Comparative X-Ray Structure analysis   and structure activity relationship of Two Systemic fungicides

***** Jyotsna Chauhan**

***Physics department in Rajeev Gandhi Technical University Bhopal,India.**

Email: jyotsnachauhan2006@gmail.com

Abstract: 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 loosing their effects. So analogous compounds can be designed as substitute, if their structures are known. 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.

Keywords: X-ray crystallography, Triagonal Hybridization , systemic fungicides

Introduction: Fungicides are the important class of chemicals used widely for the protection of crops. A systemic fungicide is defined as a systemic fungi toxic compound that controls a fungus pathogen remote from the point of application and that can be detected or identified. These compounds are absorbed by the plant and get trans located within it, thus providing protection as well as eradicating already established infection.

Action of Systemic Fungicides: Very little is known about the mechanism of these fungicides. The following are the possibilities(a).Inactivation of the enzymes and toxins of the pathogens.(b).Selective accumulation of the fungicide due to greater permeability of the fungus cell wall.(c)Damage to the membranes of the fungal hyphens and inhibition of structures, such as aspersoria, cushion formation emergence of germ tubes and formation of haustoria's.(d)Inhibition of fungal enzymes or their destruction, Systemic fungicides are more specific in their action than non-Systemic fungicides.

The composition of the crystal **(N-(2,6 dim ethyl phenyl)-N-(2-keto-1-methyl   butyl)   3-hydroxypropanamide)** is confirmed by comparing the infra-red spectra of the two components. The unit cell parameters are a =7.865(1)Å,   b =13.122(2)Å, c =15.130(1)Å, α =90(1)^o, β=101.75(2)^o, γ=90(1)^o. The space group is determined to be P2$_1$/c. The calculated density of the crystal is 1.1919g/cm^3 and measured density is 1.192g/cm^3.All the lengths in the Benzene ring

vary from 1.3705(2)Å to   1.4176(1)Å, show a good agreement with their standard value of 1.395Å. The Unit cell parameters of **cis N-(1, 1 ,2,2-tetrachloroethylthio)-4-cyclohexene-1 ,2-dicarboximide)** are a=10.5665(7)Å, b=6.6413(3)Å, c=19.3973(12)Å and Z=4. Thus the space group is determined to be P2$_1$/c and crystal of monoclinic system. We can see that there are some differences in unit cell parameters in both the crystals. We will see how these differences affect the systemic fungicides biological activity. We compare the structures of both the systemic fungicides. Thus we determine the three-dimensional structure, molecular dimensions, molecular geometry, electronic structure and the conformation of fungicides and analyze their crystal structures also. Then correlate the chemical activity by substituting the chemically active groups at the crucial sites of the model fungicide to enhance chemical affinity and introduce conformational changes in the fungicides to make than more effective, active and to some extent cheaper.

Experimental:- crystals of **(N-(2,6 dimethyl phenyl)-N-(2-keto-1-methyl butyl) 3-hydroxypropanamide)** are grown at 4°-5° from its solution in Toluene by slow evaporation method Crystallization of **cis N-(1, 1 ,2,2-tetrachloroethylthio)-4-cyclohexene-1   ,2-dicarboximide)** is done by slow evaporation from a solution of methyl alcohol at 40°C temp. The crystals found were pale yellow in color and rectangular in shape.. The unit cell parameters are determined directly

by automatic computerized 4 - circled Enraf Nonious CAD-4 diffractometer in ω-2θ scan mode.

Data collection and Structure solution: The three dimensional intensity data are collected on a computerized automatic 4-circled CAD-4 Enraf-Nonious diffractometer and the crystal structure is solved using the SHELXS-97.

