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Part-II 3D-AFM-Microstructural Featues and Suitability of Sulfonyl-Urea Moeity as Center of Antidiabetic Drugs Families

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Abstract: *3D-AFM investigations introduce precize view on the nano-and microstructural properties of sulfonyl-urea as active moeity and link between suitability of sulfonyl urea as antidiabetic drug and its internal micro-structural features specially exposured surface area. The structural investigations are focusing on the parameters such as bond distances inside unit cell , torsion on angles and different oxidation states present together inside unit cell . All of theses structural prameters play an important role on the stability of this moeity as functionalized group which could be linked with many active groups .The visualization studies specially bond distances measurements indicated that there are three different types of N-H bonds .Furthermore visualized XRD pattern was constructed and the fingure print peaks of sulphoyl urea which lies at two theta ~25 with [200] muller index were compared and discussed in details taking into our account electronics inductive effects generated from neighboring surrounding function groups .*

Keywords: *3D-AFM ; Sulphonyl-Urea ; XRD ; Bond Lengths , Torsions ; Oxidation States.*

1. INTRODUCTION

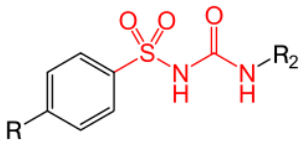

Fig1. *Chemical Structure Formula of Sulphonyl-Urea Moiety.*

Fig.1 shows the sulphonyl-urea moiety whereas Ar and R portions of this general structure provide lipophilic character whereas the -SO2-NH-CO-NH- moiety is hydrophilic. All of these functional groups are required for activity, but the lipophilic Ar and R groups account for the differences in potency (SU receptor binding), metabolism, duration, and routes of elimination [1-11] .

The arylsulfonylureas are weak organic acids (pKas = 5-6) and are largely ionized at physiological pH [2,3] . This ionization contributes significantly to drug potency SUR (affinity), extensive plasma protein binding of these agents (>95%), and drug interactions (competitivppb). Also, alkalinization of the urine enhances ionization and elimination (shortens half-life) [6,7 and 9].

The arylsulfonylureas products differ primarily in their relative potency and key pharmacokinetic properties. Duration of action (primarily a function of metabolism) is of primary importance because this influences the frequency of required dosing [12-16].

The sulfonylureas can be classified as first, second and possibly third generation agents [15-18] . The 2nd and 3rd generation sulfonylurea hypoglycemics (glipizide, glyburide and glimepiride) are the newer, "more potent" agents.

The major goal of the present investigations is giving reasons and answers why sulphonyl-urea moiety has unique and specific structural parameters as centeral moiety in most of common antidiabetic drugs.

2. EXPERIMENTAL

2.1. Structure Visualization

A visualization study made is concerned by matching and comparison of experimental and theoretical data of atomic positions, bond distances, oxidation states and bond torsion on the crystal structure formed**.** Some of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request @ccdc.cam.ac.uk, or by contacting ICSD-Fiz-Karlsruhe-Germany.

2.2. Structural Measurements

The X-ray diffraction (XRD): Measurements were carried out at room temperature on the fine ground samples using Cu-Kα radiation source, Ni-filter and a computerized STOE diffractometer/Germany with two theta step scan technique. Rietveld and indexing of structure were made via Full prof package and Gesas program.

2.3. Atomic Force Microscopy (AFM)

High-resolution Atomic Force microscopy (AFM) is used for testing morphological features and topological map (Veeco-di Innova Model-2009-AFM-USA).The applied mode was tapping non-contacting mode. For accurate mapping of the surface topology AFM-raw data were forwarded to the Origin-Lab version 6-USA program to visualize more accurate three dimension surface of the sample under investigation. This process is new trend to get high resolution 3D-mapped surface.

