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## Structure and Conformation of Solvated 1-(4-methoxybenzenesulfonyl)-5-oxo-pyrrolidine-2-carboxamide

The crystal structure and molecular conformation of solvated 1-(4-methoxybenzenesulfonyl)-5-oxo-pyrrolidine-2-carboxamide ( $C_{12}H_{14}O_5N_2S.H_2O$ ), synthesized and biologically evaluated as a possible antineoplastic agent, have been studied by X-ray analysis and AM1 molecular orbital methods. The compound crystallizes in the monoclinic space group  $P2_1$ , with  $a = 9.661(4)$ ,  $b = 7.246(3)$ ,  $c = 11.378(5)\text{\AA}$ ,  $\beta = 113.42(2)^\circ$ ,  $Z = 2$ . The structure has been solved by direct methods and refined to  $R = 0.0438$  for 1721 observed reflections. The crystal structure consists of an essentially planar methoxyphenyl ring linked to a 2-carboxamide substituted oxo-pyrrolidine moiety via sulfonyl group and a lattice water molecule. The conformational analysis of the title compound investigated by semi-empirical quantum mechanical AM1 calculations shows a good agreement with the X-ray structure except a rotation of the carboxamide moiety about the C (oxo-pyrrolidine) - C (carboxamide) bond. In the solid state, the molecules translated in the  $b$ -direction are linked by intermolecular  $NH\cdots O$  hydrogen bonds to form infinite one-dimensional chain.

Keywords: X-ray crystal structure, conformation, AM1 molecular mechanics, oxo-pyrrolidine derivative

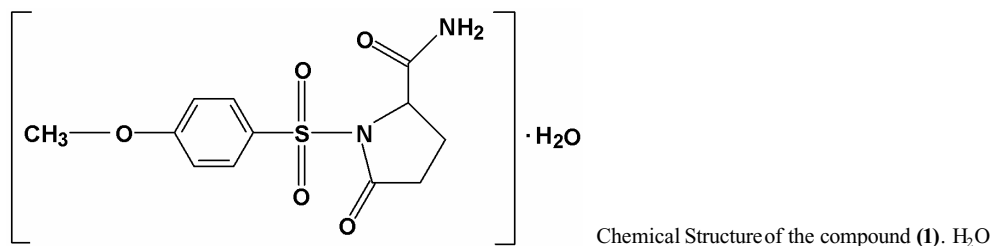
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### 1. Introduction

The oxopyrrolidine-2-carboxylic acid, an important heterocyclic system in medicinal chemistry, can be viewed as the cyclized version of glutamic acid. Several structural variants of glutamic acid such as glutarimides, glutaramides, glutamines, isoglutamines, oxopyrrolidines etc., display useful biological activity as possible antineoplastic and therapeutic agents (GOSWAMI et al., 2001; PURKAYASTHA et al., 1994; CHOI et al., 1988; BANDOLI et al., 1987). As a part of an ongoing program on the synthesis and characterization of novel biologically active systems containing an oxopyrrolidine moiety, the title compound 1-(4-methoxybenzenesulfonyl)-5-oxo-pyrrolidine-2-carboxamide (**1**) was synthesized. The compound (**1**) showed encouraging antineoplastic activity against Ehrlich Ascites Carcinoma (EAC) in Swiss albino mice (inhibition of EAC cells: 75.70%; inhibition of EAC fluid weight: 66.67%). In the present paper we report the structural characterization and molecular conformation of (**1**). $H_2O$  by X-ray analysis and semi-empirical AM1 molecular orbital calculations.

## 2. Experimental

1-(4-methoxybenzenesulfonyl)-5-oxo-pyrrolidine-2-carboxylic acid (**1b**) was synthesized as described previously (GOSWAMI et al., 2001). The corresponding acid chloride (**1a**), obtained by refluxing (**1b**) with thionyl chloride, on treatment with dry ammonia yielded the title compound (**1**). Single crystals of (**1**).H<sub>2</sub>O suitable for X-ray study were obtained by recrystallization of (**1**) from dilute ethanol. The compound (**1**) was characterized by elemental analysis (calculated for C<sub>12</sub>H<sub>14</sub>O<sub>5</sub>N<sub>2</sub>S: C 48.32, H 4.70, N 9.40%; found: C 48.14, H 4.72, N 9.39%).



