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A theoretical investigation of the dictating forces in small amino acid conformational preferences: The case of glycine, sarcosine and *N*,*N*-dimethylglycine

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ABSTRACT

Amino acid conformational analysis is widely studied in the literature. However, information about the intramolecular interactions that govern their conformational preferences is scarce and it is commonly attributed to intramolecular hydrogen bond formation. The present paper utilizes calculations at the B3LYP/aug-cc-pVDZ theoretical level and QTAIM and NBO methods for glycine, sarcosine and *N*,*N*-dimethylglycine conformers to emphasize that arbitrary literature interpretations are equivocal. Also, our results show that the interplay between steric and hyperconjugative interactions rules glycine conformer energies/geometries and such results are confirmed by sarcosine and *N*,*N*-dimethylglycine conformational preferences.

1. Introduction

In any attempt to understand protein three-dimensional structures and folding processes, the characterization of the intramolecular interactions that rule amino acid conformational energies and geometries constitutes an unavoidable first step [1–7]. Indeed, gas phase glycine and alanine conformational isomerisms have been widely studied by both theoretical and experimental approaches, but the interactions that rule their conformational preferences remain solely attributed to intramolecular hydrogen bond (IHB) formation [8–27]. Actually, it is not uncommon to find examples in the literature that invoke IHB to explain conformational preferences in molecular systems where more systematic studies have shown that such interactions should not occur [28–35].

Moreover, steric effects, repulsive short contact van der Waals interactions, and hyperconjugative effects, an electronic delocalization phenomenon resulting from a favorable overlap between a partially or completely occupied orbital, usually a σ orbital and a vicinal unoccupied orbital, are ubiquitous interactions in molecular systems, influencing conformational energies and geometries even of small hydrocarbons, whose contribution ratio between steric/hyperconjugative interactions remains controversial in the literature due to many different interpretations [36–42]. Therefore, it is surprising that steric and hyperconjugative effects are ignored in the interpretation of amino acid conformational analysis and that only the possible formation of IHB is taken into account. Actually, it was recently found, within the natural bond orbitals (NBO) [43] and quantum theory of atoms in molecules (QTAIM) frameworks [44], that glycine and alanine stereoisomerisms are governed by both hyperconjugation and steric hindrance. Indeed, in the QTAIM and NBO point of view, a IHB may be formed only to the conformer **II** (for a glycine conformer **II** geometrical representation view refer to Fig. 2 below), which is not the global minimum for both glycine and alanine. Hence, these studies have pointed out that IHB formation may be a secondary interaction in determining conformer rotational isomerism for these amino acids [32,33]. In addition, it has been showed, by comparing glycine and alanine conformational behaviors that side chain/main chain interactions should be narrowly evaluated for each individual amino acid [33].

Notwithstanding, most assignments of hydrogen bond (H-bond) formation in the majority of molecular systems have been carried out considering the following geometrical parameters: [45,46]

1 Comparison between the X–H bond length of a conformer not involved in IHB with the X–H bond length of a conformer that possibly shows a X—H···Y IHB. In this sense, the X–H bond length should increase in the later case as due to IHB formation.
2 In a generic X—H···Y H-bonding, the summation of the corresponding X and Y van der Waals atom radius should be smaller than the distance between X and Y. Accordingly, the H and Y van der Waals atomic radius sum should be smaller than the distance between H and Y.

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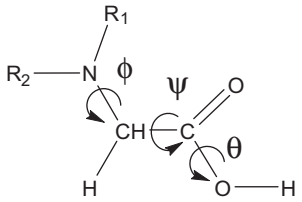

Glycine: $\mathbf{R_1} = \mathbf{R_2} = H$; Sarcosine: $\mathbf{R_1} = CH_3$, $\mathbf{R_2} = H$; DMG: $\mathbf{R_1} = \mathbf{R_2} = CH_3$

Fig. 1. Structural and **ψ** (N–C–C=O), ϕ (n_N–N–C–C) and θ (H–O–C=O) dihedral angle representations of glycine, sarcosine and DMG.

However, H-bonding involves complex interactions, which are difficult to be unambiguously characterized, and very often these geometrical parameters fail to indicate the formation/non-formation of these interactions [34,35,45,46].

