496 out of which unique reflection were 2746. The structure was solved using SHELXS- program

Table 1 Preliminary Crystal Structure of Cholrothalonil

Empirical formula	C8 Cl4 N2
Formula weight	265.90
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P21/c
Volume	971.62(13) A^3
Z / Calculated density	4 / 1.818 Mg/m^3
Absorption coefficient / F(000)	1.171mm^{-1}/ 520
Crystal size	(0.30 x 0.25 x 0.15) mm
Unit cell dimensions	a = 6.3354(5)A^0, b = 6.2233(4)A^0 c = 27.753(2)$A^{0,}$ α = 90 ^{0}, β= 95.397(2) ^{0}, γ = 90 ^{0}
θ range for data collection	3.23 – 31.22 deg.
Limiting indices	-8<=h<=9, -9<=k<=9, -35<=l<=36
Reflections collected	12288
Unique	3140 [R(int) = 0.0264]
Completeness to theta = 31.22	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. / min. transmission	0.8440 and 0.7203
Refinement method	Full-matrix least-squares on F^2
Data / Restraints / Parameters	3140 / 0 / 127
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0345, wR2 = 0.0833
R indices (all data)	R1 = 0.0506, wR2 = 0.0926
Largest diff. peak and hole	0.327 and - 0.379e.A^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for Chlorothalonil. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	6545(2)	4210(3)	990(1)	33(1)
C(2)	5917(3)	2990(3)	1418(1)	33(1)
C(3)	4158(3)	3593(3)	1677(1)	34(1)
C(4)	3029(2)	5439(3)	1505(1)	34(1)
C(5)	3632(3)	6671(3)	1076(1)	35(1)
C(6)	5403(3)	6043(3)	822(1)	34(1)
C(7)	8389(3)	3583(3)	729(1)	42(1)
C(8)	3526(3)	2353(3)	2124(1)	43(1)
N(1)	9865(3)	3070(3)	536(1)	60(1)
N(2)	3012(3)	1370(3)	2474(1)	63(1)
Cl(1)	7352(1)	776(1)	1637(1)	50(1)
Cl(2)	893(1)	6152(1)	1840(1)	51(1)
Cl(3)	2226(1)	8902(1)	864(1)	52(1)
Cl(4)	6249(1)	7534(1)	303(1)	51(1)

Table 3 Anisotropic displacement parameters (A^2 x 10^3) for Chlorothalonil. The anisotropic displacement factor exponent takes the form : -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	32(1)	37(1)	32(1)	-2(1)	6(1)	4(1)
C(2)	33(1)	32(1)	35(1)	-1(1)	2(1)	5(1)
C(3)	33(1)	36(1)	32(1)	-1(1)	6(1)	-2(1)
C(4)	29(1)	40(1)	34(1)	-6(1)	5(1)	3(1)
C(5)	34(1)	34(1)	37(1)	-1(1)	1(1)	6(1)
C(6)	36(1)	36(1)	32(1)	2(1)	4(1)	1(1)
C(7)	39(1)	46(1)	41(1)	4(1)	9(1)	8(1)
C(8)	40(1)	49(1)	42(1)	4(1)	10(1)	2(1)
N(1)	57(1)	69(1)	59(1)	9(1)	25(1)	21(1)
N(2)	58(1)	75(1)	59(1)	21(1)	21(1)	3(1)
Cl(1)	53(1)	45(1)	53(1)	11(1)	8(1)	17(1)
Cl(2)	41(1)	63(1)	50(1)	-5(1)	16(1)	13(1)
Cl(3)	51(1)	46(1)	59(1)	7(1	5(1)	18(1)
Cl(4)	57(1)	52(1)	46(1)	15(1)	15(1)	3(1)

Table 4. Bond lengths [A] and angles [deg] for Cholorothalonil.