3. RESULTS & DISCUSSION

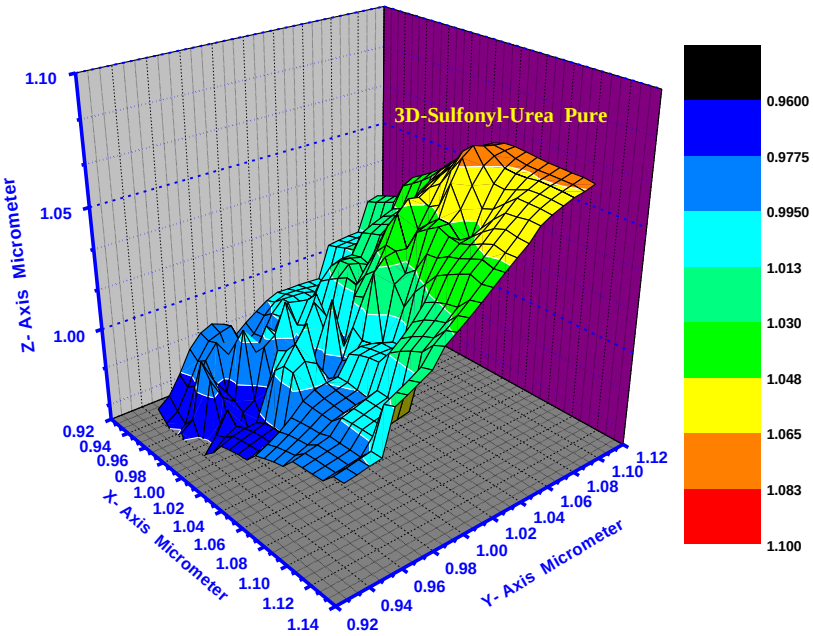

Fig1a. *3D-visuallized AFM-image for Sulfonyl-Urea Drug*

For accurate mapping of the surface topology AFM-raw data were forwarded to the Origin-Lab version 6-USA program to visualize more accurate three dimension surface of the sample under investigation sulfonyl-urea antidiabetic drug see Fig.1a.

As it clear in Fig.1a which represent very narrow 3D-scanned area with dimensional 0.2x0.2x0.2µm. The accurate analysis of this figure one can conclude the following facts; 1st the maximum heights gradient ranged in between (1.065 – 1.10µm) orange-red zones ,2nd the minimum depth gradient is ranged in between (0.96-0.995µm) pale –dark blue zones .3rd higher than 50 % of the scanned area moderate in heights and ranged in between 0.99-1.048µm

Those represented by blue-green colors .These accurate investigations interpret why sulfonyl-urea has huge unique exposure surface area with different gradients on the surface topology in contrast with others drugs.

Fig.2 shows the experimental XRD pattern recorded for pure urea which is consider the main center of all sulphonyl-urea drug. The brawn circles refer to figure print peak of highly pure urea with muller index [200] which lies at two theta value ~ 25. The matching between Fig.2 (experimental XRD) and Fig.3 (visualized XRD) indicated that the figure print peak which lies at two theta ~ 25 is present in both patterns which confirmed that the fitting between both patterns is present by some extent. The ratio of fitting is function in the surrounding groups around sulphonyl-urea moiety whether these groups are small or bulk, aliphatic or aromatic.

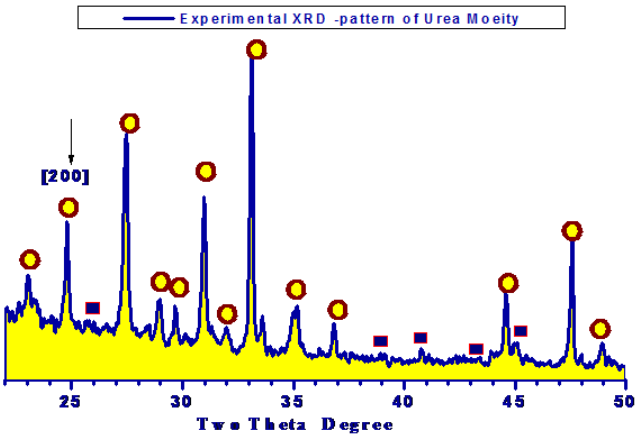

Fig2. *XRD pattern recorded of pure-urea.*

Fig.3 displays visualized XRD pattern for sulphonyl urea constructed via DIAMOND IMPACT CRYSTAL VISUALIZER depending up on atomic coordinates supplied from single crystal data of supphonyl-urea containing compound and pure urea see Table.1.

Table1. *Single crystal data of sulphonyl- urea containing compound*

Phase data								
Formula sum	C4 O4 N8 H16							
Formula weight	240.222 g/mol							
Crystal system	tetragonal							
Space-group	P 42/m (84)							
Cell parameters	a=5.5600 Å c=4.7000 Å							
Cell ratio	a/b=1.0000 b/c=1.1830 c/a=0.8453							
Cell volume	145.29 $Å^3$							
Z								
Calc. density	2.74529 g/cm^3							
Meas. density								
Melting point								
RAll								
RObs								
Pearson code	tP32							
Formula type	NOP2Q4							
Wyckoff sequence	k3i2							
Atomic parameters								
Atom	**Ox.**	**Wyck.**	**Site**	**S.O.F.**	**x/a**	**y/b**	**z/c**	**U [$Å^2$]**
C1		4i	2..		0	1/2	0.32000	
O1		4i	2..		0	1/2	0.59000	
N1		8k	1		0.14000	0.64000	0.17000	
H1		8k	1		0.25000	0.75000	0.28000	
H2		8k	1		0.14000	0.64000	-0.03000	
Anisotropic displacement parameters, in $Å^2$								