A colourless prismatic crystal (0.40 × 0.35 × 0.30 mm) was placed on a Rigaku AFC-5R diffractometer with graphite-monochromated MoK<sub>α</sub> radiation ( $\lambda = 0.71069 \text{ \AA}$ ). Accurate cell parameters were obtained by least-squares refinement of diffractometer setting angles of 25 automatically centered reflections with  $8.5 < \theta < 16.8^\circ$ . Intensity data were collected at 20°C using  $\omega - 2\theta$  scan mode. Three reference reflections monitored every 90 minutes revealed no significant crystal decay during the data collection. Lorentz-polarization and empirical absorption corrections ( $\psi$  scans) were made.

The crystal structure was solved by MULTAN 88 (DEBAERDEMAEKER et al., 1988) and refined by full matrix least-squares techniques using SHELXL 97 (SHELDRICK, 1997) on F<sup>2</sup>. The non-hydrogen atoms were anisotropically refined. The NH<sub>2</sub> and the aqua H atoms located from difference Fourier maps were held fixed while other H atoms were placed geometrically with riding model constraints. The atomic scattering factors were taken from the International Tables for Crystallography, Vol. C (WILSON, 1992). Crystal data collection and structure refinement details are listed in Table 1.

Table 1: Summary of crystal data and structure refinement parameters for (1).H<sub>2</sub>O

Empirical formula	C <sub>12</sub> H <sub>14</sub> O <sub>5</sub> N <sub>2</sub> S.H <sub>2</sub> O
Formula weight	316.33
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	P2 <sub>1</sub>
Unit cell dimensions	a= 9.661(4) Å
	b= 7.246(3) Å
	c = 11.378(5) Å
	$\beta = 113.42(2)^\circ$

Volume	730.9(5) Å <sup>3</sup>
Z	2
Density (calc.)	1.437 Mg m <sup>-3</sup>
Absorption coefficient	0.250 mm <sup>-1</sup>
Crystal size	0.40 × 0.35 × 0.30 mm
Max. and min. transmission	0.928, 0.905
F(0 0 0)	332
θ range for data collection	3.66<θ<26.30
Index ranges	h -11<h<11 k -8<k<7 l -13<l<13
Reflection collected	2033
Unique reflections	2004
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data/restraints/parameters	2004/1/191
Goodness-of-fit on F <sup>2</sup>	1.079
Final R indices [I>2σ(I)]	R1=0.0438 ωR2=0.1094
R indices (all data)	R1=0.0561 ωR2=0.1176
Flack parameter	0.00(10)
Largest diff. peak and hole	0.16, -0.22 eÅ <sup>-3</sup>

Theoretical calculations were carried out with MOPAC 5.0 program package (STEWART, 1988) which included the AM1 Hamiltonian (DEWAR et al., 1985). The initial molecular geometries were adopted from standard data incorporated in the package and subsequently fully optimized using an energy gradient method. The conformational analyses were performed with full geometrical optimizations and values of the AM1 total energy were calculated as function of three torsion angles θ<sub>1</sub> (C11-C6-S1-N2), θ<sub>2</sub> (C6-S1-N2-C2) and θ<sub>3</sub> (N1-C1-C2-N2), varied every 5°. Results are illustrated in Figs. 3-5.

### 3. Results and Discussion

The molecular structure of the title compound (**1**).H<sub>2</sub>O with atomic numbering scheme is shown in Fig. 1. The fractional coordinates with equivalent isotropic temperature factors for non-hydrogen atoms, selected bond distances, bond angles and torsion angles are listed in Tables 2, 3 and 4, respectively.

The crystal structure of (**1**).H<sub>2</sub>O consists of an essentially planar methoxyphenyl ring linked to a substituted oxopyrrolidine moiety via a sulfonyl group and a lattice water molecule. The oxo-pyrrolidine group, defined by N2, O2, C2-C5, has an envelope geometry with the C3 atom lying at the flap position displaced from the least-squares plane of the other five non-H atoms by 0.281(4) Å and is inclined to the methoxyphenyl ring (O5, C6-C12) by 79.6(1)°. Similar conformation of the pyrrolidone group has been observed in related structures (ZHENG et al., 1999; HELLIWELL et al., 1997; RAY et al., 1997). The N2 atom with the bond angles summing to 360.0(3)° is in a nearly trigonal planar environment. The conformation of the sulfonyl group is such that one of the O atoms (O3) nearly lies in the plane of the oxo-pyrrolidine ring (Table 4), whereas the other O atom (O4) is nearly *gauche* with C5 of the pyrrolidone ring (Table 4).

