INTRODUCTION

The phenomenon of polymorphism is well known of solids with different arrangement of molecules or conformations in crystal lattice. Conformational polymorphism is commonly observed in flexible molecules mainly due to single bond rotation, ring inversion and inversion of lone pair of electrons about the sp³ hybridized nitrogen. This conformational flexibility introduces complications either by generating number of conformations or by reducing the tendency of crystallization [1].

Depending upon the environment, thioglycine, like other thioamino acids exist as zwitterionic form in crystal structure or in solution but molecular form in gas phase. Thioglycine acts as H₂S donor that uses endogenous molecules as carrier scaffolds of the active moiety and are, thus non-toxic. In contrast to the commonly used H₂S donor like NaHS, thioglycine liberate H₂S at a slow rate mimicking the sustained endogenous H₂S production [2]. Thioglycine exerts cardioprotective effects in Myocardial ischemia/reperfusion in vivo [3]. Thioglycine derivatives act as fungicides. The molecular form of thioglycine has higher conformational mobility due to rotation about intermolecular axes i.e. C-N, C-S and C-C. Thioglycine is the thiol acid analogue of glycine. A large number of studies in literature are available on glycine molecule but few studies on thioglycine has been reported [3-12]. The present study includes the conformational analysis of thioglycine molecule and insight into various factors responsible for stability of different conformations.

EXPERIMENTAL

Quantum chemical calculation: Quantum chemical calculations were performed by using the Gaussian 03 program [13]. Optimal geometries and harmonic vibrational frequencies of the considered structures have been obtained using MP2 and B3LYP methods with 6-31+G(d), 6-311++G(d,p) and aug-cc-pvtz basis set. The nature of the intramolecular hydrogen bond was studied using the atoms in molecules (AIM) theory of Bader by means of AIM2000 software [14]. In the AIM analysis, we have located the bond critical points (BCPs) and acquired detailed information on the relative strength of the hydrogen bond in terms of electron density (ρ) and Laplacian (∆²ρ). Natural bond orbital (NBO) analysis at the MP2/6-311++G(d,p) level was carried out to understand the orbital interactions and charge delocalization [15].
RESULTS AND DISCUSSION

Conformational properties: The conformational analysis of thioglycine has been carried at B3LYP/6-31+G*, B3LYP/6-311++G**, B3LYP/aug-cc-pVTZ, MP2/6-31+G*, MP2/6-311++G** and MP2/aug-cc-pVTZ theoretical level. The neutral thioglycine shows interesting conformational aspects, which are related to the presence of three internal rotational degrees of freedom.

Thioglycine molecule has three internal rotational degrees of freedom, $\phi$, $\psi$ and $\theta$, associated with the bonds C-N, C-C and C-S bonds, respectively, as shown in Fig. 1. This leads to eight rotamers of $C_s$ symmetry as shown in Fig. 2 denoted with roman numerals and the letter p to indicate planar heavy atom arrangements. Small torsional changes result into other minima in the potential energy surface as displayed in Fig. 2 denoted with the letter n to indicate nonplanar heavy-atom $C_1$ arrangements.

Relative energies of each conformer with respect to the most stable $I_p$ conformer at B3LYP/6-311++G**, B3LYP/aug-cc-pVTZ and MP2/6-311++G** theoretical level are summarized in Table-1. Hessian indices (i.e., the number of imaginary harmonic vibrational frequencies) obtained at B3LYP/6-311++G** and B3LYP/aug-cc-pVTZ theoretical levels are also indicated in Table-1. Conformer $I_p$ is found to be the global minimum for thioglycine at all the levels of theory employed in this research. In $I_p$ both NH$_2$ group and S-$H_6$ bond are cis to the carbonyl group. The results are consistent with glycine molecule, which has been reported earlier [3-12].

