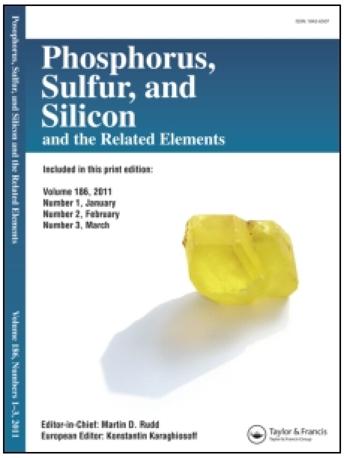

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CONFORMATIONAL ISOMERISM IN GLYCINE AND DITHIOGLYCINE: A COMPARATIVE MOLECULAR ORBITAL STUDY

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CONFORMATIONAL ISOMERISM IN GLYCINE AND DITHIOGLYCINE: A COMPARATIVE MOLECULAR ORBITAL STUDY

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The conformational potential energy surfaces (PES) of the neutral forms of glycine and its sulphur analogue dithioglycine ($NH_2CH_2C({=}S)SH$) were studied by using *ab initio* (SCF-HF/6-31G*) and semiempirical (AM1, PM3) molecular orbital calculations. Fully optimized molecular geometries, electric dipole moments and atomic charges were calculated for the different conformers with the various methods used. The conformational dependence of some relevant structural parameters was used to characterise the most important intramolecular interactions present in the molecules studied. In both cases, all methods predicted the planar conformer with both X═C-X-H and N-C-C═X dihedral angles equal to 0° and a Lp-N-C-C dihedral angle of 180° (X = O or S and Lp = lone pair) as the most stable form. However, important differences were found between the conformational behavior of the two molecules studied, which could be explained in terms of both the different sizes and electronic properties of the oxygen and sulphur substituents and the relative strength of the various possible intramolecular interactions.

Keywords: glycine; dithioglycine; conformational isomerism; molecular orbital study

1. INTRODUCTION

Although amino acids are of greater importance as the basic building blocks of proteins, their role as simple structural units of important biological systems is sometimes overemphasized relatively to some other aspects. In fact, often simple amino acids also play a decisive dynamical role in fundamental bio-

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chemical processes occuring in living systems. For instance, they may participate directly in enzyme catalysis as functional elements[1-3] or act as information carrier molecules, such as, for example, glycine or γ-aminobutyric acid (GABA) in the neuro-transmission processes occuring in the mammalian nervous system[4,5].

In addition to their biochemical interest, simple amino acids present very interesting structural and conformational properties, which also make them a challenge to fundamental chemical investigation. In both the crystalline state and aqueous solution, these molecules are known to exist as zwitterions, and these species have been extensively studied in the past, in particular in the case of the simplest amino acids (*e.g.*, glycine[6-12], α-alanine[13-17], proline[18-20]). On the other hand, both in the gas phase and isolated in low temperature noble gas matrices, amino acids are present in their neutral forms[21-31]. Although the most biochemically relevant species correspond to the zwitterionic species, the study of the neutral molecules has attracted an ever growing attention in the last few years, since its great importance is recognized for identification of interstellar amino acids, which may provide insights into the formation of large molecules in space and thus into the search for the origin and signs of life in the cool interstellar space[32].

Furthermore, contrary to their oxygen containing parent molecules, the sulphur analogues of simple amino acids have not deserved much attention in the past. Nevertheless, these molecules have also proved to be very interesting systems both from fundamental and biochemically oriented perspectives[1-3,33]. For example, dithio substituted derivatives of amino acids constitute very convenient resonance Raman spectroscopic probes for accessing the structural and mechanistic details of several biochemically important reactions catalysed by cystein proteases (*e.g.*, papain)[1-3]. To the great success already achieved by the spectroscopic studies carried out on this subject (a very interesting review on this topic may be found in[34]), much has contributed the series of extensive experimental and, in particular, theoretical studies on simple model compounds undertaken in our laboratories[35-40]. However, it is apparent that additional detailed information on the structures of the possible conformers of these molecules (especially the simplest ones such as dithioglycine) and their conformationally dependent properties are still required to further the understanding of the relevant biochemical processes[34]. Thus, in this work, the structure and molecular properties of the neutral form of dithioglycine ($NH_2CH_2C(=S)SH$) were studied using quantum chemical theoretical methods, and the results compared with those obtained for glycine. The calculations were carried out at both noncorrelated Hartree-Fock 6-31G* *ab initio* (HF/6-31G*) and semiempirical (AM1, PM3) levels, since it is fundamental to evaluate the relative performance of the much less expensive semiempirical calculations when compared to the higher level *ab initio* molecular orbital calculations. Besides, the appreciable size of the most interesting systems to be studied in the future will indeed prevent *a priori* the use of higher level correlated *ab initio* methods. As far as the studied molecules are concerned, fully optimized molecular geometries, electric dipole moments and atomic charges were calculated for the different conformers with the various methods used, and the conformational dependence of some relevant structural parameters was used to characterise the most important intramolecular interactions displayed by these species. A particular emphasis is given to the analysis of the effects of substituting sulphur for oxygen on the molecular properties.

2. COMPUTATIONAL METHODS

The *ab initio* HF/6-31G*[41] molecular orbital calculations were performed using the GAUSSIAN92 program package[42] running on a DEC ALPHA 7000 computer. Molecular geometries were fully optimized by the force gradient method using Berny's algorithm[43], the largest residual coordinate forces always being less than 3×10^{-4} hartree bohr^{-1} (1 hartree = 2625.5001 kJ mol^{-1}; 1 bohr = 5.29177×10^{-11} m) or hartree rad^{-1}, respectively for bond stretches and angle bends.

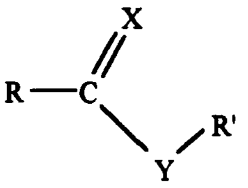
Semiempirical AM1[44] and PM3[45] calculations were carried out in a PC equipped with a Intel/80486DX processor using the PC version of MOPAC[46]. The program built-in standard convergence criteria were used throughout in the calculations (the keyword PRECISE was used to narrow down the convergence criterion in the energy minimization process), and the nature of all resulting critical point structures was systematically checked by inspection of the correspondent Hessian matrices. The potential energy profiles for internal rotation were calculated by varying the relevant dihedral angles by steps of 30° and letting all the remaining internal coordinates free during the energy minimization process.

3. RESULTS AND DISCUSSION

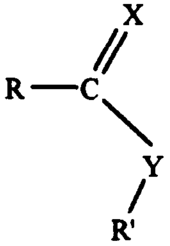
3.1. Molecular Geometries and Energies

The different conformations of the studied molecules result from rotating the three internal rotation axes (N-C, C-C and C-X, where X = O or S). With respect to the conformational properties exhibited by simple saturated unsubstituted carboxylic or dithio acids, in particular $CH_3C({=}X)XH$[47] and $CH_3CH_2C({=}X)XH$[48,49], the conformational properties of glycine and dithioglycine are essentially affected by the close proximity of the α-substituent amine (NH_2) group to the C(=X)XH moiety and, especially, by the ability of this group to act either as a hydrogen bonding donor or acceptor. In addition, in the case of the dithio compound, it may also be expected that for conformations where the nitrogen lone electron pair is directed towards the thiolic sulphur atom, an interaction involving partial electron charge transfer from the nitrogen atom to the vacant 3d orbitals of the sulphur atom can take place. Such kind of interaction was found to play an important role in the catalytic hydrolysis of dithioacyl-papain enzyme-substrate complexes[1,35], and is a specific intramolecular interaction of substituted dithio acids and dithio esters which has no counterpart in the case of the dioxygen containing molecules[1,33,35].