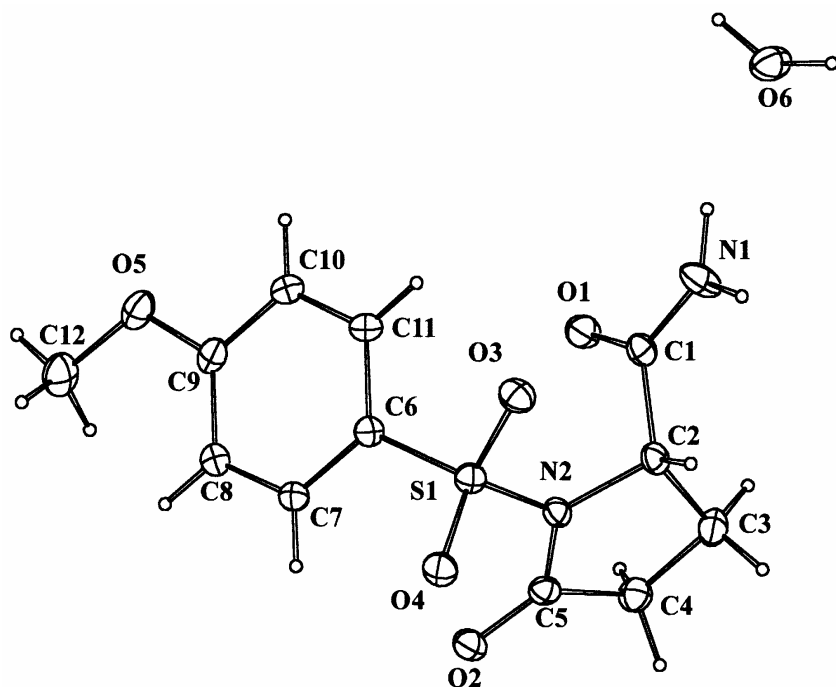


Fig. 1: Molecular structure of the title compound with atom numbering scheme

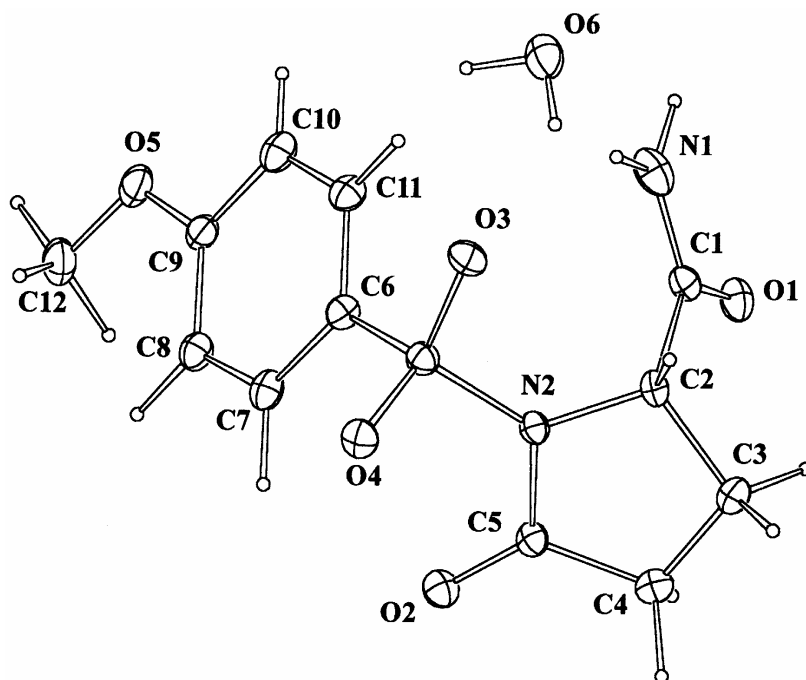


Fig. 2: Energy minimized structure of the title compound

The bond lengths and angles in the molecule are in good agreement with corresponding values reported for similar structures (ZHENG et al., 1999; GOVINDASAMY et al., 1999; MULLER et al., 1996). The C2-N2 distance [1.483(5) Å] characterizes a C-N single bond. The two shorter C-N bonds, C1-N1 [1.319(5) Å] and C5-N2 [1.377(5) Å], together with the coplanarity of the non-H atoms around N1 or N2 atoms, indicate the conjugation of the lone pair of electrons of N with the adjacent C=O group (BADORREY et al., 1999; LOUER et al., 1995; BILLING et al., 1991). The angular disposition of the bonds about the S1 atom shows significant deviation from that of a regular tetrahedron, with the largest deviation being in the O-S-O angle. The widening of the O3-S1-O4 angle [120.3(2)°] from the ideal tetrahedral value is presumably the result of repulsive interactions between the short S=O bonds [1.429(3), 1.435(3) Å] similar to that observed in related structures (BANERJEE et al., 2001; CHINNAKALI et al., 2000; WOLF, 1999). The C-C single bond distances ranging between 1.495(6) Å and 1.547(6) Å, and the C=O distances, 1.219(5) Å and 1.245(4) Å, are comparable with the corresponding bond lengths found in the literature (ALLEN et al., 1987).

