Asian Journal of Chemistry; Vol. 30, No. 12 (2018), 2723-2730

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.21564

Conformational Analysis of Thioglycine Molecule: A Theoretical Study

RUPINDER PREET KAUR* and HARPREET SINGH

[1]Department of Chemistry, Guru Nanak Dev University College, Verka, Amritsar-143 501, India
[2]Department of Bioinformatics, Hans Raj Mahila Maha Vidayala, Jalandhar-144 008, India

*Corresponding author: E-mail: rupinder_chemverka@gndu.ac.in

Received: 6 July 2018; *Accepted*: 20 September 2018; *Published online*: 31 October 2018; AJC-19138

In the present work a conformational analysis of thioglycine was performed using DFT and MP2 computational methods at different basis sets. Harmonic vibrational frequencies were estimated at the same levels to confirm the nature of the stationary points found and also account for the zero point vibrational energy correction. The intramolecular hydrogen bonds established between the polar groups were identified by structural parameters, AIM analysis and NBO analysis. Conformer Ip is found to be the global minimum for thioglycine at all the levels of theory employed in this research. In Ip both NH_2 group and S_5-H_6 bond are *cis* to the carbonyl group. Rotation barriers for the interconversion of various conformers were also calculated.

Keywords: Thioglycine, Conformations, Hydrogen bonding, AIM analysis, Bond critical point.

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 sp^3 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 H_2S donor that uses endogenous molecules as carrier scaffolds of the active moiety and are, thus non-toxic. In contrast to the commonly used H_2S donor like NaHS, thioglycine liberate H_2S at a slow rate mimicking the sustained endogenous H_2S 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 ($\Delta^2\rho$). 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, ϕ, ψ and θ, 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 results into other minima in the potential energy surface as displayed in Fig. 2 denoted with the letter n to denote nonplanar heavy-atom C_1 arrangements.

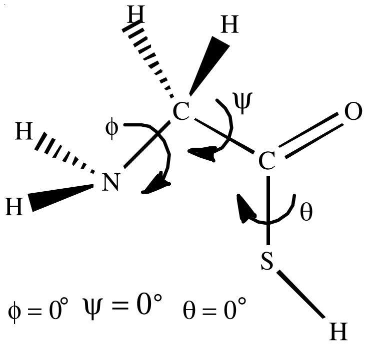


Fig. 1. Internal rotational degrees of freedom for thioglycine

Relative energies of each conformer with respect to the most stable Ip 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 Ip is found to be the global minimum for thioglycine at all the levels of theory employed in this research. In Ip both NH_2 group and S_5-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 IIIn is the second genuine local minimum in the potential energy surface where its Cs counterpart IIIp is a saddle point. Vn is the third true minimum with its Cs counterpart Vp a saddle point. Both III and V conformer differs from Ip 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 Ip 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 IIIn and its saddle point from the most stable Ip conformer is only 0.36 kcal/mol whereas for the third conformer Vn it is 0.50 kcal/mol. For the conformer IIn, Vp, IIp, VIp the energy difference from the most stable conformation Ip is only 0.69-0.97 kcal/mol but for the conformers IV, VII and VIII the energy difference from Ip 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 IIIn and IIIp (0.01 kcal/mol), Vn and Vp (0.20 kcal/mol) and IIn and IIp