In the case of the above mentioned non-substituted molecules, the internal rotation about the C-Y bond gives rise to two stable conformers, the *s-cis* form



(s-cis)



(s-trans)

being the ground conformational state by *ca.* 25–35 and 8–13 kJ mol^{-1}, respectively for carboxylic and dithio acids[48–51]. The corresponding $\Delta E_{s\text{-}cis \rightarrow s\text{-}trans}$ energy barriers are *ca.* 50–60 and 30–40 kJ mol^{-1} [48–51], whilst in both kinds of molecules the less stable *s-trans* conformer corresponds to the form having the highest electric dipole moment (2–4 D in *s-trans vs.* 1–2 D in *s-cis*; 1D = 1/3 × 10^{-2} C.m). The main intramolecular effects which were found to determine the relative stabilities of the two conformers about the C-O or C-S bond are the relative extent of the mesomerism within the -C(=X)X- fragment in the two forms, the strength of the =X...H(X) intramolecular hydrogen bonding in the more stable *s-cis* form, and the relative importance of the through space field interaction between the nearly antiparallel bond dipoles associated with the C=X and X-H bonds in this latter conformer[37–40]. As shown elsewhere[37–40], all these effects lead to a more stable *s-cis* conformation and, in addition, they may also be used to explain why both the relative *s-trans* to *s-cis* energy difference and $\Delta E_{s\text{-}cis \rightarrow s\text{-}trans}$ energy barrier to internal rotation are systematically higher in the oxygen than in the sulphur containing molecules. Indeed, these observed trends could be correlated with both the better conjugating properties of the -O- 2p orbitals when compared with the -S- 3p orbitals (leading to an increased importance of the mesomerism within the -C(=O)O- fragment) and the greater inductive effect of oxygen when compared with that of sulphur (leading both to a stronger intramolecular hydrogen bonding and a more important through space field interaction in the dioxygen compounds)[37–40].

The study of the conformational preferences of the C-C internal axes in carboxylic acids and dithio acids constitutes a much more complex problem, since the energies usually involved are much smaller than those associated with the C-O or C-S internal rotation[48–52]. However, some general trends could also be established[48–52]: (i) conformations where one of the bonds made by the α-carbon atom is eclipsing the C=X double bond are usually minima in the potential energy surface, whilst those corresponding to staggered structures are mostly conformational transition states (the detailed explanation for this trend can be found in[49–52]; it is essentially a consequence of the presence of more favorable interactions between the C=X and α-substituent π orbitals in the eclipsed conformation, when compared with the staggered form); (ii) in carbonyl compounds, the lowest energy conformation of α-substituted molecules corresponds to the conformation where the α-substituent eclipses the C=O bond (*syn* form), while in thiocarbonyl molecules the ground conformational state is in general a doubly degenerate by symmetry *skew* form with the α-substituent and the thiocarbonyl suphur atom defining a dihedral angle of *ca.* ±100–120°[49,50]. On the other hand, the *skew* conformation usually corresponds to a second observable conformer in carbonyl compounds, and the *syn* form is found to be an higher energy conformer in thiocarbonyl molecules[48–50]; (iii) for α-methyl substituted compounds (*e.g.*, $CH_3CH_2C(=X)XR$, R= H, CH_3, CH_2CH_3), it has been found that a weak intramolecular stabilizing hydrogen bond may occur for conformations where the C-C-C=X dihedral is close to 60°. This interaction involves the formation of a H-C-C-C=X five membered ring and is particularly important for carbonyl compounds[33,49,52].

The preferred conformations of the amine group have been studied extensively both by experimental and theoretical methods[53–55]. In the case of a monosubstituted amine group (RCH_2-NH_2), it is well known that the most stable conformation corresponds to the *anti* form, where the nitrogen lone electron pair is *trans* with respect to the substituent[53–55]. This conformation is lower in energy by *ca.* 1.5–2.5 kJ mol^{-1} than the *gauche* forms, corresponding to Lp-N-C-R dihedrals of ±60°. The relative energy of the two stable conformations about the C-N axis was found to be essentially linked to the existence of a more favorable stabilising electron charge transfer from the nitrogen lone pair to the π orbitals of the methylene group in the *trans* form[54].

As will be shown in detail below, besides the specific conformational properties of the C(=X)XH and NH_2 groups, in the studied molecules the close proximity of these groups leads to the following dominant interactions: (i) intramolecular hydrogen bonding (NH...X=, N...HX= and NH...-O-; the interaction between the amine group and the -S- atom, where the latter would act as hydrogen acceptor, does not appear to operate efficiently, in all probability due to both the lower negative charge and larger size[37–40] of the -S- atom); (ii) steric repulsions involving the N and -O- lone electron pairs or the NH_2 group and the -S- atom; (iii) in dithioglycine, the above mentioned N...S non-bonding interaction involving the lone electron pair of the N atom and the 3d orbitals of the -S- atom.

Tables I–IV show the structural and energetic results obtained in this study for the two molecules under analysis. The predicted conformers are drawn in Figs. 1–2, where the notation used to name the different forms is presented.

Glycine

Neutral glycine has been the subject of several experimental structural results.[21,23,27,28,30] Rotational constants were obtained from microwave spectroscopic investigations[21,23] for the two lowest energy conformers of this molecule, which are considered to be forms I and VIII in Fig. 1. Form I was found to be the most stable conformer ($\Delta E_{VIII-I} \approx 6$ kJ mol^{-1} [23]) and it corresponds to the single glycine conformer, the complete molecular geometry of which could be experimentally obtained.[30] On the other hand, the characterization of the precise structure of the second most stable conformer of glycine was for some time the subject of an intense controversy, since the then available experimental and theoretical results pointed to slightly different structures. The highest level theoretical calculations[56] predicted a nonplanar (doubly degenerate by symmetry) structure as corresponding to the true energy minimum, while the experimental results were considered to be consistent with a C_s planar geometry.[23,30] However, this controversy was settled in a recent microwave spectroscopic study undertaken for this compound in a free-expansion jet, which clearly demonstrated that if the effect of zero-point twisting vibrations is taken into consideration, the non-planar structure predicted by the calculations looks in the spectroscopic experiments as an averaged ("most probable") C_s planar structure.[28] A general consensus has since then emerged on the geometry of the second most

TABLE I Experimental and calculated geometries for the various conformers of glycine[a]