The discussion in the paper is at B3LYP/aug-cc-pVTZ theoretical level until and unless mentioned. Conformer $III_n$ is the second genuine local minimum in the potential energy surface where its $C_s$ counterpart $III_p$ is a saddle point. $V_n$ is the third true minimum with its $C_s$ counterpart $V_p$ a saddle point. Both $III$ and $V$ conformer differs from $I_p$ in orientation of NH$_2$ group where it is trans to carbonyl group. The third set includes $VI$ and $VIII$ conformations where S-$H$ bond is trans as compared to $I_p$ and fourth set consists of $II$ and $VII$ conformation where both NH$_2$ and S-$H$ are trans to carbonyl group. The energy difference of $III_n$ and its saddle point from the most stable $I_p$ conformer is only 0.36 kcal/mol whereas for the third conformer $V_n$ it is 0.50 kcal/mol. For the conformer $II_n$, $V_p$, $II_p$, $VIp$ the energy difference from the most stable conformation $I_p$ is only 0.69-0.97 kcal/mol but for the conformers $IV$, $VII$ and $VIII$ the energy difference from $I_p$ increases from 1.55 to 6.42 kcal/mol. For all the conformers the non-planar conformation is more stable than the planar one. This energy difference is almost similar in the pairs $III_n$ and $III_p$ (0.01 kcal/mol), $V_n$ and $Vp$ (0.20 kcal/mol) and $II_n$ and $II_p$.
(0.28 kcal/mol) but increases in the pairs IVn and IVp (2.85 kcal/mol) and VIIIn and VIIIp (4.69 kcal/mol). The stability order remains same (except for the VI and VIII where the order is interchanged) on inclusion of ZPE. An interesting fact that the energy order for planar and non-planar counterparts gets reversed by adding ZPE to the $\Delta E$ values (except for VIII and IV conformations).

With regard to MP2 dipole moments listed in Table-1, only three conformers display significantly larger values than the rest: IIn, IIp and VIIIp. The structure identified by all of the methods as the most stable conformer, Ip, happens to have the smallest dipole moment in all the conformational PES.

**Rotational barriers:** The rotational barriers for the interconversion of different conformations have been calculated at different theoretical levels. Fig. 3 displays the conversion of different conformations and Fig. 4 shows the energy profile diagram at B3LYP/6-311++G(d,p) theoretical level.

The energy difference between Ip and IIIp is quite small (0.3 kcal/mol). Therefore, the rotational barrier for the interconversion is also small (about 2.32 kcal/mol). Conversion of Ip to VIp is relatively difficult process. The estimated energy barrier for this process is 6.99 kcal/mol. The high barrier for Ip to VIp is associated with the breakage of the stable O5----H6-S4 intramolecular hydrogen bond. Similarly, the barrier for the conversion of IIIp to VIIp is estimated to be 9.65 kcal/mol, because the process involves again the breakage of O5----H6-S4 intramolecular hydrogen bond and formation of N3----H6-S4 hydrogen bond. The instability of VIIp as predicted in AIM analysis also indicates higher barrier. A low energy barrier of 0.53 kcal/mol is predicted for VIIp to VIp interconversion.

**Intramolecular hydrogen bonding:** The change in geometrical parameters plays an important role in predicting the strength of hydrogen bonding. Geometrical parameters listed in Table-2 shows that both in planar and non-planar conformations C-C bond distance increases (except IVn, Vp) whereas C-N and C-S decreases with few exceptions. The stability of the conformations has been assumed to be explained in terms of intramolecular H-bond. Four types of H-bond are
expected in thioglycine; (1) Bond $S_r-H_n-O_{ij}$ in all the conformers with $S_r-H_n$ bond $cis$ to carbonyl group, (2) Bond $S_r-H_n-N_i$ in $II_n, Ip$ and $VIIp$ conformations (3) Bifurcated H-bond between hydrogen of amino group and $O_k$ atom where amino group is $cis$ to carbonyl group, (4) Bifurcated H-bond between hydrogen of amino group and $S_i$ atom in $III_n$ and $IIP$ conformers.