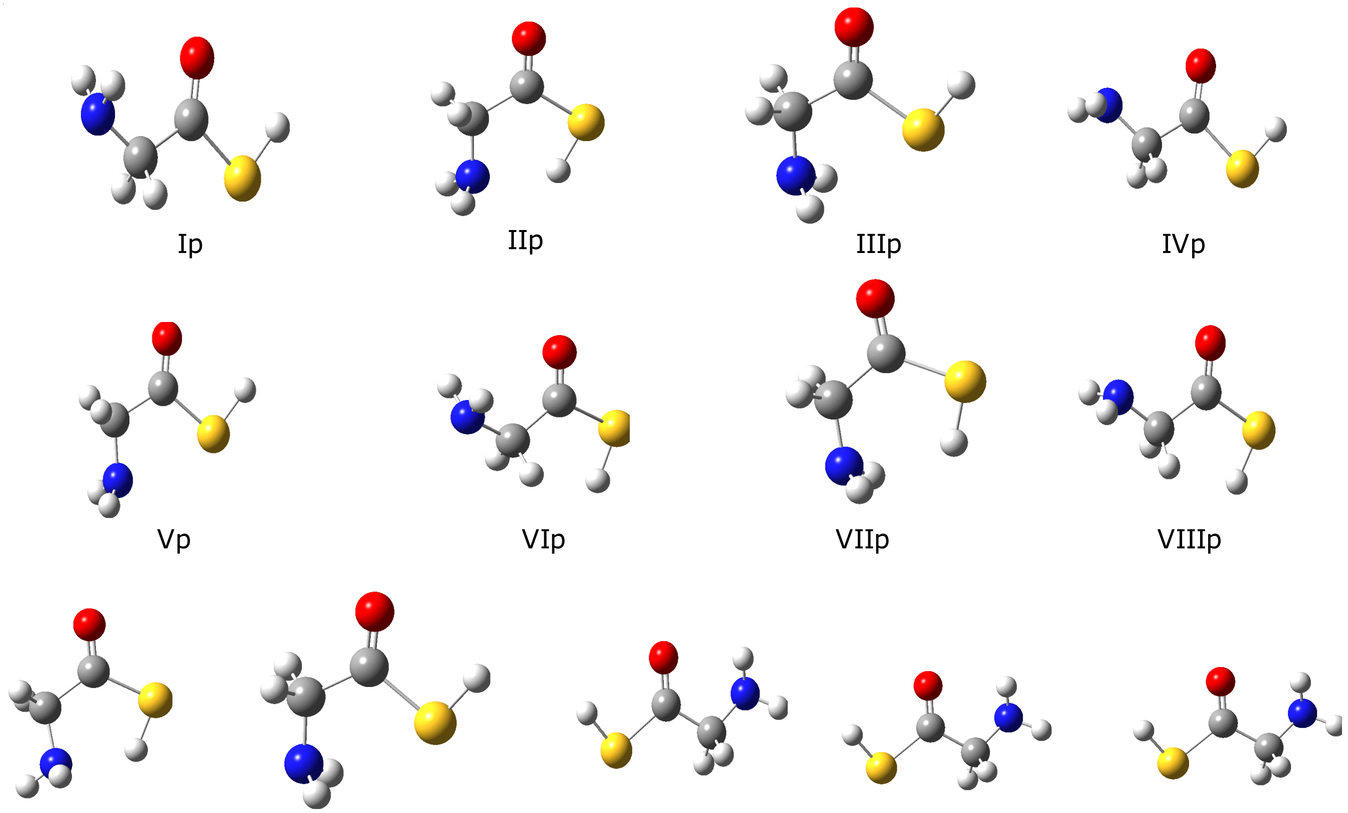

Ip IIp IIIp IVp
Vp VIp VIIp VIIIp
IIn IIIn IVn Vn VIIIn

Fig. 2. Conformers of thioglycine found at B3LYP/aug-cc-pVTZ theore-tical level

TABLE-1
RELATIVE ENERGIES OF THIOGLYCINE CONFORMERS OBTAINED AT DIFFERENT THEORETICAL LEVELS

Conformer/state/ symmetry	B3LYP/6-31+G*	B3LYP/6-311++G**	B3LYP/aug-cc-pVTZ	MP2/6-31+G*	MP2/6-311++G**	
	ΔE (Hessian Index)	ΔE (Hessian Index)	ΔE (Hessian Index)	ΔE	ΔE	Dipole moment (D)
Ip (1-A') Cs	0.0	0.0 (0)	0.0 (0)	0.0	0.0	1.1153
IIp (1-A') Cs	0.82	0.67 (1)	0.97 (1)	1.03	0.92	5.2665
IIIp (1-A') Cs	0.33	0.36 (0)	0.37 (0)	0.40	0.54	1.9163
IVp (1-A') Cs	5.13	4.54 (2)	4.40 (2)	5.42	4.91	3.3511
Vp (1-A') Cs	0.79	0.56 (0)	0.70(1)	1.01	0.94	3.2767
VIp (1-A') Cs	1.20	1.04 (0)	0.56 (0)	1.73	1.09	2.6702
VIIp (1-A') Cs	3.69	3.40 (0)	2.91 (0)	4.62	4.06	3.7186
VIIIp (1-A') Cs	6.74	5.96 (1)	5.25 (1)	7.60	6.42	5.2601
IIn (1-A) C1	0.51	0.42 (0)	0.69 (0)	0.45	0.36	4.9074
IIIn (1-A) C1	0.32	0.36 (0)	0.36 (0)	0.39	0.54	1.9232
IVn (1-A) C1	2.01	1.78 (0)	1.55 (0)	1.53	1.37	2.5739
Vn (1-A) C1		1.04 (0)	0.50 (0)	0.04	0.20	3.0545
VIIIn (1-A) C1	3.78	1.04 (0)	0.56 (0)	1.73	1.09	2.6719

(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 ΔE 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.