	Conformer															
	I					II				III[b]			IV			
Parameter	*Exp [30]*	*AM1*	*PM3*	*RHF*	*MP2*	*AM1*	*PM3*	*RHF*	*MP2*	*PM3*	*RHF*	*MP2*	*AM1*	*PM3*	*RHF*	*MP2*
	r_α^0			6-31G*	6-311 ++ G**			6-31G*	6-311 ++ G**		6-31G*	6-311 ++ G**			6-31G*	6-311 ++ G**
C═O	120.4	123.5	121.9	118.8	120.9	123.4	121.8	118.8	120.9	121.8	118.7	120.9	123.2	121.6	118.6	120.8
C-C	152.9	151.4	151.4	151.5	151.9	151.4	151.5	152.0	152.2	151.3	150.8	150.8	151.0	151.5	151.0	151.0
C-N	146.6	143.1	147.0	143.9	144.7	143.0	146.9	140.5	144.9	147.8	144.3	145.4	144.0	147.8	144.9	146.0
C-O	135.4	136.0	135.2	133.0	135.6	136.3	135.5	133.0	135.6	135.2	132.9	135.3	136.2	135.5	133.1	135.6
C-H	108.1	112.8	110.9	108.5	109.4	113.0	111.0	108.4	109.4	111.0	108.3	109.2	112.9	110.9	108.0	109.0
C-H′	108.1	112.8	110.9	108.5	109.4	113.0	111.0	108.4	109.4	111.2	109.3	110.2	113.2	111.2	109.2	110.2
N-H	100.1	100.1	99.8	100.1	101.4	100.1	99.8	100.1	101.4	99.8	100.0	101.3	100.1	99.8	100.1	101.4
N-H′	100.1	100.1	99.8	100.1	101.4	100.1	99.8	100.1	101.4	99.8	100.0	101.5	100.0	99.7	100.1	101.4
O-H	96.6	97.2	95.2	95.2	96.8	97.2	95.2	95.3	96.8	95.2	95.2	96.8	97.2	95.2	95.2	96.8
C-C═O	125.0	128.8	128.9	125.4	125.7	127.7	127.9	123.6	123.9	128.7	125.2	125.0	128.0	128.6	125.1	125.8
C-C-N	113.0	115.7	114.9	115.0	115.6	118.7	117.3	118.3	119.0	109.9	110.2	109.6	113.5	110.0	111.2	111.1
C-C-O	111.5	114.0	115.1	111.8	110.9	115.8	116.8	113.9	113.0	115.1	112.0	111.4	114.8	115.3	111.3	111.0
C-C-H		107.3	109.3	107.7	107.4	106.1	108.3	106.2	105.9	111.2	108.6	108.7	107.4	109.4	106.9	107.0
C-C-H′		107.3	109.3	107.7	107.4	106.1	108.3	106.2	105.9	107.7	105.7	105.4	105.7	108.7	106.5	106.2
C-N-H		111.5	110.3	110.4	110.0	111.4	110.5	111.2	110.4	110.4	110.7	109.7	111.4	110.2	111.0	110.2
C-N-H′		111.5	110.3	110.4	110.0	111.4	110.5	111.2	110.4	108.9	111.0	110.5	110.2	109.0	110.4	109.8
C-O-H	110.5	109.7	110.0	108.4	106.3	109.8	109.8	107.8	105.7	110.1	108.3	106.1	109.7	110.0	108.2	106.2
O═C-C-N	0.0	0.0	0.0	0.0	0.0	180.0	180.0	180.0	180.0	54.0	21.9	24.3	−133.2	−114.7	−137.8	−138.5
C-C(═O)-O	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0	−178.4	−177.0	−177.5	−177.1	−178.2	−177.0	−177.4
O═C-C-H		122.1	122.0	123.0	123.1	57.3	57.3	56.2	56.1	173.0	142.8	142.7	−13.8	4.0	−18.1	−16.2
O═C-C-H′		−122.1	−122.0	−123.0	−123.1	−57.3	−57.3	−56.2	−56.1	−70.8	−103.0	−102.6	101.3	119.9	96.0	98.2
C-C-N-H		61.1	60.4	58.6	58.3	61.0	60.6	59.5	58.8	−56.6	−46.1	−45.3	−49.5	−65.9	−65.0	−62.5
C-C-N-H′		−61.1	−60.4	−58.6	−58.3	−61.0	−60.6	−59.5	−58.8	−176.8	−166.7	−164.6	171.8	174.0	175.4	179.0
O═C-O-H	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.2	4.0	2.7	2.9	2.1	0.8
NH...O═/-O-[d]		291.3	288.8	277.7	280.6	275.8	275.0	269.0	268.5	275.7	244.3	241.2	251.1	274.0	249.1	242.6
NH′...O═/-O-[d]		291.3	288.8	277.7	280.6	278.5	275.0	269.0	268.5	392.7	370.1	370.8	376.3	390.0	368.9	367.2

TABLE I (Continued) Experimental and calculated geometries for the various conformers of glycine[a]

	Conformer												
	V				VI			VII		VIII			
Parameter	AM1	PM3	RHF 6-31G*	MP2 6-311++G**	AM1[c]	RHF 6-31G*	MP2 6-311++G**	RHF 6-31G*	MP2 6-311++G**	AM1	PM3	RHF 6-31G*	MP2 6-311 ++ G**
C═O	123.1	121.3	118.1	120.3	122.9	118.3	120.4	118.1	120.3	123.1	121.3	118.4	120.7
C-C	151.7	152.0	152.3	152.9	151.9	152.9	153.4	151.8	152.0	151.7	152.1	152.5	153.2
C-N	143.2	146.9	143.7	144.5	143.2	144.0	144.8	144.1	145.1	144.0	147.9	145.4	146.5
C-O	136.6	135.2	133.5	136.1	136.8	132.0	135.4	133.3	135.8	136.1	134.9	132.0	134.1
C-H	112.9	110.9	108.7	109.6	112.8	108.3	109.2	108.7	109.6	113.0	111.1	108.3	109.3
C-H′	112.9	110.9	108.7	109.6	112.8	108.3	109.2	109.4	110.2	112.9	110.9	108.4	109.3
N-H	100.2	99.8	100.2	101.4	100.0	99.8	101.0	100.1	101.5	100.0	99.8	100.1	101.4
N-H′	100.2	99.8	100.2	101.4	100.0	99.8	101.0	100.0	101.3	100.0	99.8	100.0	101.2
O-H	96.7	94.9	94.8	96.4	96.7	94.8	96.7	94.8	96.3	96.8	95.0	95.6	98.0
C-C═O	127.0	127.8	123.9	124.4	127.0	121.5	122.0	123.5	123.5	124.8	126.4	122.0	122.6
C-C-N	116.3	115.2	115.2	115.6	116.0	118.9	119.6	110.3	109.6	113.1	110.3	111.7	111.0
C-C-O	119.0	121.3	115.2	115.1	119.2	117.1	116.5	115.5	115.6	120.9	112.4	115.0	113.8
C-C-H	107.5	109.3	108.1	107.8	107.6	106.3	106.0	109.5	109.7	106.8	109.4	107.6	107.6
C-C-H′	107.5	109.3	108.1	107.8	107.6	106.3	106.0	105.8	105.3	106.7	108.4	106.2	106.2
C-N-H	111.2	110.2	110.1	109.7	112.0	115.9	115.3	110.3	109.0	111.4	109.8	111.6	111.6
C-N-H′	111.2	110.2	110.1	109.7	112.0	115.9	115.3	111.4	110.9	110.8	109.3	111.9	111.8
C-O-H	109.7	110.6	112.2	109.3	109.8	110.8	107.0	112.4	109.0	110.4	110.6	108.6	104.1
O═C-C-N	0.0	0.0	0.0	0.0	113.2	180.0	180.0	21.2	24.7	141.5	136.7	163.9	169.5
C-C(═O)-O	180.0	180.0	180.0	180.0	−179.6	180.0	180.0	176.9	176.4	177.4	178.2	178.3	178.5
O═C-C-H	121.9	121.8	122.6	122.6	−125.3	56.4	56.3	142.0	141.8	15.8	11.0	37.2	42.2
O═C-C-H′	−121.9	−121.8	−122.6	−122.6	−9.1	−56.4	−56.3	−103.4	−103.1	−99.0	−107.4	−77.3	−72.5
C-C-N-H	60.8	60.3	58.3	58.1	53.2	67.1	66.6	−38.6	−38.8	−70.8	−71.4	−89.8	−100.2
C-C-N-H′	−60.8	−60.3	−58.3	−58.1	−70.7	−67.1	−66.6	−159.6	−158.1	166.6	168.8	149.5	139.2
O═C-O-H	180.0	180.0	180.0	180.0	175.6	180.0	180.0	−177.5	−176.4	−178.4	−177.0	−178.6	−177.2
NH...O═	288.9	287.7	275.0	278.1				234.6	232.0				
NH′...O═	288.9	287.7	275.0	278.1				364.6	365.4				
OH...N										249.9	254.0	204.4	190.4