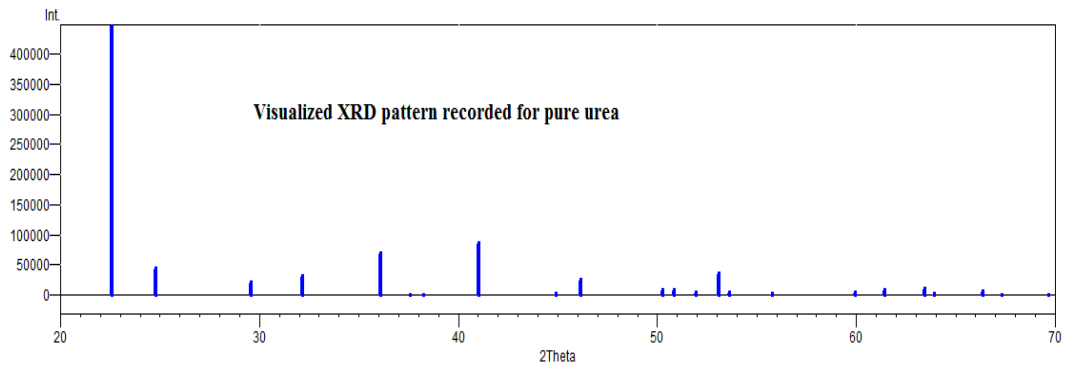

Fig3. *Visualized XRD pattern for pure urea.*

The visualized pattern Fig.3 has 23 peaks all of them is related to pure urea-moeity while Fig.2 has lower number of (peaks 18 peaks) due to the overlapping and interferences between rest structure of sulphonyl-urea with urea peaks .Although the line at two theta ~ 25 in Fig.3 is not the most intense reflection peak but it consider the characteristic line for urea existence phase with [200] muller index.

From table 2 one can indicate that There are two different types of O-H bonds such that O1-H1 bond length was found to be 2.058 Å while O1-H2 was 2.098 Å . These notification is attributable to that electron density at oxygen atom is impacted sharply by inductive effects of the neighboring function groups specially those with high negatively inductive effects as S, N,P, or halogen atoms that could be present in the drug constituents.

Table.3 indicates that there are three different types of N-H bond namely N1-H2, N1-H2 and N1-H1 with measured bond distances 0.658 , 0.940 and 1.077 Å respectively .Although type one and type two is for (N1-H2) but it is clear that existent of bond distance differences between both bond due to environmental inductive effect variations .

Data inside tables 4 and 5 confirmed that existence of two different types of hydrogen and three different types of N-H bonding and the variations in the measured bond distances are due to differences in the environmental neighboring groups which affected sharply on the average of electron density on the nitrogen and hydrogen atoms whether their effects having positive or negative inductive effects.

Table2. *Selected bond distances and lattice atomic coordinates inside unit cell of sulphonyl-urea containing drug.*

Atom1	*Atom2*	*x/a*	*y/b*	*z/c*	D1-2 Å
O1	C1	0	1/2	0.68000	0.4230
	O1	0	1/2	0.41000	0.8460
	C1	0	1/2	0.32000	1.2690
	N1	0.14000	0.64000	0.83000	1.5761
	N1	-0.14000	0.36000	0.83000	1.5761
	H1	0.25000	0.75000	0.72000	2.0585
	H1	-0.25000	0.25000	0.72000	2.0585
	H2	-0.14000	0.36000	0.97000	2.0980
	H2	0.14000	0.64000	0.97000	2.0980

Table3. *Selected bond distances and lattice atomic coordinates inside unit cell of sulphonyl-urea containing drug.*

Atom1	*Atom2*	*x/a*	*y/b*	*z/c*	D1-2 Å
N1	H2	0.14000	0.64000	0.03000	0.6580
	H2	0.14000	0.64000	-0.03000	0.9400
	H1	0.25000	0.75000	0.28000	1.0077
	C1	0	1/2	0.32000	1.3072
	O1	0	1/2	0.41000	1.5761
	N1	0.14000	0.64000	-0.17000	1.5980
	N1	-0.14000	0.36000	0.17000	2.2016
	O1	0	1/2	0.59000	2.2602
	H1	0.25000	0.25000	0.22000	2.2652
	H1	-0.25000	0.75000	0.22000	2.2652