Nevertheless, even if geometrical parameters indicate that an IHB should be formed, as occurs only for conformer **II** of glycine and alanine, this may not be the driving force of the conformational equilibrium, since that conformer is not the global minimum in either case [32,33]. Indeed, Popelier H-bonding criteria, which use QTAIM descriptors, have been considered more reliable than geometrical parameters and are indicated as an ideal tool for the evaluation of H-bond formation [45–52]. These criteria were used to show that an IHB is formed only in glycine and alanine conformer **II** [32,33].

Popelier criteria may be summarized as follows: [49]

1 Consistent topology with H-bond formation: occurrence of a bond critical point (BCP), a (3, −1) saddle point in the electronic density, and a bond path (BP), a line of maximum electron density linking neighboring nuclei of a molecular system in an equilibrium geometry, are the necessary and sufficient conditions to recognize a stabilizing interaction between atoms participating in H-bonding.
2 Electronic density (ρ_b) and its Laplacian ($\bigtriangledown^2\rho_b$)($\Delta^2_{\rho_b}$) values at the H-bond BCP (HBCP) must lie from 0.002 au to 0.04 au and from 0.024 au to 0.139 au, respectively.

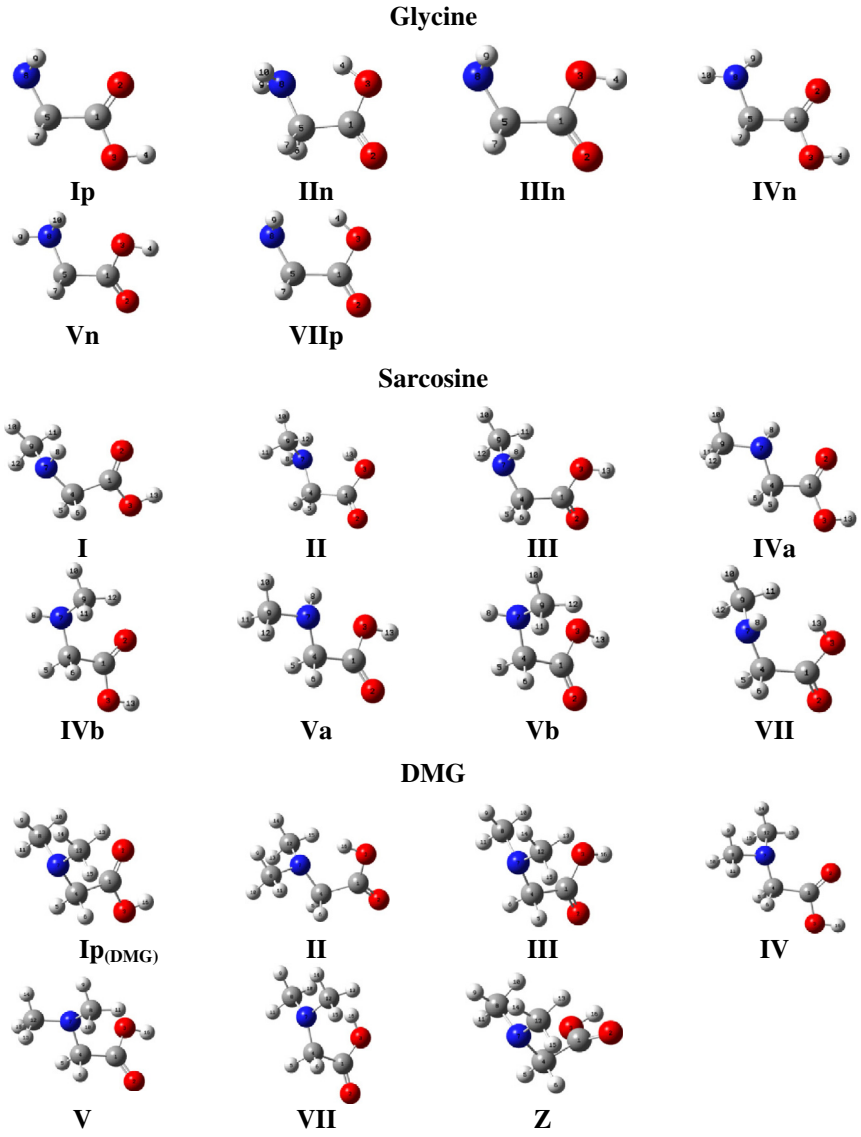

Fig. 2. Geometrical representations of glycine, sarcosine and DMG conformers. The conformer nomenclatures used were adapted from the glycine study of Császár [8], where the roman numerals indicate the stability order and **p** and **n** designate planar and non-planar heavy atom arrangements, respectively. Sarcosine has two glycine **IVn** and **Vn** analog conformers, which are differentiated by the **a** and **b** letters. No sarcosine conformers are planar. Only conformer **I** is planar for the DMG and, hence, the "**n**" nomenclature was omitted for the remaining DMG conformers.

Table 1