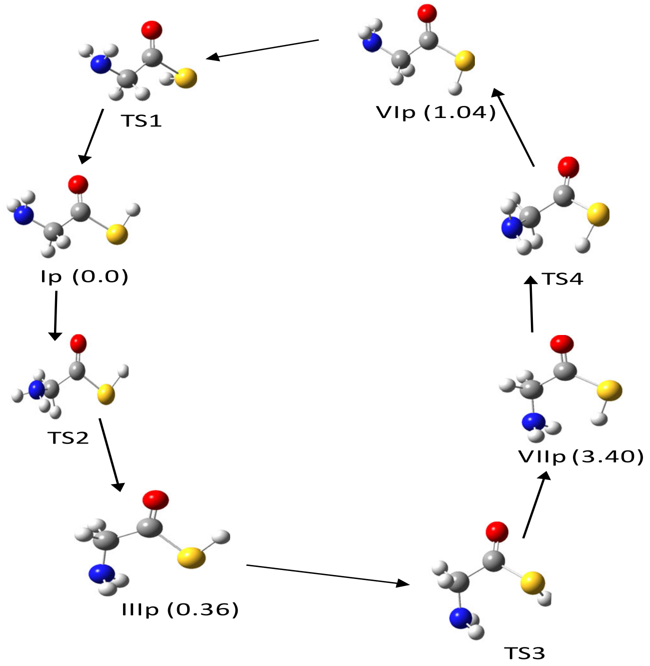


Fig. 3. Rotational barrier for interconversion of different conformations of thioglycine at B3LYP/6-311++G(d,p) level

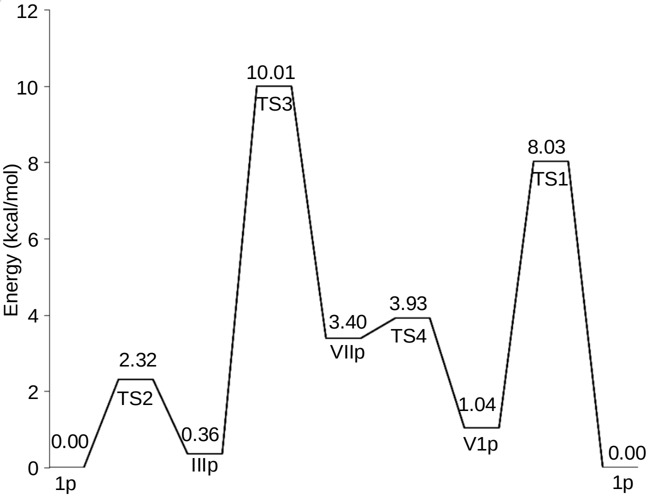


Fig. 4. Energy profile (kcal/mol) for the interconversion of conformations at B3LYP/6-311++G(d,p) level of theory