[a] Bond lengths in pm; angles in degrees. See also Fig. 1, where the notation used to identify the conformers is presented. [b] This form does not correspond to an energy minimum in the potential energy surface obtained using this particular Hamiltonian. [c] This form does not correspond to the symmetric conformer VI, but is a non-symmetric distorted structure (see text). [d] Hydrogen-bonding distance between H or H′ and the closest oxygen atom (O═ or -O-).

TABLE II Calculated relative energies for the various conformers of glycine[a]

	ΔE/kJ mol^{-1}			
Conformer	*AM1*	*PM3*	*RHF/6-31G**	*MP2/6-311++G** [26]*
I	0.0	0.0	0.0	0.0
II	1.6	4.7	7.9	6.7
III[b]	-	9.0	9.2	5.2
IV	14.8	10.4	13.0	10.5
V	25.0	10.5	29.3	19.8
VI/VId[b,c]	33.2	–	38.9	24.1
VII[b]	–	–	38.9	25.3
VIII	31.7	14.5	12.1	2.1

[a] Relative energy values to the most stable conformer (form I). Calculated absolute energy values for conformer I are: AM1 −43.136624 hartrees; PM3 −39.118168 hartrees; 6-31G* −282.831096 hartrees; MP2/6-311++G** −284.009528 hartrees [26] (1 hartree = 2625.5001 kJ mol^{-1}). See also Fig. 1, where the notation used to identify the conformers is presented.

[b] This form does not correspond to a minimum in the potential energy surface obtained using AM1 or/and PM3 semiempirical methods.

[c] The precise nature of the stable form obtained at the *ab initio* level of theory (VI) and by the AM1 calculations (VId) are different (see text).

stable conformer of glycine, which is nowadays accepted to be non-planar (form VIII, in Fig. 1).

The nature of the third most stable conformer of glycine is still the subject of controversy. In a recent study of this molecule isolated in noble gas matrices (Ne, Ar, Kr),[27] three different conformers have been observed experimentally for the first time. The experimental data are consistent with the third conformer being form II of Fig. 1, and their energy estimated to be higher than that of form I by *ca.* 3.8–6.3 kJ mol^{-1}.[27] However, these results were not totally supported by a recent high level correlated *ab initio* theoretical study (MP2/6-311++G**; fully optimized geometries[26]), which suggests that the experimental $\Delta E_{VII\text{-}I}$ (5.4–6.7 kJ mol^{-1}) and $\Delta E_{II\text{-}I}$ (3.8–6.3 kJ mol^{-1}) values obtained in the matrix-isolated infrared spectroscopic study[27] are probably too high and too low, respectively (see calculated values in Table II). Moreover, the MP2/6-311++G** theoretical data predict form III in Fig. 1 as being slightly more stable than form II ($\Delta E_{II\text{-}III}$ = 1.5 kJ mol^{-1}). However, increasing the level of the calculation, this energy difference tends to reduce significantly to close to zero ($\Delta E_{II\text{-}III}$[MP4(SDTQ)/6-311 + G**] = 0.3 kJ mol^{-1}[26]). Hence, the precise characterization of the third more stable form of glycine is still open to discussion, and a careful experimental examination of this question is still required. It is, however, clear that forms II and III should have similar energies and, then, at least four conformational states contribute significantly to the conformational equilibrium in neutral glycine (forms I, VIII, II and III in Fig. 1).

TABLE III Calculated geometries for the various conformers of dithioglycine[a]

Conformer																		
	I			III			IV/IV'[b]			V			VId			VIII		
Parameter	*AM1*	*PM3*	*6-31G**	*AM1*	*PM3*	*6-31G**	*AM1*	*PM3*	*6-31G**	*AM1*	*PM3*	*6-31G**	*AM1*	*PM3*	*6-31G**	*AM1*	*PM3*	*6-31G**
C=S	153.9	157.8	162.0	154.0	157.9	162.2	153.1	157.1	162.5	153.7	157.4	161.8	153.2	157.2	161.9	154.0	157.8	162.2
C-C	152.1	151.7	153.1	151.4	151.5	152.5	151.6	151.6	152.1	151.4	151.5	153.1	151.6	151.8	152.9	151.0	151.4	152.5
C-N	143.2	146.7	143.3	144.3	148.1	144.9	144.3	148.2	144.5	143.3	146.7	143.2	143.5	147.2	144.7	144.4	148.2	144.9
C-S	168.2	174.9	175.5	168.2	174.1	174.4	169.1	175.2	174.8	167.8	175.0	175.5	168.2	174.7	175.5	167.3	174.2	174.5
C-H	113.0	111.1	108.6	113.2	111.3	108.3	113.0	111.0	108.5	113.0	111.1	108.6	113.0	111.0	108.4	113.2	111.4	108.6
C-H'	113.0	111.1	108.6	113.3	111.3	108.9	113.3	111.4	108.5	113.0	111.1	108.6	113.0	111.0	107.9	113.1	111.1	108.4
N-H	100.2	99.9	100.1	100.4	99.9	100.1	100.1	99.8	100.1	100.2	99.9	100.1	100.1	99.8	100.1	100.1	99.8	100.1
N-H'	100.2	99.9	100.1	100.1	99.7	100.1	100.0	99.7	100.0	100.2	99.9	100.1	100.1	99.8	100.1	100.0	99.8	100.1
S-H	132.9	131.8	132.3	132.7	131.6	132.4	132.9	131.7	132.4	132.0	131.0	132.7	132.0	131.0	132.7	132.2	131.1	132.5
C-C=S	123.9	125.4	124.6	123.9	123.8	122.3	123.2	123.6	121.5	124.4	125.1	124.7	123.6	122.3	122.8	121.8	121.2	121.2
C-C-N	117.4	117.5	117.8	113.8	110.7	110.0	113.1	109.9	112.6	117.7	117.8	117.8	116.8	114.9	113.8	113.4	110.9	113.5
C-C-S	107.4	108.1	111.1	107.0	108.6	112.8	108.0	109.0	113.6	115.4	115.2	115.6	116.4	117.2	117.3	118.1	117.9	118.1
C-C-H	107.9	109.0	107.1	110.0	111.1	110.1	108.3	109.6	107.5	107.9	109.1	107.1	108.3	110.7	109.8	107.8	109.3	105.8
C-C-H'	107.9	109.0	107.1	106.4	108.4	106.4	107.4	109.8	105.6	107.9	109.1	107.1	108.3	109.8	107.6	107.8	109.4	107.0
C-N-H	111.3	110.5	111.0	111.3	110.0	110.5	111.6	110.1	112.0	111.2	110.4	111.0	111.7	110.5	110.9	111.2	109.8	110.8
C-N-H'	111.3	110.5	111.0	110.1	108.9	110.1	110.2	109.0	111.5	111.2	110.4	111.0	112.1	110.5	112.6	110.4	109.0	111.2
C-S-H	101.1	101.3	97.5	101.3	101.8	97.9	101.2	101.6	95.5	103.1	102.7	98.4	103.4	102.8	98.6	104.8	103.1	97.5
S=C-C-N	0.0	0.0	0.0	42.4	65.8	61.5	−114.2	−92.5	−158.7	0.0	0.0	0.0	109.4	96.3	97.5	133.7	121.7	−147.7
C-C(=S)-S	180.0	180.0	180.0	179.4	179.1	−179.1	−178.5	−179.0	177.4	180.0	180.0	180.0	179.6	179.9	176.8	178.2	178.3	−176.3
S=C-C-H	122.0	121.6	123.4	162.1	−175.4	−179.4	4.8	25.9	−31.0	122.0	122.1	123.1	−128.6	−141.5	−140.2	8.1	−3.6	20.5
S=C-C-H'	−122.0	−121.6	−123.4	−82.5	−59.2	−63.2	120.2	142.3	83.1	−122.0	−122.1	−123.1	−12.6	−24.9	−22.9	−106.9	−119.2	−93.8
C-C-N-H	60.7	60.5	59.4	−34.0	−58.8	−63.8	−60.4	−71.6	82.2	60.7	60.4	59.2	−68.1	−66.2	−60.5	−66.6	−67.3	−78.0
C-C-N-H'	−60.7	−60.5	−59.4	155.6	−179.1	177.0	177.2	168.1	−156.4	−60.7	−60.4	−59.2	55.3	55.3	60.7	171.7	173.0	162.4
S=C-S-H	0.0	0.0	0.0	2.6	−0.2	0.8	3.4	4.0	−2.3	180.0	180.0	180.0	177.2	177.2	176.6	179.4	−177.5	−176.4
NH...S=	299.4	308.9	301.5	262.6	266.0	267.1				297.8	301.9	301.1						
NH'...S=	299.4	308.9	301.5	392.2	332.3	331.1				297.8	301.9	301.1						
SH...N																260.4	276.4	230.7
N...-S-							307.9	336.0	285.4									