Structural parameters[a] and calculated relative energies[b] (ΔE, kcal mol^{-1}), for the optimized structures of glycine, sarcosine and DMG conformers at the B3LYP/aug-cc-pVDZ level.

	Glycine						Sarcosine						DMG						
	Ip	IIn	IIIn	IVn	Vn	VIIp	I	II	III	IVa	IVb	Va	Vb	VII	$Ip_{(DMG)}$	II	III	IV	V	VII	Z
ΔE	0.00	0.86	1.66	1.20	2.65	5.50	0.00	0.40	1.27	0.20	1.98	1.63	2.84	5.86	0.67	0.00	2.00	1.12	1.93	6.55	2.12
r(O–H)	0.971	0.986	0.972	0.971	0.971	0.972	0.972	0.985	0.971	0.971	0.971	0.971	0.972	0.970	0.971	0.984	0.972	0.971	0.972	0.967	0.972
r(N–Ha/C–H^{c})	1.018	1.014	1.017	1.018	1.016	1.012	1.017	1.014	1.016	1.017	1.014	1.016	1.014	1.107	1.105	–	1.106	–	1.097	–	1.107
r(N–Hb/C–H^{c})	1.018	1.015	1.017	1.015	1.017	1.012	1.105	1.105	1.106	1.096	1.096	1.109	1.098	1.107	1.105	–	1.107	1.095	–	–	1.109
r(NHa/NCH_3^{c}···O)	2.828	–	2.788	2.392	–	–	2.676	–	2.598	2.384	–	2.375	–	–	2.658	–	2.580	–	2.759	–	2.764
r(NHb/NCH_3^{c}···O)	2.828	–	2.671	–	2.457	–	2.787	–	2.829	–	2.602	–	2.756	–	2.658	–	2.610	2.481	–	–	2.902
r(OH···N)	–	1.923	–	–	–	2.250	–	1.948	–	–	–	–	–	2.291	–	1.973	–	–	–	2.358	–
r(N···O)	2.883	2.628	2.782	2.776	2.712	2.850	2.887	2.638	2.822	2.787	–	2.730	2.730	2.868	2.937	2.654	2.836	2.873	2.783	2.913	3.211
∠ N–Ha/C–H^{c}···O	82.8	–	79.1	101.2	–	–	91.5	–	92.0	102.5	–	99.3	–	–	109.3	–	107.6	–	108.8	–	99.4
∠ N–Hb/C–H^{c}···O	82.8	–	85.4	–	93.3	–	108.1	–	105.2	–	113.6	–	107.6	–	109.3	–	–	117.7	–	–	104.9
∠ O–H···N	–	126.1	–	–	–	119.0	–	124.8	–	–	–	–	–	117.2	114.9	113.1	115.7	112.8	112.1	117.6	114.4
ψ (N–C–C=O)	0.0	186.3	186.3	19.1	149.8	180.1	344.5	165.2	148.7	20.4	354.6	212.6	195.4	196.2	0.00	162.8	176.7	0.3	210.9	183.7	81.2
ϕ [n_N–N–C–C(O)]	180.0	13.8	178.9	278.6	59.6	180.0	189.5	25.7	181.6	280.4	41.6	294.0	40.8	176.9	180.0	328.0	178.9	313.7	49.0	181.2	180.5
θ (H–O–C=O)	0.0	180.4	0.2	178.9	0.8	180.0	1.2	180.8	0.2	358.8	0.1	359.2	0.3	178.4	0.0	178.5	0.1	0.3	0.3	180.3	0.0

[a] Bond lengths in angstroms, bond and torsional angles in degrees.
[b] ZPE correction included.
[c] Methyl group hydrogen atom that can possibly form H-bonding.