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

TABLE-2
GEOMETRICAL PARAMETERS OF DIFFERENT CONFORMATIONS OF THIOGLYCINE AT B3LYP/aug-cc-pVTZ THEORETICAL LEVEL

		Ip	IIp	IIn	IIIp	IIIn	IVp	IVn	Vp	Vn	VIp	VIIp	VIIIp	VIIIn
C1-C2	R1	1.532	1.542	1.536	1.533	1.533	1.535	1.517	1.529	1.526	1.535	1.544	1.540	1.536
N3-C2	R2	1.444	1.454	1.454	1.443	1.443	1.442	1.452	1.450	1.450	1.443	1.439	1.440	1.443
S4-C1	R3	1.819	1.789	1.792	1.821	1.821	1.831	1.807	1.808	1.808	1.813	1.807	1.823	1.813
O5-C1	R4	1.199	1.203	1.203	1.198	1.198	1.193	1.200	1.200	1.201	1.199	1.200	1.193	1.199
H6-S4	R5	1.345	1.353	1.352	1.345	1.346	1.344	1.345	1.348	1.348	1.346	1.345	1.346	1.346
H7-C2	R6	1.093	1.091	1.094	1.092	1.092	1.094	1.093	1.092	1.092	1.093	1.092	1.093	1.093
H8-C2	R7	1.093	1.091	1.092	1.092	1.092	1.094	1.101	1.092	1.095	1.093	1.092	1.093	1.093
N3-H9	R8	1.012	1.009	1.011	1.010	1.010	1.007	1.013	1.008	1.009	1.012	1.009	1.006	1.012
N3-H10	R9	1.012	1.009	1.010	1.010	1.010	1.007	1.010	1.008	1.010	1.012	1.009	1.006	1.012
N3-C2-C1	A1	115.9	116.8	115.7	119.2	119.2	113.5	110.6	113.7	113.2	115.6	122.3	113.2	115.6
S4-C1-C2	A2	112.7	118.4	118.1	113.8	113.8	111.0	113.0	113.5	113.7	116.6	120.3	115.1	116.6
O5-C1-C2	A3	124.4	119.9	120.6	123.1	123.1	126.3	123.7	122.6	122.7	123.9	120.5	125.7	123.9
H6-S4-C1	A4	94.1	93.2	93.8	92.9	92.9	93.7	94.2	91.8	92.0	97.0	97.2	97.5	97.04
H7-C2-C1	A5	107.5	104.7	105.0	105.7	105.7	106.3	109.1	105.8	105.5	107.5	104.4	106.5	107.5
H8-C2-C1	A6	107.4	104.7	105.0	105.7	105.7	106.3	105.1	105.8	106.2	107.5	104.4	106.5	107.5
H9-N3-C2	A7	111.0	112.9	112.1	113.3	113.3	113.8	110.3	113.6	112.5	111.0	114.4	114.2	111.0
H10-N3-C2	A8	111.0	112.9	111.8	113.3	113.3	113.8	111.5	113.6	112.7	111.0	114.4	114.2	111.0
N3-C2-C1-S4	D1	180.0	0.0	19.5	0.0	0.1	180.0	158.8	0.0	-13.4	180.0	0.0	180.0	180.2
N3-C2-C1-O5	D2	0.0	180.0	-162.6	180.0	180.1	0.0	-22.9	180.0	-192.4	0.0	180.0	0.00	0.2
H6-S4-C1-C2	D3	180.0	0.0	-3.2	180.0	180.0	180.0	173.6	180.0	181.6	0.0	0.0	0.00	-0.0
H7-C2-C1-S4	D4	56.8	124.2	147.0	124.0	123.9	56.1	37.0	123.8	106.0	57.0	124.6	56.3	57.2
H7-C2-C1-S4	D5	-56.8	-124.2	-100.6	-124.0	-124.1	-56.1	-76.8	-123.8	-141.1	-57.0	-124.6	-56.3	-56.8
H9-N3-C2-C1	D6	59.2	118.2	85.9	-62.6	62.7	116.5	37.2	-117.1	149.6	59.2	64.6	115.8	-59.2
H10-N3-C2-C1	D7	-59.2	-118.2	-152.5	62.6	-62.6	-116.5	158.1	117.1	-87.10	-59.2	-64.6	-115.8	59.1

expected in thioglycine: (1) Bond $S_4–H_6 \cdots O_5$ in all the conformers with S_4-H_6 bond *cis* to carbonyl group, (2) Bond $S_4–H_6 \cdots N_3$ in IIn, IIp and VIIp conformations (3) Bifurcated H-bond between hydrogen of amino group and O_5 atom where amino group is *cis* to carbonyl group, (4) Bifurcated H-bond between hydrogen of amino group and S_4 atom in IIIn and IIIp 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 IIIn, IIIp, Ip, IVn, IVp, Vp and Vn is less than 2.72 Å, which indicates the presence of H-bond but the angle is less than 90°. In conformations IIn, IIp and VIIp the non-bonded distance and the angle at H atom confirms the presence of H-bond between N3 and H6. The $N_3H_6S_4$ bond angle is 119.6, 121.5 and 114.6 in IIn, IIp and VIIp conformations respectively. Since S-H bond is involved in H-bond, as expected the S-H bond distance in IIn and IIp conformation is larger than all other conformers. But in VIIp it is almost similar to other conformers.