Refinement :   The structure determination is carried out on VAX machine using SHELXS-97 program. All the non hydrogen atoms are located in the beginning itself.   The co-ordinates thus obtained are fed to SHELXL-97 for refinement. The final R index is 0.045 for all the observed reflection 3849 (including all the unique reflections) for **(N-(2,6 dimethyl phenyl)-N-(2-keto-1-methyl butyl) 3-hydroxypropanamide).** For **cis N-(1, 1 ,2,2-tetrachloroethylthio)-4-cyclohexene-1 ,2-dicarboximide)** the R factor dropped to 0.0516 after several cycles of refinement. To reduce R factor to 0.0437, further refinement of the structure was carried out with individuals' anisotropic temperature factors exponent of the form.

-2Pi ^ 2[h^2a*^2U$_{11}$+------------------+2hKa*b*U$_{12}$]

The hydrogen atoms are fixed by geometrical consideration at this stage, but not included in refinement. Refinement of the structure is terminated after two more cycles when all the shifts in Parameter's become much smaller than the corresponding estimated standard deviations. The final R value is 0.0437 for all the   8018   reflections   for   **cis   N-(1,1,2,2-tetrachloroethylthio)-4-cyclohexene-1,2-dicarboximide).**

Table 1 Bond distances in{A}involving non – hydrogen atoms with estimatestandard deviations in parentheses:

O(1)	- C(10)	1.2191(1)
O(2)	- C(14)	1.1953(2)
O(3)	- C(11)	1.2382(2)
N(1)	- C(1)	1.4429(2)
N(1)	- C(10)	1.3618(1)
N(1)	- C(13)	1.4680(1)
C(1)	- C(2)	1.4056(2)
C(1)	- C(6)	1.4176(1)
C(2)	- C(3)	1.3972(1)
C(2)	- C(8)	1.4987(1)
C(3)	- C(4)	1.3811(2)
C(4)	- C(5)	1.3705(2)
C(5)	- C(6)	1.3900(1)
C(6)	- C(7)	1.4859(2)
C(10)	- C(20)	1.5530(2)
C(11)	- C(20)	1.3919(1)
C(13)	- C(14)	1.5112(2)
C(13)	- C(17)	1.5321(1)
C(14)	- C(15)	1.3435(1)
C(15)	- C(16)	1.4389(2)

Table 2 Bond angles {A} of non-hydrogenatoms with estimated standard deviations in parentheses:-

C(1)	- N(1)	- C(10)	121.43(1)
C(1)	- N(1)	- C(13)	120.97(1)
C(10)	- N(1)	- C(13)	116.33(2)
N(1)	- C(1)	- C(2)	118.39(1)
C(2)	- C(1)	- C(6)	121.87(1)
N(1)	- C(1)	- C(6)	119.73(2)
C(1)	- C(2)	- C(3)	117.40(2)
C(1)	- C(2)	- C(8)	121.63(2)
C(3)	- C(2)	- C(8)	120.93(2)
C(2)	- C(3)	- C(4)	121.54(2)
C(3)	- C(4)	- C(5)	119.86(1)
C(4)	- C(5)	- C(6)	122.12(2)
C(1)	- C(6)	- C(5)	117.15(1)
C(5)	- C(6)	- C(7)	121.05(1)
C(1)	- C(6)	- C(7)	121.80(1)
O(1)	- C(10)	- N(1)	122.35(1)
O(1)	- C(10)	- C(20)	121.96(2)
C(10)	- N(1)	- C(13)	116.33(1)
O(3)	- C(11)	- C(20)	113.99(2)
N(1)	- C(13)	- C(14)	111.32(1)
C(14)	- C(13)	- C(17)	108.37(1)
N(1)	- C(13)	- C(17)	112.44(2)
N(1)	- C(13)	- C(17)	112.44(1)
O(2)	- C(14)	- C(13)	126.87(1)
C(13)	- C(14)	- C(15)	109.26(1)
C(14)	- C(15)	- C(16)	116.79(2)
C(10)	- C(20)	- C(11)	112.98(2)

Table 3.bond length [A] with estimated standard deviation in parenthesis for cis N-(1, 1 ,2,2-tetrachloroethylthio)-4-cyclohexene-1 ,2-dicarboximide