3 A hydrogen atom participating in a H-bond must have a more positive atomic charge [q(H)], increased atomic energy [E(H)], decreased first dipole moment M_1(H) and atomic volume V(H) values, in comparison to a hydrogen atom that is not involved in H-bond formation.

Nevertheless, even after these findings, amino acid conformational preferences continue to be attributed to IHB formation in recent literature papers [53–56]. Thus, the present work utilizes a different approach, by studying glycine, sarcosine and *N,N*-dimethylglycine (DMG) together in order to emphasize that IHB has minor contributions for small amino acid conformational preferences in comparison to steric/hyperconjugative effects.

2. Computational details

The Gaussian 03 program [57] was used to build fully relaxed potential energy surfaces (PES) at the B3LYP/cc-pVDZ theoretical level, by scanning the ψ (N–C–C=O), ϕ (n_N–N–C–C) and θ (H–O–C=O) dihedral angles (dihedral represented in Fig. 1) in steps of 10° for glycine, sarcosine and DMG gas phase structures, i.e. the ϕ and ψ torsional angles were varied simultaneously and holding θ fixed, e.g., scanning ψ and ϕ from 0° to 360° in steps of 10°: at 0°, 10°, 20°, etc. The same protocol was done with ϕ and θ dihedral angles. The resulting energy minima were subsequently optimized at the B3LYP/aug-cc-pVDZ level. It is worth to mention that amino acid compounds here studied are in the isolated environment, which refer to the neutral gas phase structure (H_2N–R–COOH; R = amino acid side chain), which is closer to a peptidic environment than the bipolar zwitterionic structure ($^{+}H_3N$–R–COO^{-}). Thus, only isolated structures calculations were carried out in the present work. Frequency calculations performed for each PES resulting conformer provided zero-point energy (ZPE) corrections and confirmed that such conformers are true minima, since imaginary frequencies were not observed. This theoretical level is in good agreement with CCSD(T)/CBS and with some experimental results, indicating that it is the least costly method that represents adequately these rotational isomerisms [9,53,58]. NBO[43] and QTAIM [44] methods were applied for the wave functions obtained from the B3LYP/aug-cc-pVDZ optimized geometries by using the NBO Gaussian03 implemented program and the AIMALL software, respectively [59,60]. QTAIM zero flux surface qualities were evaluated through the integrated Laplacian of ρ values over each atomic basin (Ω), which were lower than 10^{-3} au for all Ω.

3. Results and discussion

Geometric representations and the nomenclature of glycine, sarcosine and DMG are illustrated in Fig. 2 and their geometrical parameters are shown in Table 1. It is important to note that although not all conformers were found by previous experimental studies, the relative stabilities obtained by our theoretical data are in agreement with the experimentally detected conformers [26,61–63]. By comparing glycine and sarcosine conformational energies (Table 1), it is possible to note that conformer **II** is much closer in energy to conformer **I** for the latter compound. Also, sarcosine conformer **IVa** is almost isoenergetic with conformer **I** and conformer **Va** has a decreased relative energy (relative to sarcosine conformer **I**) than conformer **Vn** of glycine (relative to glycine conformer **Ip**). It is noteworthy that sarcosine conformers **II**, **IVa** and **Va** have their methyl groups far from the bulky COOH functional group and should experience less steric effects than sarcosine conformer **I**, which has a methyl group relatively closer to the COOH group.