Table 2: Fractional atomic coordinates and equivalent isotropic displacement parameters (Å<sup>2</sup>) for non-hydrogen atoms of (1).H<sub>2</sub>O

Atom	x	y	z	U <sub>eq</sub>
S1	0.7271(1)	0.4609(1)	0.4412(1)	0.052(1)
N1	0.7648(5)	0.8523(5)	0.1862(3)	0.079(1)
N2	0.8451(3)	0.4347(4)	0.3669(2)	0.046(1)
O1	0.6765(3)	0.5665(4)	0.1124(2)	0.066(1)
O2	0.8753(3)	0.1209(4)	0.3892(2)	0.061(1)
O3	0.7005(3)	0.6562(4)	0.4362(2)	0.066(1)
O4	0.7926(3)	0.3685(4)	0.5618(2)	0.062(1)
O5	0.1693(3)	0.0912(5)	0.0992(2)	0.072(1)
C1	0.7661(4)	0.6706(6)	0.1946(3)	0.052(1)
C2	0.8953(4)	0.5925(6)	0.3107(3)	0.050(1)
C3	1.0179(4)	0.5041(6)	0.2733(4)	0.065(1)
C4	0.9960(5)	0.2972(6)	0.2741(4)	0.064(1)
C5	0.9019(4)	0.2674(6)	0.3497(3)	0.050(1)
C6	0.5618(4)	0.3468(6)	0.3438(3)	0.052(1)
C7	0.5426(4)	0.1604(6)	0.3607(3)	0.060(1)
C8	0.4133(4)	0.0685(7)	0.2807(3)	0.059(1)
C9	0.3019(4)	0.1669(7)	0.1833(3)	0.058(1)
C10	0.3207(4)	0.3530(7)	0.1663(4)	0.065(1)
C11	0.4504(4)	0.4435(7)	0.2457(3)	0.060(1)
C12	0.1460(6)	-0.1005(8)	0.1108(4)	0.082(1)
O6	0.6221(3)	1.1842(5)	0.0372(3)	0.084(1)

Table 3: Selected bond lengths (Å) and bond angles (°) in (1).H<sub>2</sub>O

	X-ray	AM1		X-ray	AM1
S1-N2	1.678(3)	1.660	S1-C6	1.748(4)	1.657
S1-O3	1.435(3)	1.424	S1-O4	1.429(3)	1.402
N2-C2	1.483(5)	1.461	N2-C5	1.377(5)	1.417
C1-O1	1.245(4)	1.248	C1-N1	1.319(5)	1.364

C2-C3	1.547(6)	1.552	C3-C4	1.514(6)	1.522
C4-C5	1.495(6)	1.517	C5-O2	1.219(5)	1.236
N2-S1-C6	105.1(2)	104.6	N2-S1-O3	103.8(2)	107.3
N2-S1-O4	107.5(2)	109.7	O3-S1-C6	109.7(2)	109.3
O3-S1-O4	120.3(2)	114.6	O4-S1-C6	109.4(2)	110.8
S1-N2-C2	122.3(2)	123.5	S1-N2-C5	124.1(2)	126.5
C2-N2-C5	113.6(3)	109.4	N2-C2-C3	102.5(3)	107.3
N2-C5-C4	108.8(3)	110.8	N2-C5-O2	124.1(3)	122.7
C2-C3-C4	106.5(3)	105.5	C3-C4-C5	105.4(3)	105.3
O1-C1-N1	124.5(4)	121.2	O1-C1-C2	120.8(4)	121.2