S (1)	- N (8)	1.6854 (17)
S (1)	- C (10)	1.820 (2)
C1(1)	-C (10)	1.773 (2)
C1(2)	- C (10)	1.767 (2)
C1(3)	- C (11)	1.764 (2)
C1(4)	- C (11)	1.768 (2)
C (1)	- C (2)	1.309 (4)
C (1)	- C (6)	1.491 (4)
C (3)	- C (4)	1.534 (3)
C (4)	- C (9)	1.502 (3)
C (4)	- C (5)	1.533 (3)
C (5)	-C (7)	1.517 (3)
C (5)	-C (6)	1.543 (3)
C (7)	- O (13)	1.196 (3)
C (7)	- N (8)	1.414 (3)
N (8)	-C (9)	1.400 (3)
C (9)	-C (12)	1.203 (3)
C (10)	- C (11)	1.537 (3)

Table 4 Bond Angle [Degree] with estimated standard deviation in parenthesis

N (8) -S (1) - C (10)	102.23 (9)
C (2) -C (1) -C (6)	120.2 (2)
C (2) -C (1) -H (1)`	119.9
C (6) - C (1) - H (1)	119.9
C (6) -C (1) - C (3)	120.1 (2)
C (1) - C (2) - H (2)	120.0
C (1) - C (2) - H (2)	120.0
C (2) - C (3) -C (4)	110.7 (2)
C (2) - C (3) - H (3A)	109.5
C (4) - C (3) -H (3A)	109.5
C (2) - C (3) -H (3B)	109.5
C (4) - C (3) -H (3B)	109.5
H (3A) -C (3) - H (3B)	108.1
C (9) - C (4) - C (5)	105.33 (16)
C (9) - C (4) - C (3)	109.33 (18)
C (5) -C (4) - C (3)	114.73 (18)
C (9) - C (4) -H (4)	109.0
C (5) - C (4) -H (4)	109.0
C (3) -C (4) - H (4)	109.0
C (7) -C (5) - C (4)	105.50 (16)
C (7) -C (5) -C (6)	110.37 (19)
C (4) -C (5) -C (6)	114.00 (19)
C (7) -C (5) -H (5)	108.9
C (4) -C (5) -H (5)	108.9
C (6) -C (5) -H (5)	108.9
C (1) -C (6) -C (5)	111.56 (19)
C (1) -C (6) -H (6A)	109.3
C (5) -C (6) -H (6A)	109.3
C (1) -C (6) -H (6B)	109.3
C (5) -C (6) -H (6B)	109.3
H (6A) -C (6) -H (6B)	108.0
O (13) -C (7) -N (8)	124.32 (19)
O (13) -C (7) -C (5)	127.97 (19)
N (8) -C (7) -C (5)	107.71 (17)
C (9) -N (8) -C (7)	112.26 (17)
C (9) -N (8) -S (1)	123.74 (14)
C (7) -N (8) -S (1)	122.99 (14)
O (12) -C (9) -N (8)	123.40 (19)
O (12) -C (9) -C (4)	127.6 (2)
N (8) -C (9) -C (4)	108.95 (17)
C (11) -C (10) - C1(2)	109.07 (15)
C (11) -C (10) - C1(1)	110.81 (15)
C1 (2) -C (10) - C1 (1)	109.99 (12)
C (11) -C (10) -S (1)	113.91 (15)
C1 (2) - C (10) -S (1)	110.64 (11)
C (1) -C (10) -S (1)	102.26 (11)
C (10) -C (11) -C1 (3)	111.09 (16)
C (10) -C (11) -C1 (4)	111.84 (16)
C1 (3) -C (11) -C1 (4)	109.11 (13)