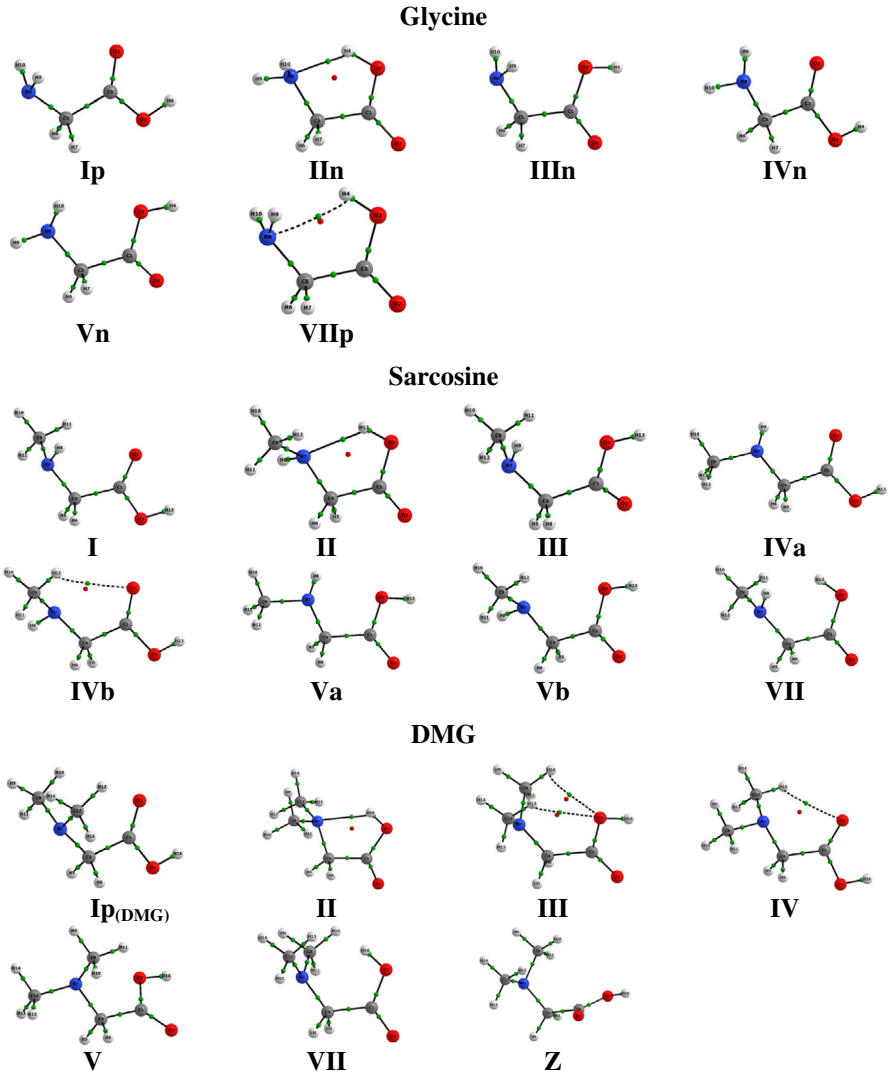

Fig. 3. Glycine, sarcosine and DMG molecular graphs obtained from QTAIM. Green points represent bond critical points (BCPs) and red points represent ring critical points (RCPs). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

QTAIM molecular graphs and Popelier criteria applied over glycine and sarcosine conformers (Fig. 3 and Table 2, respectively) indicate that only conformers **II** form N···H—O IHB, which has the same 0.035 au eletronic density value at the IHB BCP (ρ_{HBCP}) for both glycine and sarcosine. Although QTAIM indicates that sarcosine conformer **IVb** forms a non-usual C—H···O IHB, which meets Popelier criteria but is unstable due to a high ellipicity value of 0.808 au at the HBCP and, thus, has a high energy value, this interaction has no importance for sarcosine conformational preferences.

Thereby, QTAIM suggests that glycine conformer **Ip** should not form an IHB (Table 2, Fig. 3 and reference **32**), while glycine and sarcosine conformers **II** present the same IHB strength (ρ_{HBCP} = 0.035 au for both conformers). Hence, the closer energy of sarcosine conformer **II** to conformer **I**, in comparison to glycine conformer **IIn** and **Ip** should have origin in other intramolecular effects than IHB. Thus, in order to evaluate steric and hyperconjugative effect contributions for glycine and sarcosine conformers, NBO analysis was carried out (Table 3). NBO gives structures with localized bonds and lone-pairs and also $\sigma*$ and $\pi*$ antibonding and Rydberg orbitals, which may participate in hyperconjugative interactions. The deletion of all antibonding and Rydberg orbitals removes the hyperconjugative interactions and the resulting molecular structure resembles an idealized Lewis structure with only classical (steric and electrostatic) interactions. In this way, the hyperconjugative and steric energies may be obtained by the equation $E_{FULL} = E_{Lewis} - E_{hyper}$.