Table4. *Selected bond distances and lattice atomic coordinates inside unit cell of sulphonyl-urea containing drug.*

Atom1	*Atom2*	*x/a*	*y/b*	*z/c*	D1-2 Å
H1	N1	0.14000	0.64000	0.17000	1.0077
	H2	0.14000	0.64000	0.03000	1.4590
	H2	0.14000	0.64000	-0.03000	1.6944
	C1	0	1/2	0.32000	1.9747
	C1	1/2	1.00000	0.18000	2.0212
	O1	0	1/2	0.41000	2.0585
	H1	0.25000	0.75000	0.72000	2.0680
	O1	1/2	1.00000	0.09000	2.1591
	N1	0.64000	0.86000	0.33000	2.2652
	N1	0.36000	1.14000	0.33000	2.2652
	N1	0.14000	0.64000	-0.17000	2.2850

Table5. *Selected bond distances and lattice atomic coordinates inside unit cell of sulphonyl-urea containing drug.*

Atom1	*Atom2*	*x/a*	*y/b*	*z/c*	D1-2 Å
H2	H2	0.14000	0.64000	0.03000	0.2820
	N1	0.14000	0.64000	-0.17000	0.6580
	N1	0.14000	0.64000	0.17000	0.9400
	H1	0.25000	0.75000	-0.28000	1.4590
	H1	0.25000	0.75000	0.28000	1.6944
	C1	0	1/2	-0.32000	1.7520
	C1	0	1/2	0.32000	1.9794
	O1	0	1/2	-0.41000	2.0980

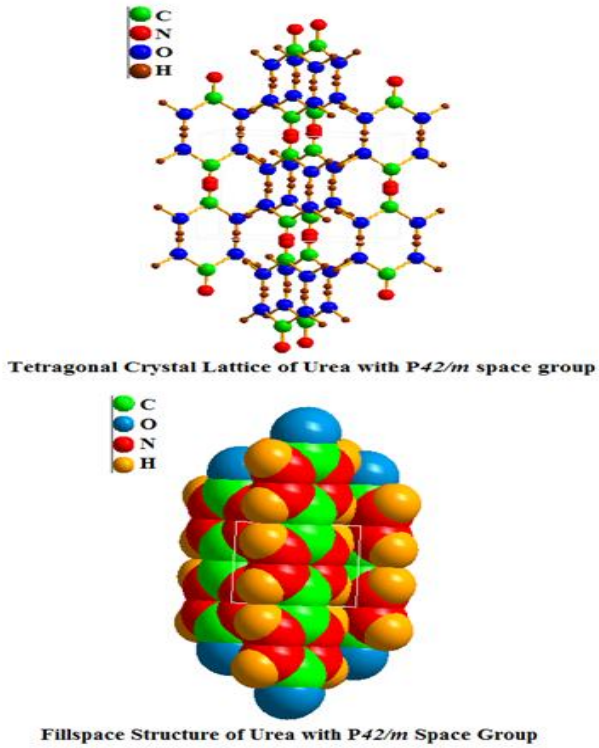

Fig4. *Tetragonal lattice structure of pure urea with P42/m Space Group*

The unit cell structure of pure tetragonal urea was constructed with both models (ball-stick and space filling) to estimate the maximum stability can be achieved inside tetragonal unit cell of urea . The most important notifications were 1st both nitrogen and oxygen atoms of urea moiety molecule have capability to coordinates without causing any torsion on the angle of tetragonal unit cell ,2nd high charge density on these atoms make stabilization to the unit cell reinforced by extra coordinative bonds and finally 3rd vacancies inside unit cell can compensate any defect resulted from steric or stereo-orientation of bulky groups attached to sulphonyl-urea moiety.

4. CONCLUSIONS

The present visualization investigations introduce the following conclusive remarks;

- 3D-AFM investigations confirmed that sulfonyl-urea moiety has huge exposure surface area that responsible for their biological activity as anti-diabetic drug.
- Varieties of oxidations states inside tetragonal unit cell of sulphonyl-urea lead to differentiation on the regular bond distances and hence compensate lattice defects by increasing stability factor .
- Nitrogen and oxygen atoms of sulphonyl-urea play an important role in reinforcing lattice stability by hydrogen or other coordination bons.
- No extra torsion on angles of tetragonal unit cell was noticeable.

The mentioned conclusive remarks are answering why sulphonyl-urea moiety has unique and specific structural parameters as centeral moiety in most of common antidiabetic drugs.

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