Result and Discussion : The ORTEP diagram of **(N-(2,6 dimethyl phenyl)-N-(2-keto-1-methyl butyl) 3-hydroxypropanamide)** is shown in **fig 1** and the ORTEP diagram of **cis N-(1, 1 ,2,2-tetrachloroethylthio)-4-cyclohexene-1 ,2-dicarboximide)**

is shown in **fig 2**. Bond length for **(N-(2,6 dimethyl phenyl)-N-(2-keto-1-methyl butyl) 3-hydroxypropanamide)** is given in **Table 1** and Bond Angles in **Table 2.** Bond length for **cis N-(1, 1 ,2,2-tetrachloroethylthio)-4-cyclohexene-1 ,2-dicarboximide)** is given in **Table 3** and Bond Angles in **Table 4.** In **N-(2,6 dimethyl phenyl)-N-(2-keto-1-methyl butyl) 3-hydroxypropanamide)** the geometry around N(1), C(13) and C(10) appears to be normal as all the lengths are close to single bond normal valuesand the angles are according to the configuration. The C-N distances are similar to that observed in structures having triangonal hybridization.The equations for the mean planes were calculated by the method suggested by Blow (1960). All the lengths in the Benzene ring vary from 1.3705(2)Å to 1.4176(1)Å, show a good agreement with their standard value of 1.395Å. The deviations of the inner bond angles in the Benzene ring from 120º are slightly greater than 2σ (=0.7º).The geometry around N(1), C(13) and C(10) appears to be normal as all the lengths are close to single bond normal values and the angles are according to the