TABLE-3
HYDROGEN BOND DISTANCES (Å) AND ANGLE AT HYDROGEN IN DIFFERENT THIOGLYCINE CONFORMERS OBTAINED AT B3LYP/aug-cc-pVTZ THEORETICAL LEVEL

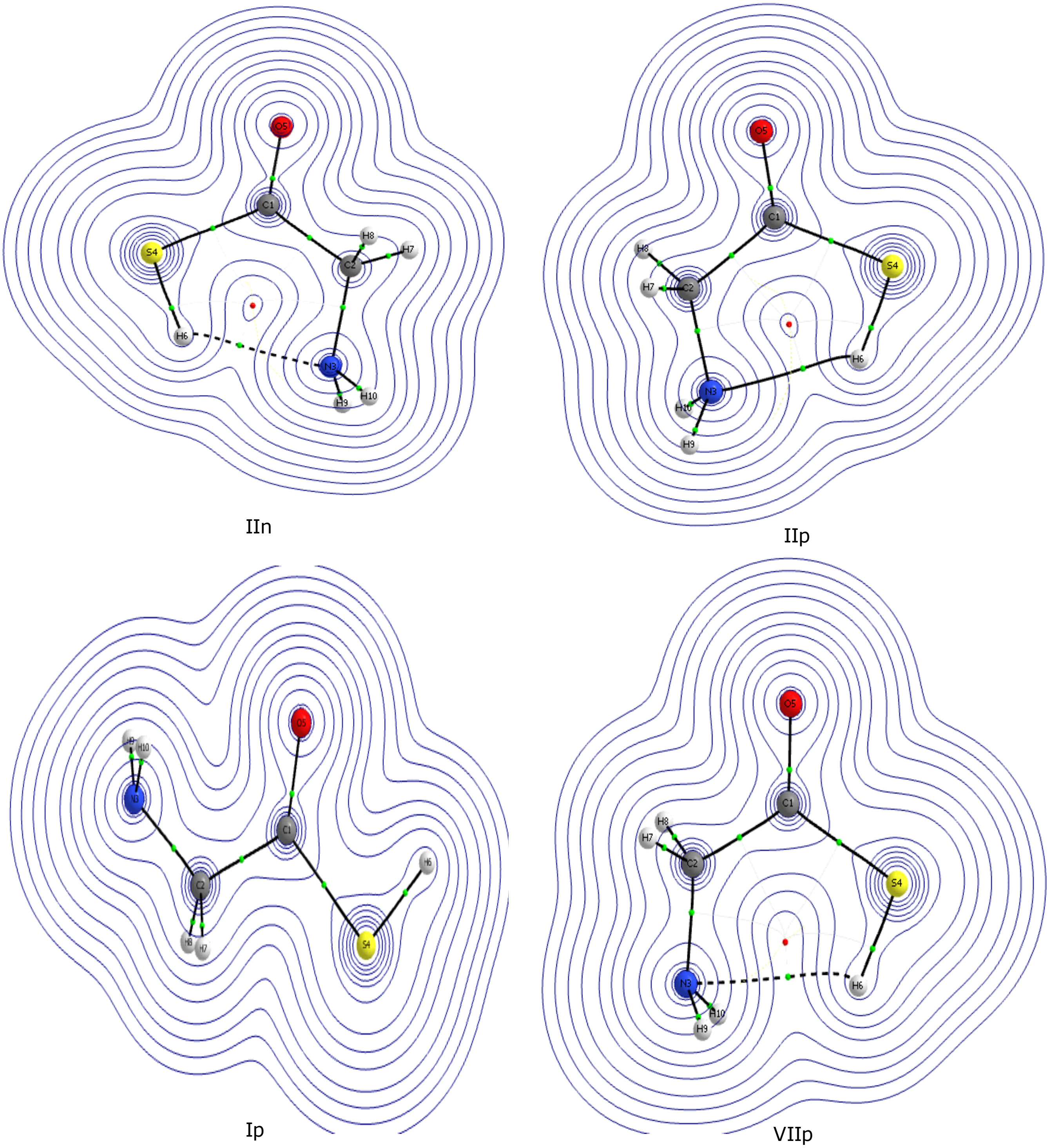
Conformer	$O_5 \cdots H_6–S_4$	$\angle O_5 \cdots H_6–S_4$	$N_3 \cdots H_6–S_4$	$\angle N_3 \cdots H_6–S_4$
Ip	2.580	78.8	–	–
IIp	–	–	2.115	121.5
IIIp	2.565	79.6	–	–
IVp	2.583	80.0	–	–
Vp	2.543	80.4	–	–
VIp	–	–	–	–
VIIp	–	–	2.456	114.6
VIIIp	–	–	–	–
IIn	–	–	2.148	119.6
IIIn	2.565	79.6	–	–
IVn	2.585	78.4	–	–
Vn	2.543	80.0	–	–
VIIIn	–	–	–	–