The glycine **Ip** conformer has 6.76 kcal mol^{-1} (9.93–3.17 kcal mol^{-1}) less energy due to steric effects than the conformer **IIn** (Table 3; ΔE_{Lewis} values). If the $n_N \rightarrow \sigma^*_{O-H}$ hyperconjugative interaction (Fig. 4) energy value (12.40 kcal mol^{-1}; data included in Fig. 4) is not taken into account in the ΔE_{hyper} value of conformer **IIn** (Table 3), i.e. by not considering the hyperconjugative IHB stabilization of this conformer, its ΔE_{hyper} value would be of −0.46 kcal mol^{-1} (From Table 3 and Fig. 4: 11.94 − 12.40 = −0.46 kcal mol^{-1}), which indicate that the IHB is the source of hyperconjugation stabilization for this conformer. Indeed, in this situation, conformer **Ip** should have a ΔE_{hyper} value of 6.24 kcal mol^{-1} higher than **IIn** (|0.46| + 5.78 = 6.24 kcal mol^{-1}; refer above discussion and to Table 3).

By the same token, sarcosine conformer **II** has a ΔE_{Lewis} value that is 4.17 kcal mol^{-1} higher than conformer **I** (9.09 − 4.92 = 4.17 kcal mol^{-1}; Table 3). Also, if the $n_N \rightarrow \sigma^*_{O-H}$ interaction energy value (9.92 kcal mol^{-1}; Fig. 4) is subtracted from sarcosine conformer **II** ΔE_{hyper} value (10.74 kcal mol^{-1}; Table 3), the result is only 0.82 kcal mol^{-1} (10.74 − 9.09 = 0.82 kcal mol^{-1}) of

Table 2
Electronic density (ρ_{HBCP}) and eletronic density Laplacian ($\Delta^2_{\rho_{HBCP}}$) at the IHB BCP and integrated atomic properties of the IHB hydrogen atoms[a] in au. Bold values are used to represent hydrogen reference atoms that cannot form IHB.

Glycine						
	ρ_{HBCP}	$\Delta^2_{\rho_{HBCP}}$	$q(H_4)$	$E(H_4)$	$M_1(H_4)$	$V(H_4)$
Ip	**–**	**–**	**+0.606**	**−0.3387**	**0.166**	**30.41**
IIn	0.035	+0.104	+0.583	−0.3487	0.175	26.13
VIIp	0.020	+0.064	+0.612	−0.3304	0.150	20.85
Sarcosine						
	ρ_{HBCP}	$\Delta^2_{\rho_{HBCP}}$	$q(H_{12})$	$E(H_{12})$	$M_1(H_{12})$	$V(H_{12})$
I	**–**	**–**	**−0.027**	**−0.6238**	**0.138**	**51.036**
IVb	0.008	+0.033	+0.013	−0.6113	0.128	46.689
	ρ_{HBCP}	$\Delta^2_{\rho_{HBCP}}$	$q(H_{13})$	$E(H_{13})$	$M_1(H_{13})$	$V(H_{13})$
I	**–**	**–**	**+0.605**	**−0.3390**	**0.166**	**21.944**
II	0.035	+0.099	+0.610	−0.3327	0.152	17.019
DMG						
	ρ_{HBCP}	$\Delta^2_{\rho_{HBCP}}$	$q(H_{16})$	$E(H_{16})$	$M_1(H_{16})$	$V(H_{16})$
I	**–**	**–**	**+0.604**	**−0.3395**	**0.168**	**21.999**
II	0.032	+0.094	+0.607	−0.3344	0.154	17.277
	ρ_{HBCP}	$\Delta^2_{\rho_{HBCP}}$	$q(H_{10})$	$E(H_{10})$	$M_1(H_{10})$	$V(H_{10})$
I	**–**	**–**	**−0.019**	**−0.6185**	**0.142**	**50.131**
III	0.008	+0.034	−0.031	−0.6223	0.146	50.849
	ρ_{HBCP}	$\Delta^2_{\rho_{HBCP}}$	$q(H_{13})$	$E(H_{13})$	$M_1(H_{13})$	$V(H_{13})$
I	**–**	**–**	**−0.019**	**−0.6185**	**0.1 42**	**50.072**
III	0.009	+0.035	−0.029	−0.6223	+0.146	50.535
	ρ_{HBCP}	$\Delta^2_{\rho_{HBCP}}$	$q(H_{15})$	$E(H_{15})$	$M_1(H_{15})$	$V(H_{15})$
I	**–**	**–**	**−0.028**	**−0.6249**	**0.137**	**50.626**
IV	0.011	+0.038	+0.017	−0.6114	0.124	45.274