Table 4: Selected torsion angles (°) in (1).H<sub>2</sub>O

	X-ray	AM1		X-ray	AM1
O3-S1-N2-C2	-1.7 (3)	0.9	O4-S1-N2-C5	51.3(3)	46.2
S1-N2-C2-C1	-68.6(4)	-79.4	S1-N2-C5-O2	-1.8(5)	13.9
C2-N2-C5-C4	-1.6(4)	5.7	C3-C4-C5-N2	12.3(4)	2.8
N2-C2-C3-C4	16.4(4)	13.1	C2-C3-C4-C5	-17.8(4)	-9.5
C5-N2-C2-C3	-9.4(4)	-11.7	O1-C1-C2-N2	-43.5(5)	-99.0
N1-C1-C2-N2	140.5(4)	81.2	O1-C1-C2-C3	70.4(5)	20.3

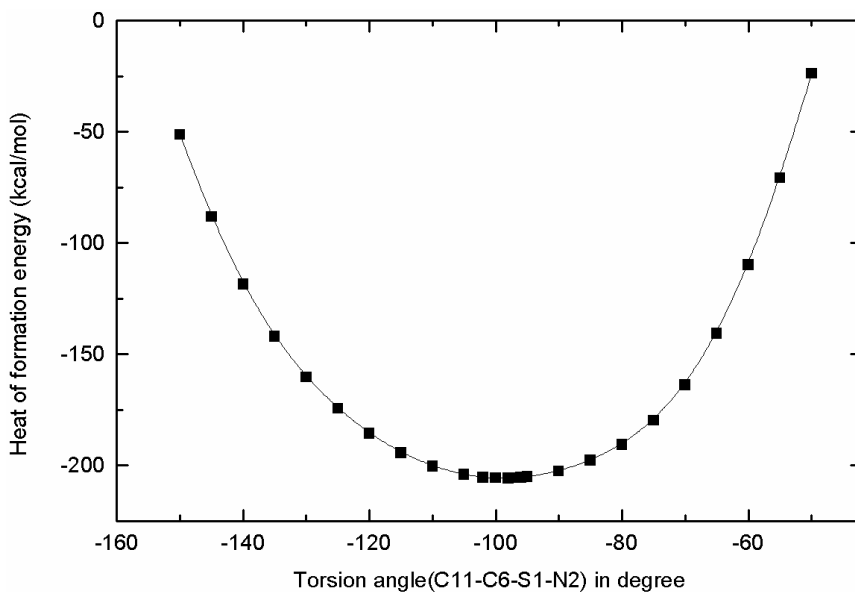


Fig. 3: Variation of heat of formation of energy (kcal/mol) against torsion angle (C11-C6-S1-N2) in degree

The semi-empirical AM1 molecular orbital calculations were carried out in order to define the conformational flexibility of the title molecule as a function of torsion angles  $\theta_1$ ,  $\theta_2$  and

$\theta_1$ ,  $\theta_2$  and  $\theta_3$  values obtained from the AM1 calculations are  $-101.5$ ,  $117.0$  and  $81.2^\circ$ , respectively, whereas the corresponding torsion angles in the X-ray structure are  $-89.3(4)$ ,  $113.5(3)$  and  $140.5(4)^\circ$ , respectively. The energy profiles as functions of  $\theta_1$  and  $\theta_2$  show minima at  $-98.0$  and  $120.0^\circ$ ; the corresponding heat of formation energy values are  $-205.7$  kcal/mol and  $-205.2$  kcal/mol, respectively. The bond distances and angles in the AM1 calculated structure are similar to the X-ray structure (Table 3). A comparison of the molecular conformations of the AM1 optimized structure (Fig. 2) and the X-ray structure shows a good agreement between the two except a rotation of the carboxamide group with respect to the C (oxo-pyrrolidine) - C (carboxamide) bond by  $\sim 60^\circ$ . The observed conformational difference is presumably due to strong inter-molecular hydrogen bonding (Table 5) involving the carboxamide N, O atoms and the lattice water molecules.

The molecular conformation and crystal packing in the title compound are influenced by different types of hydrogen bonds (Table 5). The lattice water molecule in (**1**) acts as a double donor of hydrogen bonds, with a carboxamide oxygen in each of two different molecules acting as acceptors. In the solid state, the molecules translated in the b-direction are linked through N1-H1A $\cdots$ O2 intermolecular hydrogen bonds to form infinite one-dimensional chain.