[a] Bond lengths in pm; angles in degrees. See also Fig. 2, where the notation used to identify the conformers is presented. [b] The precise nature of the stable form obtained at the *ab initio* level of theory (IV') and by both semiempirical calculations (IV) are different. In particular, in contrast to the AM1 and PM3 methods, the *ab initio* calculations account for the N...-S- non-bonding intramolecular interaction involving charge transfer from the lone electron pair orbital of the N atom to the vacant 3d orbitals of the thiolic sulhphur atom (see text).

TABLE IV Calculated relative energies for the various conformers of dithioglycine[a]

	ΔE/kJ mol⁻¹		
Conformer	*AM1*	*PM3*	*6-31G**
I	0.0	0.0	0.0
III	12.9	7.0	13.7
IV/IV'[b]	18.1	10.4	3.4
V	1.2	5.4	5.4
VId	9.0	9.3	16.4
VIII	9.9	8.6	6.2

[a] Relative energy values to the most stable conformer (form I). Calculated absolute energy values for conformer I are: AM1 −33.812939 hartrees; PM3 −31.145462 hartrees; 6-31G* −928.089212 hartrees (1 hartree = 2625.5001 kJ mol^{-1}). See also Fig. 2, where the notation used to identify the conformers is presented. [b] The precise nature of the stable form obtained at the *ab initio* level (IV') and at both semiempirical levels of theory (IV) are different (see text).

When compared with the high level correlated *ab initio* calculations, the results on energies obtained using the 6-31G* basis set at the SCF Hartree-Fock level of theory and, in particular, those obtained with the two semiempirical methods tested in this study (AM1, PM3) show important differences. However, most of the observed discrepancies can be easily explained taking into account the difficulty of these lower level calculations to describe properly intramolecular hydrogen bonding. In fact, all those conformers where intramolecular hydrogen bonding is specially important reduce substantially their energy difference relatively to the most stable form (I) upon increasing the level of the calculations (see Table II). This is particularly evident in the case of form VIII (stabilized by an OH...N intramolecular hydrogen bonding), but also important in forms III and VII (where an NH...O═ hydrogen bonding is prevalent).

It can also be concluded that the *ab initio* HF/6-31G* calculations, though underestimating the importance of the intramolecular hydrogen bonding (clearly reflected in the calculated relative energies of the various conformers), yield optimized geometries that show a general agreement with the results obtained at the highest level of calculation. Thus, for example, the HF/6-31G* calculations yield optimised structures for forms III, VII and VIII where the relevant dihedral angles (H-N-C-C and N-C-C═O) assume values that lead to relatively close hydrogen bonding distances (OH...N: 204.4 pm, in form VIII, NH...O═: 244.3 pm and 234.6 pm, in forms III and VII, respectively, and even NH...-O-: 249.1 pm, in form IV; see Table I and Fig. 1). The semiempirical methods fail to predict conformers VI, VII and III (only AM1) as minimum energy conformations, since in this case the strongly destabilizing NH_2...HO (in VI) or CH_2...HO (in both VII and III) repulsions are not properly compensated by intramolecular hydrogen bonding, and yield structures for forms III (PM3), IV

