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Original Article

Structure Visualization and Suitability of Sulfonyl-Urea Moeity as Center of Antidiabetic Drugs Families

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ABSTRACT

The present investigations are focusing on the structural parameters such as bond distances inside unit cell, torsion on angles and different oxidation states present together inside unit cell. All of these 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

1. INTRODUCTION

Figure 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].

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The arylsulfonylureas are weak organic acids (pKas = 5-6) and are largely ionized at physiological pH [2,3].

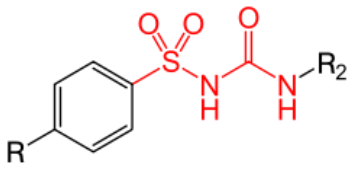

Fig 1: Chemical Structure Formula of Sulphonyl-Urea Moiety

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- 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.

3. RESULTS AND DISCUSSION

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 .

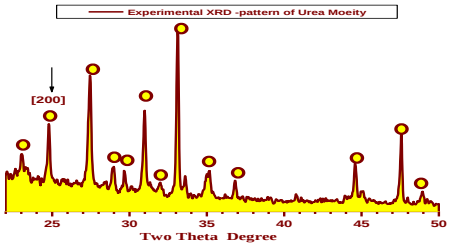

Fig 2: XRD pattern recorded of pure-urea

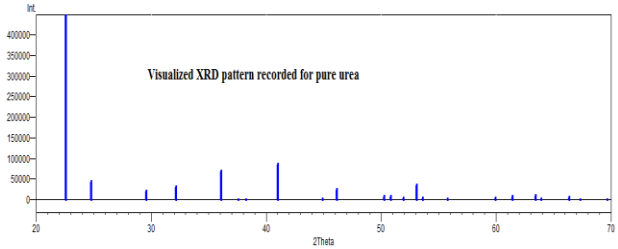

Fig 3: Visualized XRD pattern for pure urea

The ratio of fitting is function in the surrounding groups around sulphonyl-urea moiety whether these groups are small or bulk, aliphatic or aromatic. 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.

Table 1: 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
Pearson code	tP32
Formula type	NOP2Q4
Wyckoff sequence	k3i2

Atomic parameters					
Atom	**Wyck.**	**Site**	**x/a**	**y/b**	**z/c**
C1	**4i**	**2..**	**0**	**01-Feb**	**0.32**
O1	**4i**	**2..**	**0**	**01-Feb**	**0.59**
N1	**8k**	**1**	**0.14**	**0.64**	**0.17**
H1	**8k**	**1**	**0.25**	**0.75**	**0.28**
H2	**8k**	**1**	**0.14**	**0.64**	**-0.03**

Anisotropic displacement parameters, in $Å^2$

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 thatexistent 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.

Table 2 : 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	01/2	0.68	0.423
	O1	0	01/2	0.41	0.846
	C1	0	01/2	0.32	1.269
	N1	0.14	0.64	0.83	1.5761
	N1	-0.14	0.36	0.83	1.5761
	H1	0.25	0.75	0.72	2.0585
	H1	-0.25	0.25	0.72	2.0585
	H2	-0.14	0.36	0.97	2.098
	H2	0.14	0.64	0.97	2.098

Table 3 : 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	0.14	0.64	0.03	0.658
	H2	0.14	0.64	-0.03	0.94
	H1	0.25	0.75	0.28	1.0077
	C1	0	01/2	0.32	1.3072
	O1	0	01/2-	0.41	1.5761
	N1	0.14	0.64	-0.17	1.598
	N1	-0.14	0.36	0.17	2.2016
	O1	0	01/2-	0.59	2.2602
	H1	0.25	0.25	0.22	2.2652
	H1	-0.25	0.75	0.22	2.2652

Table 4: Selected bond distances and lattice atomic coordinates inside unit cell of sulphonyl-urea containing drug

Atom1	Atom 2	x/a	y/b	z/c	D1-2 Å
H1	N1	0.14	0.64	0.17	1.0077
	H2	0.14	0.64	0.03	1.459
	H2	0.14	0.64	-0.03	1.6944
	C1	0	01/2-	0.32	1.9747
	C1	1/2	1	0.18	2.0212
	O1	0	01/2	0.41	2.0585
	H1	0.25	0.75	0.72	2.068
	O1	01/2	1	0.09	2.1591
	N1	0.64	0.86	0.33	2.2652
	N1	0.36	1.14	0.33	2.2652
	N1	0.14	0.64	-0.17	2.285

Table 5: Selected bond distances and lattice atomic coordinates inside unit cell of sulphonyl-urea containing drug

Atom 1	Atom 2	x/a	y/b	z/c	D1-2 Å
H2	H2	0.14	0.64	0.03	0.282
	N1	0.14	0.64	-0.17	0.658
	N1	0.14	0.64	0.17	0.94
	H1	0.25	0.75	-0.28	1.459
	H1	0.25	0.75	0.28	1.6944
	C1	0	01/2	-0.32	1.752
	C1	0	01/2	0.32	1.9794
	O1	0	01/2	-0.41	2.098

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.

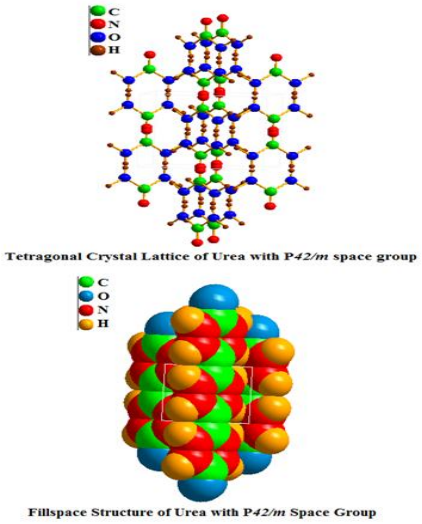

Fig 4: Tetragonal lattice structure of pure urea with P*42/m* Space Group

4. CONCLUSION

The present visualization investigations introduce the following conclusive remarks:

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 bonds .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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