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 $\nabla^2\rho_b$ 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 $\nabla^2\rho_b < 0$. 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 $\nabla^2\rho_b > 0$ [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 C_1C_2, C_2N_3, $N_3 \cdots H_6$, H_6S_4 and S_4C_2. In IIn and IIp conformations the $N_3 \cdots H_6$ bond distance is nearly same *i.e.* 2.148 Å and 2.115 Å respectively and the distance between $N_3 \cdots H_6$ 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 $N_3 \cdots H_6$ bond distance in VIIp is 2.456 Å and the distance between $N_3 \cdots H_6$ 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 (ρ_b), its Laplacian $\nabla^2\rho_b$ and ellipticities (ε) for the different conformations of



IIn

IIp

Ip

VIIp

Fig. 5. Contour map of the electron density for conformer in the plane containing the heavy atom and H_6. Green spheres indicate the bond critical point and red spheres indicate ring critical points

TABLE-4
ELECTRON DENSITIES (ρ), LAPLACIAN OF ELECTRON DENSITIES ($\nabla^2\rho$) AND BOND ELLIPTICITIES (ε) FOR ALL THE BONDS FOR DIFFERENT CONFORMATIONS

Bond	ρ	$\nabla^2\rho$	ε	ρ	$\nabla^2\rho$	ε	ρ	$\nabla^2\rho$	ε	ρ	$\nabla^2\rho$	ε
	Ip			IIp			IIIp			IVp		
C1-C2	0.245	-0.554	0.081	0.240	-0.529	0.089	0.244	-0.551	0.088	0.243	-0.552	0.093
C2-N3	0.275	-0.734	0.041	0.266	-0.704	0.043	0.273	-0.737	0.037	0.274	-0.741	0.060
C1-S4	0.178	-0.249	0.195	0.188	-0.288	0.208	0.177	-0.241	0.202	0.174	-0.229	0.190
C1-O5	0.417	-0.001	0.040	0.416	-0.061	0.052	0.419	-0.010	0.043	0.423	0.050	0.045
S4-H6	0.215	-0.629	0.087	0.214	-0.608	0.076	0.215	-0.631	0.080	0.215	-0.628	0.087
C2-H7	0.277	-0.934	0.034	0.278	-0.937	0.032	0.278	-0.940	0.035	0.276	-0.925	0.031
C2-H8	0.277	-0.934	0.034	0.278	-0.937	0.032	0.278	-0.940	0.035	0.276	-0.925	0.031
N3-H9	0.338	-1.518	0.049	0.339	-1.544	0.053	0.339	-1.532	0.055	0.341	-1.552	0.061
N3-H10	0.338	-1.518	0.049	0.339	-1.544	0.053	0.339	-1.532	0.055	0.341	-1.552	0.061
N3-H6				0.026	0.075	0.108						
RCP				0.018	0.094	-0.004						
	Vp			VIp			VIIp			VIIIp		
C1-C2	0.247	-0.572	0.090	0.242	-0.540	0.078	0.236	-0.511	0.090	0.240	-0.535	0.090
C2-N3	0.269	-0.721	0.051	0.276	-0.740	0.042	0.273	-0.743	0.035	0.276	-0.750	0.063
C1-S4	0.182	-0.265	0.220	0.180	-0.256	0.199	0.181	-0.256	0.201	0.176	-0.238	0.194
C1-O5	0.416	-0.034	0.044	0.419	-0.010	0.048	0.418	-0.035	0.051	0.424	0.038	0.052
S4-H6	0.215	-0.628	0.083	0.214	-0.620	0.098	0.215	-0.622	0.093	0.213	-0.613	0.098
C2-H7	0.277	-0.931	0.031	0.277	-0.934	0.033	0.278	-0.943	0.035	0.276	-0.925	0.031
C2-H8	0.277	-0.931	0.031	0.277	-0.934	0.033	0.278	-0.943	0.035	0.276	-0.925	0.031
N3-H9	0.340	-1.548	0.056	0.338	-1.521	0.048	0.339	-1.535	0.059	0.341	-1.558	0.062
N3-H10	0.340	-1.548	0.056	0.338	-1.521	0.048	0.339	-1.535	0.059	0.341	-1.558	0.062
							0.015	0.043	0.199			
RCP							0.013	0.056	-0.002			