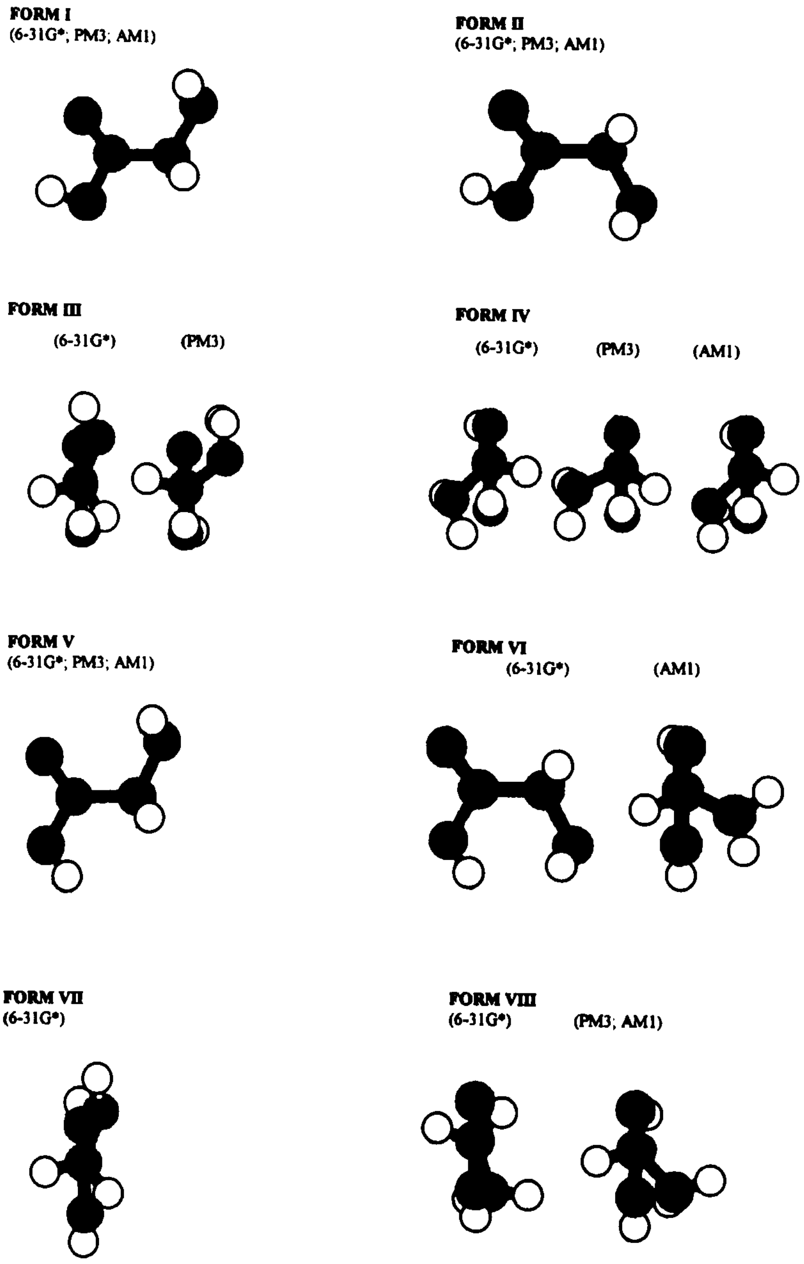
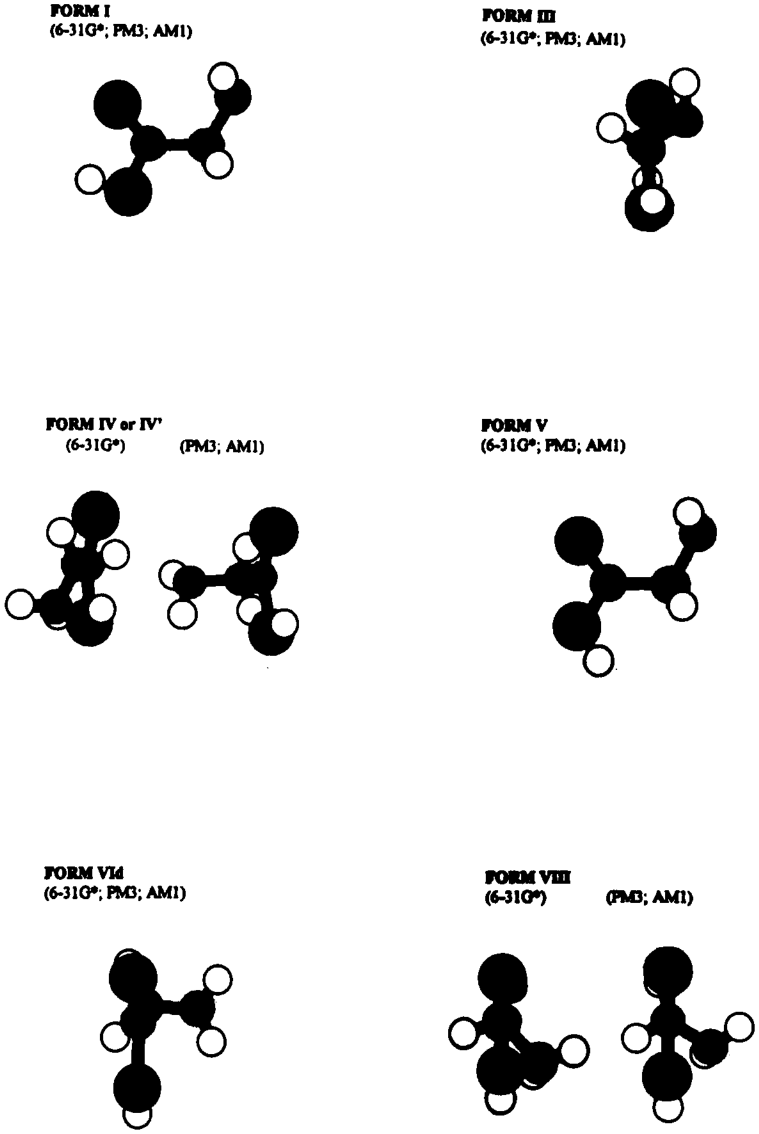


FIGURE 1 Conformers of glycine predicted by HF/6-31G* *ab initio*, AM1 and PM3 calculations.



FORM I
(6-31G*; PM3; AM1)

FORM III
(6-31G*; PM3; AM1)

FORM IV or IV'
(6-31G*) (PM3; AM1)

FORM V
(6-31G*; PM3; AM1)

FORM VId
(6-31G*; PM3; AM1)

FORM VIII
(6-31G*) (PM3; AM1)

FIGURE 2 Conformers of dithioglycine predicted by HF/6-31G* *ab initio*, AM1 and PM3 calculations.

and VIII that show rather large "H-bond" distances (see Table I and Fig. 1). The structures of forms I, II and V are well predicted by all methods used, since no strong specific intramolecular interactions are expected to occur for these structures.

A closer look at the 6-31G* calculated relevant structural parameters for the different conformers enable us also to conclude that, in agreement with our previous results on non-substituted carboxylic acis[47–49], in the *s-cis* (C-O) like conformers of glycine (forms I, II, III and IV) the mesomerism within the -C(═O)O- fragment is more important than in the *s-trans* (C-O) like forms (V, VI, VII and VIII). Thus, the C═O bond length is systematically larger in the *s-cis* (C-O) forms than in the *s-trans* (C-O) forms (118.6–118.8 pm *vs.* 118.1–118.4 pm), while the C-O bond is systematically shorter in these conformers (133.0–133.1 pm in *s-cis* (C-O) *vs.* 133.0–133.5 pm in *s-trans* (C-O)). These trends also reflect the existence in the *s-cis* like forms of both the through space field interaction between the nearly antiparallel bond dipoles associated with the C═O and O-H bonds and the ═O...HO intramolecular hydrogen bonding. This later effect also leads to longer OH bond lengths in the *s-cis* (C-O) forms (95.2–95.3 pm *vs.* 94.8 pm). Very interestingly, both the C-O and O-H bond lengths in form VIII deviate from the above referred trends. Indeed, this conformer was found to possess a shorter C-O bond and a longer O-H bond than all other forms. This is however easily correlated with the presence in this form of the above mentioned OH...N intramolecular hydrogen bond, which is certainly stronger than the ═O...HO one. It is also important to note that the above trends in geometrical parameters are also reasonably well accounted for by both semiempirical levels (see Table I), though they are not able to predict properly the specific behaviour of form VIII (ascribable essentially to the presence of the OH...N hydrogen bonding).

The PM3 potential energy contour map obtained for glycine, assuming an *s-cis* (C-O) geometry, and the minimum energy pathways for inter-conversion between the four *s-cis* (C-O) conformers are presented in Fig. 3. The calculated energy barriers going from conformer I to either forms II or III are relatively high (5.5 and 10.6 kJ mol^{-1}), while the corresponding barriers to the inverse reactions are very small (1.0 and 1.6 kJ mol^{-1}, respectively). However, the energy barriers associated with the isomerization reactions for conversion of form IV to forms II and III are 4.1 and 6.0 kJ mol^{-1}, respectively. These results show a good general agreement with the MP2/6-31G* data reported in[29] and, thus, give further support to the interpretation of the low temperature matrix-isolation spectroscopic results made in[18].