Geometry of the thioglycine conformers has been optimized at different theoretical levels. The H-bond distance and the angle at the H-bonded hydrogen are reported in Table-3. The non-bonded distance between the O5 and H6 in $II_n, Ip$ and $IIP$ is less than 0.2 Å, which indicates the presence of H-bond but the angle is less than 90°. In conformations $II_n, Ip$ and $VIIp$ the non-bonded distance and the angle at H atom confirms the presence of H-bond between N3 and H6. The $N_iH_S_i$ bond angle is 119.6, 121.5 and 114.6 in $II_n, Ip$ and $VIIp$ conformations respectively. Since S-H bond is involved in H-bond, as expected the S-H bond distance in $II_n$ and $Ip$ is larger than all other conformers. But in $VIIp$ it is almost similar to other conformers.

Bifurcated H-bond between NH$_2$ hydrogens and O5 or S4 atom is predicted. But the bond distances does not indicate it to be a H-bond. In case of NH$_2$ group where bifurcated H-bond is there, N-H bond distance varies for all conformers. First set includes conformers where N-H bond distance is shorter $i.e.$ IVp (1.007 Å) and VIIIp (1.006 Å). Second set includes conformers VIIIn, IVn and VIp where N-H bond distance is largest. The third set includes the rest of the conformations where N-H bond distance is intermediate.

**AIM analysis:** AIM is a technique, which is useful in looking at the hydrogen bond and studies the bonding properties. It helps to understand that whether the bond is covalent or ionic. It is known that the electron density at the bond critical point (BCP-$r_b$) and its Laplacian $\nabla^2 r_b$ may be very useful parameter for estimation of relative strength of hydrogen bonding [16]. The property of the Laplacian of the electron density, which is used to determine regions of concentration and depletion of the electron charge density, forms a basis for the classification of the atomic interactions. The atomic interactions were classified in two general classes, shared interactions and closed-shell interactions. The shared interactions (as covalent and polar bonds) are caused by a contraction of the charge density towards the line of interaction linking the nuclei. For these interactions the electronic charge is concentrated in the internuclear region and $\nabla^2 r_b < 0$. The closed-shell interactions are governed by the contraction of the charge density towards each of interacting nuclei. In this case, the electronic charge is depleted in the interatomic surface and $\nabla^2 r_b > 0$ [17].
AIM analysis of thioglycine indicate that the BCP observed are those located at the interatomic paths defined by covalent bonds except for IIn, IIp and VIIp conformations. An additional BCP is observed for these three conformers. Fig. 5 shows the electron density map for the most stable Ip conformer. Fig. 5 also displays the map for IIn, IIp and VIIp conformers. Only in these three conformations we observe (i) an extra (3,-1) BCP between the N3 and H6 atoms and (ii) a (3, +1) RCP of five atoms formed by the bonds C1C2, C2N3, N3···H6, H6S4 and S4C2. In IIn and IIp conformations the N3···H6 bond distance is nearly same \(i.e.\) 2.148 Å and 2.115 Å respectively and the distance between N3···H6 BCP and RCP for the IIn and IIp conformer is 1.651 Å and 1.213 Å, respectively. But VIIp conformer displays a totally different situation. The N3···H6 bond distance in VIIp is 2.456 Å and the distance between N3···H6 BCP and RCP is only 0.788 Å. This close proximity between the BCP and RCP indicates the instability of the VIIp conformation of the molecule.

Tables 4 and 5 include electron density (\(\rho_b\)), its Laplacian \(\nabla^2 \rho_b\) and ellipticities (\(\varepsilon\)) for the different conformations of

Fig. 5. Contour map of the electron density for conformer in the plane containing the heavy atom and H6. Green spheres indicate the bond critical point and red spheres indicate ring critical points.
The natural bonding orbital analysis: The natural bonding orbital (NBO) analysis has been a reliable tool for the rationalization of H-bonds that correlate well with changes in bond density values for VIIp (0.015 a.u.) and thioglycine. The values of $\rho_\text{N-H}$, $\nabla^2\rho_{\text{p}}$ and topology of $N_{\text{H}}\ldots\text{H}_{\text{N}}$ BCP indicate the presence of H-bond. In fact $\rho_\text{N}$ values for N3-H6 bond in IIIp and IIp is 0.025 a.u. and 0.026 a.u. while $\nabla^2\rho_{\text{p}}$ is about 0.072 a.u. and 0.075 a.u., respectively in these conformers.