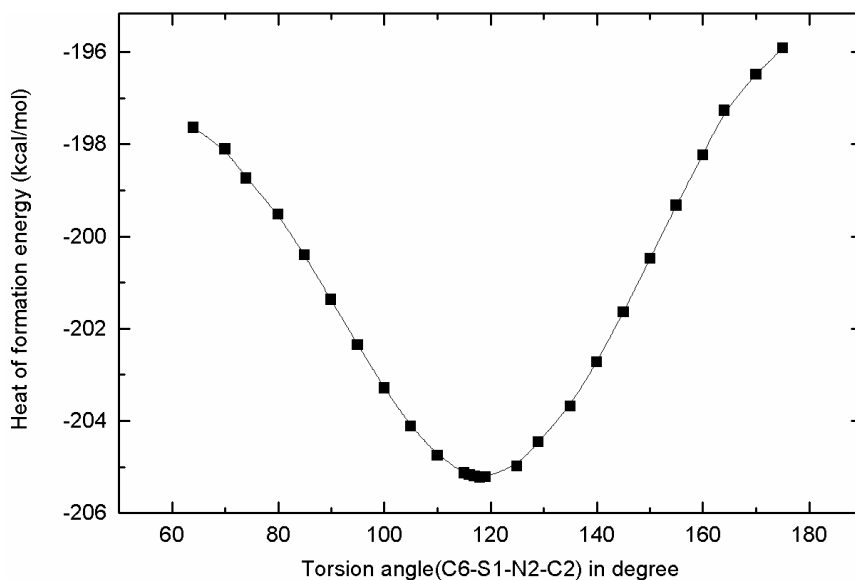


Fig. 4: Variation of heat of formation of energy (kcal/mol) against torsion angle (C6-S1-N2-C2) in degree

Table 5: Selected hydrogen bonds geometry ( $\text{\AA}$ ,  $^\circ$ )

D—H $\cdots$ A	D $\cdots$ A	D—H	H $\cdots$ A	D—H $\cdots$ A
N1—H1A $\cdots$ O2 <sup>i</sup>	2.881(5)	1.03	1.91	155.0
O6—H62 $\cdots$ O1 <sup>i</sup>	2.885(5)	0.89	2.06	155.8

O6—H63...O1 <sup>ii</sup>	2.836(4)	1.01	1.88	156.0
C2—H2...O2 <sup>iii</sup>	3.256(4)	0.96	2.56	129.3
C2—H2...O4 <sup>iii</sup>	3.423(5)	0.96	2.71	131.8
C3—H3B...O4 <sup>iii</sup>	3.334(5)	0.97	2.66	127.1
C4—H4A...O5 <sup>iv</sup>	3.413(6)	0.97	2.97	109.5

Symmetry codes: (i)  $x, y+1, z$ ; (ii)  $1-x, y+1/2, -z$ ; (iii)  $2-x, y+1/2, 1-z$ ; (iv)  $1+x, y, z$

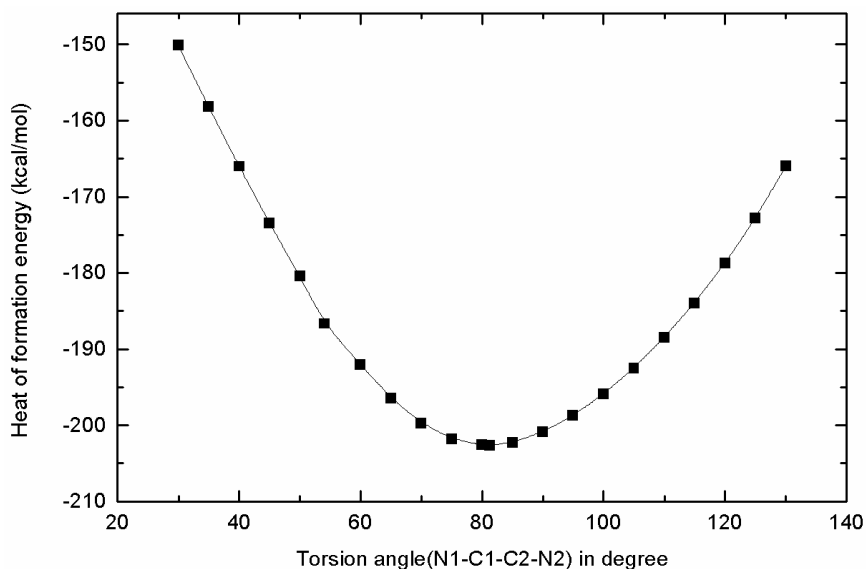


Fig. 5: Variation of heat of formation of energy (kcal/mol) against torsion angle (N1-C1-C2-N2) in degree

In summary, the semi-empirical AM1 calculations show a good agreement with the X-ray structure. The results strongly indicate that the intermolecular H-bonds between the lattice water molecule and the carboxamide group significantly contribute to the conformational energy of the title compound.

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