C(1)-C(2)	1.391(2)	C(3)-C(2)-C(1)	120.24(14)
C(1)-C(6)	1.393(2)	C(3)-C(2)-Cl(1)	119.76(12)
C(1)-C(7)	1.441(2)	C(1)-C(2)-Cl(1)	119.97(12)
C(2)-C(3)	1.389(2)	C(2)-C(3)-C(4)	119.41(14)
C(2)-Cl(1)	1.7110(16)	C(2)-C(3)-C(8)	120.29(15)
C(3)-C(4)	1.398(2)	C(4)-C(3)-C(8)	120.29(14)
C(3)-C(8)	1.436(2)	C(5)-C(4)-C(3)	121.02(14)
C(4)-C(5)	1.391(2)	C(5)-C(4)-Cl(2)	120.87(13)
C(4)-Cl(2)	1.7108(16)	C(3)-C(4)-Cl(2)	118.11(12)
C(5)-C(6)	1.392(2)	C(4)-C(5)-C(6)	118.72(14)
C(5)-Cl(3)	1.7061(16)	C(4)-C(5)-Cl(3)	120.70(12)
C(6)-Cl(4)	1.7112(16)	C(6)-C(5)-Cl(3)	120.58(13)
C(7)-N(1)	1.135(2)	C(5)-C(6)-C(1)	120.89(14)
C(8)-N(2)	1.134(2)	C(5)-C(6)-Cl(4)	120.63(12)
C(2)-C(1)-C(6)	119.71(14)	C(1)-C(6)-Cl(4)	118.48(12)
C(2)-C(1)-C(7)	119.69(15)	N(1)-C(7)-C(1)	178.3(2)
C(6)-C(1)-C(7)	120.59(15)	N(2)-C(8)-C(3)	179.4(2)

Table 5. Torsion angles [deg] for Chlorothalonil

C(6)-C(1)-C(2)-C(3)	0.0(2)	C(1)-C(2)-C(3)-C(8)	-179.05(16)
C(7)-C(1)-C(2)-C(3)	179.18(16)	Cl(1)-C(2)-C(3)-C(8)	-0.7(2)
C(6)-C(1)-C(2)-Cl(1)	-178.28(12)	C(2)-C(3)-C(4)-C(5)	0.4(2)
C(7)-C(1)-C(2)-Cl(1)	0.8(2)	C(8)-C(3)-C(4)-C(5)	179.34(16)
C(1)-C(2)-C(3)-C(4)	-0.1(2)	C(2)-C(3)-C(4)-Cl(2)	-179.15(12)
Cl(1)-C(2)-C(3)-C(4)	178.18(12)	C(8)-C(3)-C(4)-Cl(2)	-0.2(2)
C(3)-C(4)-C(5)-Cl(3)	179.16(12)	C(3)-C(4)-C(5)-C(6)	-0.6(2)
Cl(2)-C(4)-C(5)-Cl(3)	-1.3(2)	Cl(2)-C(4)-C(5)-C(6)	178.96(12)
C(4)-C(5)-C(6)-C(1)	0.5(2)	C(7)-C(1)-C(6)-C(5)	-179.35(16)
Cl(3)-C(5)-C(6)-C(1)	-179.27(13)	C(2)-C(1)-C(6)-Cl(4)	178.81(13)
C(4)-C(5)-C(6)-Cl(4)	-178.51(13)	C(7)-C(1)-C(6)-Cl(4)	-0.3(2)
Cl(3)-C(5)-C(6)-Cl(	1.7(2)	C(2)-C(1)-C(7)-N(1)	-34(8)
C(2)-C(1)-C(6)-C(5)	-0.2(2)	C(6)-C(1)-C(7)-N(1)	146(7)
		C(2)-C(3)-C(8)-N(2)	-118(23)
		C(4)-C(3)-C(8)-N(2)	63(23)

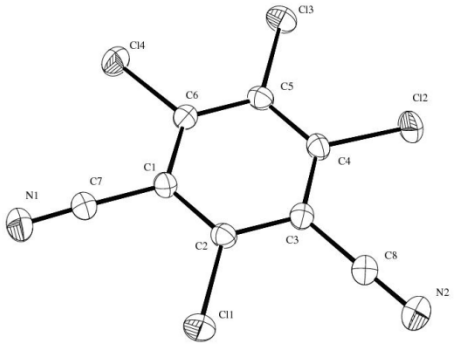

Figure 1 ORTEP of Chlorothalonil

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