The values are near the upper limit (0.002-0.04 for electron density) which suggests moderate H-bond. The electron density values for VIIp (0.015 a.u.) and $\nabla^2\rho_\text{p}$ value of 0.043 a.u. altogether represent different situation from IIIp and IIp. The ellipticity value is 0.13 and 0.11 for IIIp and IIp conformers whereas comparatively higher i.e. 0.20 for VIIp conformer. Comparative higher value of ellipticity for VIIp indicates close proximity to a RCP and hence instability of $N_{\text{H}}\ldots\text{H}_{\text{N}}$ bond.

**Natural bonding orbital analysis:** The natural bonding orbital (NBO) analysis has been a reliable tool for the rationalization of H-bonds that correlate well with changes in bond density values for VIIp (0.015 a.u.) and $\nabla^2\rho_\text{p}$ value of 0.043.

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<th>$\rho$</th>
<th>$\nabla^2\rho_{\text{p}}$</th>
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**Table-4**

**Table-5**

The natural bonding orbital (NBO) analysis has been a reliable tool for the rationalization of H-bonds that correlate well with changes in bond density values for VIIp (0.015 a.u.) and $\nabla^2\rho_\text{p}$ value of 0.043.
length in accordance with the basic chemical concepts. It also used to derive information on the changes of charge densities in proton donor and acceptor as well as in the bonding and antibonding orbitals. Table-6 includes $E^{(2)}$ (kcal/mol) energies and occupancies for different conformations.

In conformations IIIn and IIp, the $E^{(2)}$ value for $n_N \rightarrow \pi^*_{S\text{-H}}$ delocalization is observed (6.66 kcal/mol and 5.52 kcal/mol respectively). The $E^{(2)}$ value for VIIp conformation is very low (i.e. only 1.28 kcal/mol). Higher value of $\sigma^*_{S\text{-H}}$ occupancies in IIIn (0.034) and IIp (0.031) conformations indicate comparatively stronger H-bond than VIIp (0.018) conformer.

Another important factor related to the strength of hydrogen bonds is the shifting of S-H stretching frequencies. It is well established that greater the shift in frequency higher will be the bond strength. To analyze the effect on hydrogen bond, a reference system is required. For this Ip conformation is taken where no N---H–S bond is there. Only IIp and IIIn conformation shows a shift of 97.79 cm$^{-1}$ and 84.75 cm$^{-1}$ for S-H bond.

Conclusion

Theoretical calculations are applied to conformational study of thioglycine and harmonic vibrational frequencies also calculated to confirm the nature of the stationary points found and to discuss the ZPVE correction. The analysis of 13 conformers at B3LYP/6-311++G** level of theory demonstrated that Ip is the most stable conformation for thioglycine molecule. These 13 conformers were calculated to lie within an energy range of 6 kcal/mol. The stability orders for the thioglycine conformers in gas phase are:

Ip > IIIn > IIIp > Vn > VIp ~ VIIIn > Vp ~ IIIn > IIp > IVn > VIIp > IVp > VIIIp

VIIIIP

It has been established that while the lowest-energy conformer of neutral thioglycine, Ip, has a planar equilibrium structure, the second lowest-energy conformer, IIIn, has a non-planar structure.

By analyzing the topology of the electron density in AIM, we have found unambiguous evidence on the existence of intramolecular hydrogen bonds in only three conformers. In addition to topological data, two of these conformers (IIp and IIIn) fulfill the criteria deduced by Popelier in the framework of AIM theory to identify hydrogen bonding. The third conformer (VIIp) fails to meet some of these criteria while it displays a very close proximity of critical points of (3,+1) and (3,−1) topology, which is known to indicate the unstability of the associated bond.

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**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interests regarding the publication of this article.

### REFERENCES