TABLE-5
ELECTRON DENSITIES (ρ), LAPLACIAN OF ELECTRON DENSITIES ($\nabla^2\rho$) AND BOND ELLIPTICITIES (ε) FOR ALL THE BONDS FOR DIFFERENT CONFORMATIONS

Bond	ρ	$\nabla^2\rho$	ε	ρ	$\nabla^2\rho$	ε	ρ	$\nabla^2\rho$	ε
	IIn			IIIn			IVn		
C1-C2	0.242	-0.540	0.082	0.244	-0.550	0.088	0.252	-0.599	0.069
C2-N3	0.266	-0.702	0.037	0.273	-0.737	0.037	0.271	-0.710	0.060
C1-S4	0.187	-0.286	0.209	0.177	-0.241	0.202	0.338	-1.507	0.050
C1-O5	0.416	-0.057	0.055	0.419	-0.009	0.043	0.183	-0.269	0.206
S4-H6	0.214	-0.612	0.077	0.215	-0.631	0.080	0.417	-0.015	0.046
C2-H7	0.278	-0.933	0.033	0.278	-0.940	0.035	0.215	-0.631	0.088
C2-H8	0.277	-0.937	0.027	0.278	-0.939	0.035	0.279	-0.946	0.030
N3-H9	0.338	-1.523	0.049	0.339	-1.532	0.055	0.271	-0.886	0.028
N3-H10	0.338	-1.531	0.052	0.339	-1.532	0.055	0.337	-1.542	0.050
N3-H6	0.025	0.072	0.131						
RCP	0.018	0.091	-0.004						
	Vn			VIIIn					
C1-C2	0.248	-0.578	0.087	0.242	-0.540	0.078			
C2-N3	0.270	-0.719	0.043	0.276	-0.738	0.042			
C1-S4	0.182	-0.265	0.219	0.180	-0.256	0.199			
C1-O5	0.416	-0.034	0.046	0.419	-0.012	0.048			
S4-H6	0.215	-0.628	0.083	0.213	-0.618	0.098			
C2-H7	0.277	-0.934	0.027	0.277	-0.935	0.033			
C2-H8	0.277	-0.924	0.033	0.277	-0.935	0.033			
N3-H9	0.339	-1.538	0.055	0.338	-1.520	0.048			
N3-H10	0.339	-1.532	0.052	0.338	-1.520	0.048			

thioglycine. The values of ρ_b, $\nabla^2\rho_b$ and topology of $N_3 \cdots H_6$ BCP indicate the presence of H-bond. In fact ρ_b values for N3-H6 bond in IIn and IIp is 0.025 a.u. and 0.026 a.u. while $\nabla^2\rho_b$ 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 $\nabla^2\rho_b$ value of 0.043 a.u. altogether represent different situation from IIn and IIp. The ellipticity value is 0.13 and 0.11 for IIn 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 $N_3 \cdots H_6$ 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

TABLE-6
$E^{(2)}$ (kcal/mol) ENERGIES FOR DIFFERENT DELOCALIZATIONS AND LONE PAIR OCCUPANCIES OF S-H BOND

Conformation	$N_{N3} \rightarrow \pi^*_{C1-C2}$	$N_{N3} \rightarrow \pi^*_{C2-H7}$	$N_{N3} \rightarrow \pi^*_{C2-H8}$	$N_{N3} \rightarrow \pi^*_{S4-H6}$	Occupancy of S-H bond
Ip	–	–	–		0.0038
IIp	6.27	–	–	6.66	0.0340
IIn	–	5.58	–	5.52	0.0306
IIIp	10.78	–	–		0.0111
IIIn	10.77	–	–		0.0111
IVp	6.99	1.99	1.99		0.0036
IVn	–	3.50	7.73		0.0049
Vp	6.88	–	–		0.0160
Vn	–	–	6.14		0.0149
VIp	9.65	–	–		0.0078
VIIp	11.94	–	–	1.28	0.0184
VIIIp	7.37	2.03	2.03		0.0086
VIIIn	9.62	–	–		0.0079