To summarize, while sophisticated high level correlated *ab initio* calculations appear to be necessary to account in detail for the structural and energetic properties of amino acids, the essential features can be reasonably well predicted at a SCF-HF level of theory using a moderate size basis set. In addition, despite the above mentioned important discrepancies displayed by semiempirical methods, they still appear useful for the study of more complex α-amino acid based

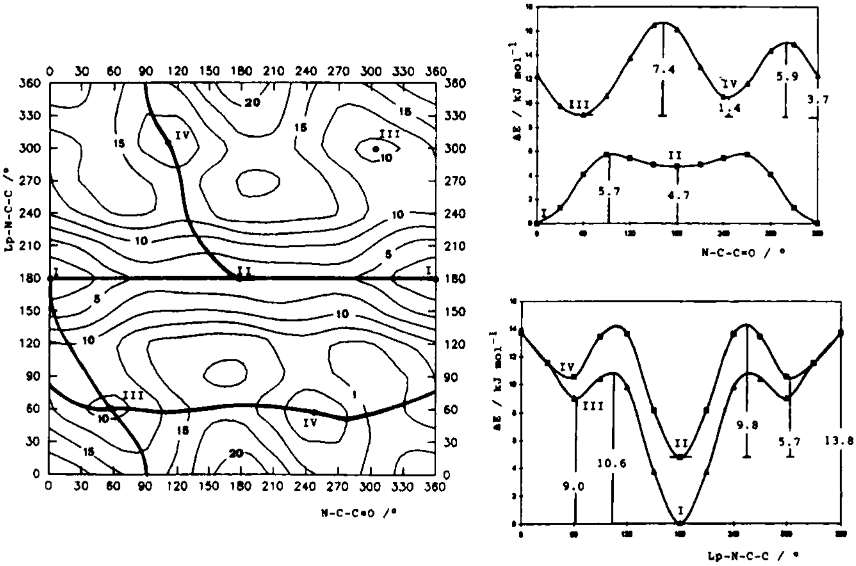


FIGURE 3 Potential energy (E-E$_{(\text{form I})}$/kJ mol^{-1}) contour map for glycine, obtained using the PM3 semiempirical method and assuming a fixed *s-cis* (C-O) geometry. The isoenergy contour lines were obtained by polynomial interpolation from a grid of points obtained by varying the relevant dihedral angles by steps of 30° and letting all the remaining internal coordinates free during the energy minimization process. The minimum energy pathways for conformational interconversions are shown in the contour map, and the correspondent potential energy profiles presented as insertions to the Figure.

systems, since besides their well-known low cost in terms of computational resources, they seem to yield reasonable structural and even energetic results for the most stable conformers of this kind of molecules (See Tables 1,2). In the particular case of glycine, PM3 seems to behave considerably better than AM1. In fact, this method is only clearly not useful when dealing with the highest energy forms (VI and VII) and, to some extent, with form VIIII. Thus, its use for preliminar exploratory conformational studies of more complex amino acid based systems may constitute a good choice.

Dithioglycine

In agreement with our previous studies on dithio carbonyl compounds[35–40,48–52], the calculations carried out on dithioglycine reveal that this molecule has a conformational behaviour considerably distinct from its dioxygen analogue. The main observed differences can be summarized as follows, and can be easily correlated with the larger size of the sulphur atoms and their smaller ability to interact either by mesomerism or induction, when compared with the oxygen atoms:

(i) Both NH...S= and NH...-S- hydrogen bonding interactions are not found to play any significant role. Consequently, form VII was not found to be a minimum in the potential energy surface of dithioglycine (in this form the CH_2...HS repulsion was found to be the dominant intramolecular interaction, reflected, for instance, in the larger calculated values for the H-C-C and H-S-C angles in this conformation). In addition, the calculated geometries for form III obtained either at the *ab initio* HF/6-31G* level or using the two semiempirical methods (see Table III and Fig. 2) do not differ very much. If hydrogen bonding were operating, the 6-31G* calculations would lead, for instance, to a significantly shorter NH...S= non bonding distance, since this method has been shown to account for the intramolecular hydrogen bonding effects considerably better than the semiempirical methods (calculated values: 267.1 pm, 6-31G*; 262.6 pm, AM1; 266.0 pm, PM3);

(ii) The SH...NH_2 hydrogen bonding interaction is still important in stabilizing form VIII (the 6-31G* calculated SH...NH_2 distance is 230.7 pm). However, the relative stabilization of form VIII with respect to the most stable form (I) ascribable to this interaction was found to be much smaller than that observed in glycine (compare, for instance, the relative ΔE_{VIII-I} values calculated at the 6-31G* and semiempirical levels of theory in the two compounds—Tables II, IV). Thus, as could be expected, the results are consistent with the presence of a considerably weaker SH...NH_2 hydrogen bond in the dithio compound when compared with the OH...NH_2 hydrogen bonding in the dioxygen molecule;

(iii) All methods used predict that form VI is not a minimum in the potential energy surface. Instead of this form, a non-symmetric conformer (VId), where the N-C-C=S dihedral is close to 90°, was found (see Table III and Fig. 2). This is, however, predicted to correspond to a high energy conformational state and thus, as in the case of the equivalent conformers of glycine (VI or VId; see Table I and Fig. 1), its precise characterization does not seem to be of great relevance in practical terms. Nevertheless, it is interesting to note that the results obtained at all levels of theory used agree on this particular point (this may also support, to some extent, the hypothesis of form VI of glycine being just an artifact of calculations undertaken using large basis sets, as suggested in[57]);

(iv) When compared with the equivalent form in glycine, form V of dithioglycine is stabilized relative to the most stable conformer, since the CH_2...HS repulsion is minimized in this molecule due to its longer C-S bond length when compared with the C-O bond distance in glycine. The larger volume of the -S- atom, together with its reduced ability to act as hydrogen bond acceptor (in a

NH_2...SH bond), causes the equivalent conformation of form II of glycine not to be an energy minimum in the potential energy surfaces of dithioglycine obtained either at the *ab initio* 6-31G* or semiempirical levels of theory. Indeed, this conformation is predicted by all methods as corresponding to a saddle point;

(v) According with the *ab initio* results, in glycine the high energy form IV shows a weak intramolecular NH...-O- hydrogen bond. As referred to above, such weak interaction is not properly taken into account by the semiempirical AM1 and PM3 methods, but these calculations also predict an energy minimum in this region of the potential energy surface. In the sulphur compound, both semiempirical methods also predict an equivalent form to IV to exist as a high energy conformer (see Tables III–IV and Fig. 2). However, instead of form IV, the *ab initio* calculations predict the existence in the potential energy surface of dithioglycine of a different minimum—form IV′ in Fig.2—, where the lone electron pair of the nitrogen atom is directed towards the thiolic sulphur atom. The stabilization of this conformer may be ascribed to the above mentioned N...-S- interaction involving partial electron charge transfer from the nitrogen atom to the 3d vacant orbitals of the sulphur that have also been found to play an important role in similar molecules[1–3,35,38]. As expected, the semiempirical methods are not able to account properly for this specific intramolecular interaction of substituted dithio compounds, which has no counterpart in the case of the dioxygen containing molecules. Significantly, form IV′ is predicted by the *ab initio* calculations to be the second more stable form of dithioglycine, with an energy very similar to that of form I.