configuration. The C-N distances are similar to that observed in structures having triangonal hybridization.It is of interest to see in **cis N-(1, 1 ,2,2-tetrachloroethylthio)-4-cyclohexene-1 ,2-dicarboximide)** the geometry of Phthalimide group. The C (1)-C (2) bond length is much shorter 1.309(4) Å compared to standard values, whereas the largest bond distance is C (5)-C (6) of 1.543(3)Å But as far as bond angles are concerned, they vary from 110.7 (2) ° to 120.2(3) °, thus suggest that the ring is compressed as expected. The five-member ring shows usual behavior. The geometry around S (1), C (10) and C(12) appears to be normal as all the lengths are close to single normal bond values and angles are according to the configuration. The N (8)-S(1)-C(1O) angle of 102.2(9)° shows that the chain is almost right angle to phthalimide group. The angle of twist between phthalimide group and remaining chain N (8)-S (1)-C (10)-C (11) is of -74.9(2) °. The phthalimide group appears to be planner, as we calculated mean planes using Blow's method. If we look to the angles between different planes, it appears that the molecule is highly twisted and folded.
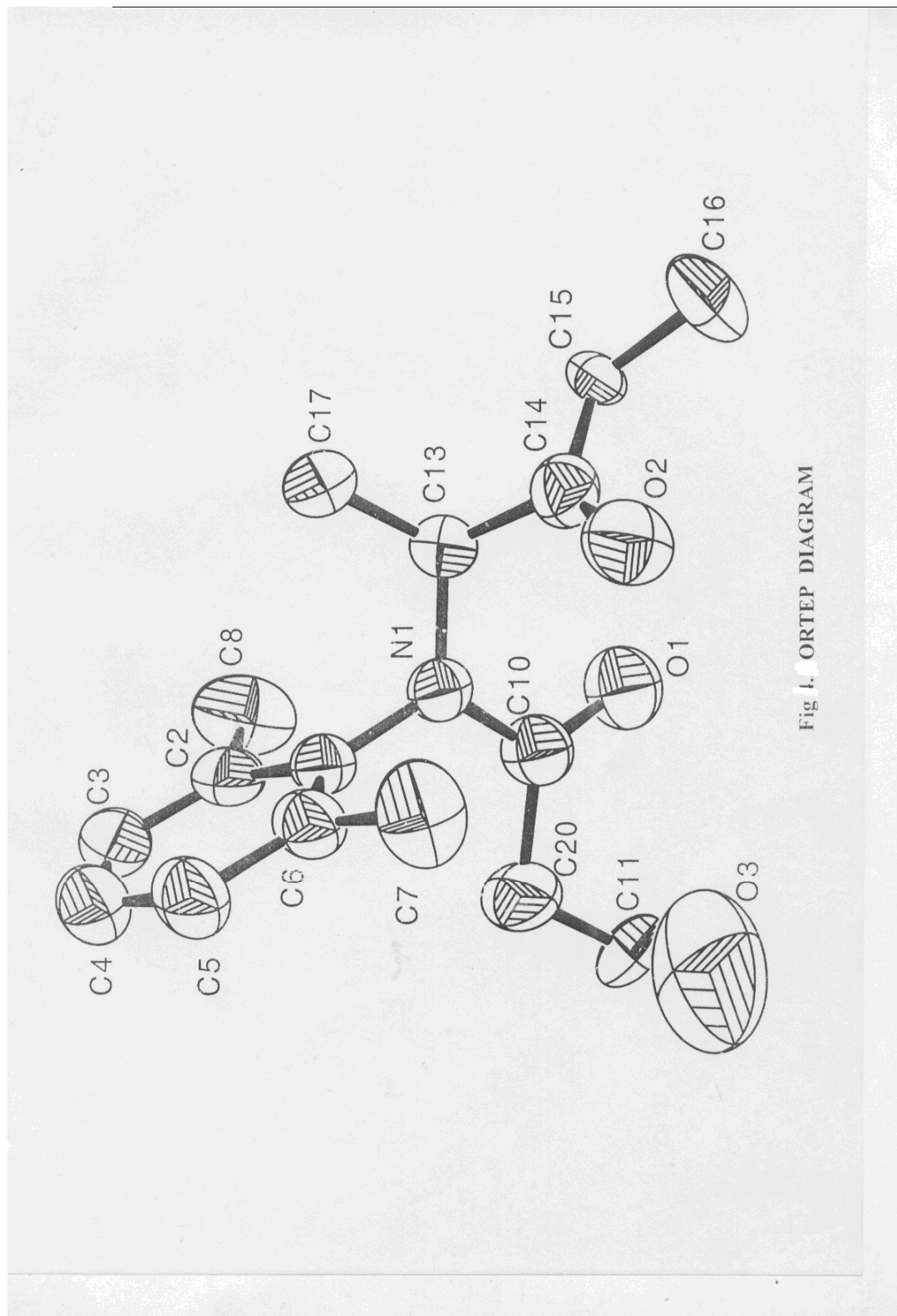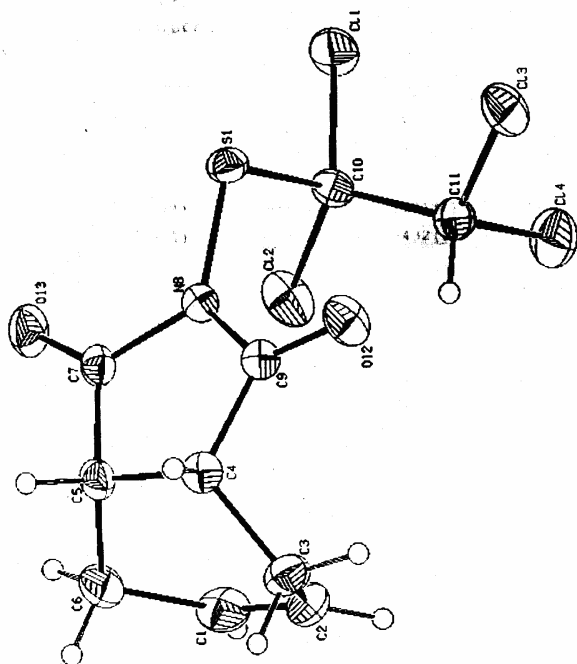
Fig 1. ORTEP DIAGRAM

Fig. 2: ORTEP for cis-N-(1,1,2,2-tetrachloroethylthio)-4-cyclohexene-1,2-dicarboximide

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