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 IIn and IIp, the $E^{(2)}$ value for $n_N \rightarrow \sigma^*_{S-H}$ 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 σ^*_{S-H} occupancies in IIn (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 IIn 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:

$$\text{Ip} > \text{IIIn} > \text{IIIp} > \text{Vn} > \text{VIp} \sim \text{VIIIn} > \text{Vp} \sim \text{IIn} > \text{IIp} > \text{IVn} > \text{VIIp} > \text{IVp} > \text{VIIIp}$$

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 unambigous evidence on the existence of intramolecular hydrogen bonds in only three conformers. In addition to topological data, two of these conformers (IIp and IIn) 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.

ACKNOWLEDGEMENTS

The authors are grateful to Guru Nanak Dev University, Amritsar for providing the necessary facilities and support to carry out the research.

CONFLICT OF INTEREST

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

REFERENCES

1. L. Yu, S.M. Reutzel-Edens and C.A. Mitchell, *Org. Proc. Res. Dev.*, **4**, 396 (2000); https://doi.org/10.1021/op000028v.
2. Z. Zhou, M. von Wantoch Rekowski, C. Coletta, C. Szabo, M. Bucci, G. Cirino, S. Topouzis, A. Papapetropoulos and A. Giannis, *Bioorg. Med. Chem.*, **20**, 2675 (2012); https://doi.org/10.1016/j.bmc.2012.02.028.
3. C. Coletta, S.I. Bibli, Z. Zhou, A. Chatzianastasiou, A. Giannis, E.K. Iliodromiti, I. Andreadou, C. Szabo and A. Papapetropoulos, Slow Releasing H_2S Donor-Thioglycine Exerts Cardioprotective Effects in Myocardial Ischemia/Reperfusion *in vivo*. Proceedings of British Pharmacological Society, vol. 11, No. 3, 090P (1962).
4. L.E. Pacios and P.C. Gomez, *J. Comput. Chem.*, **22**, 702 (2001); https://doi.org/10.1002/jcc.1038.
5. L.F. Pacios, O. Gálvez and P.C. Gómez, *J. Phys. Chem. A*, **105**, 5232 (2001); https://doi.org/10.1021/jp004128e.
6. R.M. Balabin, *Chem. Phys. Lett.*, **479**, 195 (2009); https://doi.org/10.1016/j.cplett.2009.08.038.
7. S. Millefiori and A. Millefiori, *J. Mol. Struct. THEOCHEM*, **91**, 391 (1983); https://doi.org/10.1016/0166-1280(83)80083-9.
8. C.H. Hu, M. Shen and H.F. Schaefer, *J. Am. Chem. Soc.*, **115**, 2923 (1993); https://doi.org/10.1021/ja00060a046.
9. J.H. Jensen and M.S. Gordon, *J. Am. Chem. Soc.*, **113**, 7917 (1991); https://doi.org/10.1021/ja00021a015.
10. V. Kasalova, W.D. Allen, H.F. Schaefer, E. Czinki and A.G. Csaszar, *J. Comput. Chem.*, **28**, 1373 (2007); https://doi.org/10.1002/jcc.20680.
11. A.G. Csaszar, *J. Am. Chem. Soc.*, **114**, 9568 (1992); https://doi.org/10.1021/ja00050a041.
12. H.W. Ke, L. Rao and Y.J. Yan, *J. Theor. Comput. Chem.*, **7**, 889 (2008); https://doi.org/10.1142/S0219633608004192.
13. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant,

J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez and J.A. Pople, Gaussian, Inc., Wallingford CT (2004).

14. F.W. Biegler-könig, R.F.W. Bader and T.-H. Tang, *J. Comput. Chem.*, **3**, 317 (1982); https://doi.org/10.1002/jcc.540030306.
15. D.E. Glendening, A.E. Reed, J.E. Carpenter and F. Weinhold, NBO, Version 3.1.
16. E. Espinosa, M. Souhassou, H. Lachekar and C. Lecomte, *Acta Cryst.*, **B55**, 563 (1999); https://doi.org/10.1107/S0108768199002128.
17. R.F.W. Bader, Atoms in Molecule: A Quantum Theory, Oxford University Press: New York (1990).