(vi) The N...-S- interaction observed in form IV′ is clearly reflected in some geometrical parameters, since it leads to an increased mesomerism within the S=C-S fragment. Accordingly, the calculated C=S bond length in this conformer is larger than in all other forms, while the C-S bond is predicted to be considerably shorter.

(vii) Finally, the calculations also clearly show that, as in glycine, the mesomerism within the -C(=S)S- fragment is also more important in the *s-cis* (C-S) like forms of dithioglycine (I, III and IV) than in the *s-trans* (C-S) like forms (V, VI and VIII). However, in consonance with our previous data on dithiocarbonyl compounds[35–40], it was found that this effect is much less pronounced than in the case of the dioxygen compounds, as shown, for instance, in the relatively small differences in the C=S bond lengths in the *s-cis* (C-S) *vs.* *s-trans* (C-S) like forms (162.0–162.5 pm *vs.* 161.8–162.2 pm). In addition, the calculations also show that the through space field interaction between the bond dipoles associated with the C=S and S-H bonds and the S=...HS intramolecular hydrogen bonding do not seem to play any relevant role both in structural and energetic terms, a fact that may be correlated with the considerably smaller eletronegativity of the sulphur atom when compared with the oxygen atom, as well as with the well-known reduced strength of a SH...S═ hydrogen bond when compared with a OH...O═ hydrogen bond.

3.2. Charge Distribution Analysis

Tables V and VI show the calculated electric dipole moments and atomic charges for the most important conformers of glycine and dithioglycine, calculated at the HF/6-31G* level of theory (the semiempirical results were found to show a general good qualitative agreement with the *ab initio* results discussed below; these data can be obtained from the authors, upon request). From these Tables, the following main conclusions can be drawn:

(i) As expected considering previous data on similar compounds[33–40], in both studied molecules the conformers having a H-X-C═X (X═O or S) dihedral angle near to 0° (*s-cis* (C-X) forms) have smaller dipole moments than the *s-trans* (C-X) forms. In particular, the most stable conformer (form I) is the less polar conformer in both molecules, while conformer VIII (where the OH...N or SH...N hydrogen bonding interaction is operating) corresponds to the most polar form.

(ii) The dependence of the calculated changes on the hydrogen atoms upon the change of conformation clearly reflects the most important intramolecular interactions acting in the studied molecules. Thus, the positive charges on the H(O) and H(S) atoms attain their maximum values in conformer VIII (glycine: q[H(O)]═ 0.50 e in form VIII *vs.* 0.46–047 e in the remaining forms; dithiogly-

TABLE VI HF/6-31G* calculated Mulliken atomic charges and electric dipole moments for the various conformers of dithioglycine[a]

	Conformer					
Atom	*I*	*III*	*IV'*	*V*	*VI*	*VIII*
C═	−0.203	−0.169	−0.200	−0.203	−0.200	−0.191
S═	−0.148	−0.148	−0.165	−0.131	−0.120	−0.140
-S-	0.058	0.078	0.112	0.099	0.095	0.069
C	−0.164	−0.155	−0.162	−0.164	−0.158	−0.156
H(S)	0.135	0.130	0.085	0.089	0.086	0.145
H(C)	0.213	0.194	0.216	0.205	0.191	0.209
H'(C)	0.213	0.190	0.207	0.205	0.227	0.212
N	−0.816	−0.831	−0.816	−0.816	−0.825	−0.866
H(N)	0.356	0.365	0.360	0.358	0.359	0.358
H'(N)	0.356	0.348	0.357	0.358	0.346	0.360
$\|\mu\|$	1.170	2.301	2.928	2.528	2.890	4.694

[a] Charges in units of $\underline{e}$ ($\underline{e}$ = 1.6021892 × 10^{-19} C); Dipole moments ($|\mu|$) in Debyes (1 D = 1/3 × 10^{-2} C.m).

TABLE V HF/6-31G* calculated Mulliken atomic charges and electric dipole moments for the various conformers of glycine[a]

	Conformer							
Atom	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
C=	0.714	0.720	0.752	0.761	0.745	0.729	0.776	0.763
O=	−0.559	−0.556	−0.558	−0.556	−0.529	−0.534	−0.530	−0.548
-O-	−0.694	−0.700	−0.698	−0.700	−0.695	−0.696	−0.696	−0.706
C	−0.229	−0.237	−0.214	−0.225	−0.275	−0.238	−0.246	−0.261
H(O)	0.467	0.467	0.468	0.468	0.465	0.459	0.465	0.499
H(C)	0.210	0.216	0.207	0.213	0.197	0.225	0.178	0.208
H'(C)	0.210	0.216	0.179	0.175	0.197	0.225	0.178	0.215
N	−0.816	−0.823	−0.643	−0.842	−0.812	−0.882	−0.844	−0.901
H(N)	0.349	0.348	0.364	0.358	0.353	0.354	0.374	0.363
H'(N)	0.349	0.348	0.344	0.348	0.353	0.354	0.344	0.368
$\lvert\mu\rvert$	1.332	2.040	2.302	2.746	3.284	4.480	4.737	5.692

[a] Charges in units of e (e = $1.6021892 \times 10^{-19}$ C); Dipole moments ($\lvert\mu\rvert$) in Debyes (1 D = $1/3 \times 10^{-2}$ C.m).

cine: q[H(S)]= 0.15 e in form VIII *vs.* 0.09–0.13 e) due to the relatively strong OH...N or SH...N hydrogen bonding. On the other hand, the changes on the H(N) atoms which participate in a NH...O= (in forms III and VII of glycine) or NH...-O- (in form IV of glycine) intramolecular hydrogen bond have a more positive charge (0.36–0.37 e) than the equivalent atoms not involved in hydrogen bonding (0.34–0.35 e). It is also interesting to note that the charge on the H(N) atom placed closer to the S= atom in form III of dithioglycine is also slightly more positive (by *ca.* 0.01 e) than those calculated for the H(N) atoms in the remaining conformers. This result is in consonance with the presence in this conformer of a very weak NH...S= intramolecular hydrogen bond.

(iii) Finally, in agreement with our previous calculations on sulphur compounds[33–40], the calculated charge of the thiolic sulphur atom is predicted to be slightly positive. Very interestingly, the N...-S- non-bonded interaction, though implying an electron charge transfer from the N towards the -S- atom, leads to

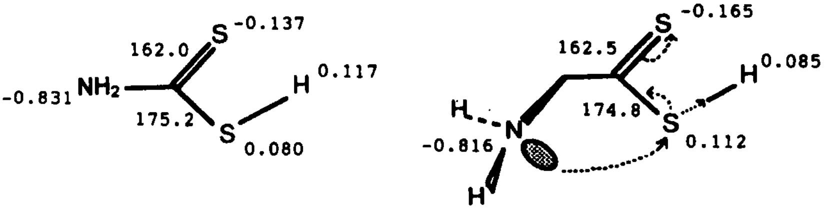


FIGURE 4 Schematic representation of the main electron density changes associated with the N...-S- non-bonding interaction, taken as reference the average values obtained for all conformers but IV'. The values presented (bond lengths in pm; charges in units of e) were obtained at the HF/6-31G* level of theory.

an effective reduction of the electron density on both these atoms. Indeed, it is clear from the data shown in Table VI that the electron density first transferred from the N to the -S- atom as a consequence of the above interaction is afterwards partially delocalized to the C-S bond (which becomes shorter) and, simultaneously, to the H(S) atom (which becomes less positive)—Fig. 4.

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