[a] Atom numbering in Fig. 2.

Table 3
Total energy of the real system (ΔE_{FULL}), energy of the hypothetical case where hyperconjugation is removed (ΔE_{Lewis}) and hyperconjugative energy (ΔE_{hyper}) for the glycine, sarcosine and DMG conformers (values in kcal mol^{-1}).

	Ip	IIn	IIIn	IVn	Vn	VIIp		
Glycine								
ΔE_{FULL}[a]	0.00	0.60	1.65	1.26	2.61	5.81		
ΔE_{Lewis}	3.17	9.93	3.67	2.27	0.00	11.68		
ΔE_{hyper}	5.78	11.94	4.63	3.62	0.00	8.48		
	I	II	III	IVa	IVb	Va	Vb	VII
Sarcosine								
ΔE_{FULL}[a]	0.00	0.01	1.16	0.27	1.99	1.66	2.81	6.28
ΔE_{Lewis}	4.92	9.09	4.87	3.59	5.35	0.00	6.00	13.56
ΔE_{hyper}	6.58	10.74	5.37	4.98	5.02	0.00	4.85	8.94
	$Ip_{(DMG)}$	II	III	IV	V	VII	Z	
DMG								
ΔE_{FULL}[a]	1.09	0.00	2.45	1.58	2.36	7.44	2.33	
ΔE_{Lewis}	5.27	8.02	10.25	4.63	3.18	17.56	0.00	
ΔE_{hyper}	6.51	10.35	10.13	5.38	3.15	12.45	0.00	

[a] ZPE correction is not included in these cases in order to the $E_{FULL} = E_{Lewis} - E_{hyper}$ equation be fulfilled.

stabilization by hyperconjugative effects. So, in comparison to sarcosine conformer **I**, which has ΔE_{hyper} value of 6.58 kcal mol^{-1} (Table 3), sarcosine conformer **II** is less stabilized by hyperconjugative interactions by 5.76 kcal mol^{-1}, i.e., approximately the same quantity as for glycine **Ip** and **IIn** conformers (which value is 6.24 kcal mol^{-1}, see above).

Furthermore, NBO analysis indicates that the closer energies of sarcosine conformer **II** to conformer **I** (ΔE_{Lewis} = 4.92 kcal mol^{-1}; Table 3) in comparison to glycine conformer **IIn** to conformer **Ip** (ΔE_{Lewis} = 3.17 kcal mol^{-1}; Table 3) is due to higher contributions of steric effects for the former compound. In the other hand, QTAIM suggests that only conformer **II** of sarcosine and conformer **IIn** of glycine are stabilized by one IHB and, hence, the main forces that differentiate glycine and sarcosine conformational preferences are being indicated to steric effects. In a recent work [32], it was shown that glycine conformational preferences have been attributed to an interplay between steric and hyperconjugative interactions, with higher contributions of the latter effects.

Moreover, although sarcosine conformational preferences have contributions of steric effects higher than glycine, these effects do not overcome hyperconjugative effects, but both have similar contributions. Such a balance between steric and hyperconjugative effects in sarcosine may be observed if conformer **I** and **IVa**, the two most stable sarcosine conformers, are compared. Conformer **IVa** experiences about 1.30 kcal mol^{-1} less steric effects than conformer **I**, but, on the other hand, it is 1.60 kcal mol^{-1} less stabilized by hyperconjugative effects than conformer **I** (Table 3). Since conformer **IVa** is only 0.20 kcal mol^{-1} less stable than conformer **I** and the differences between steric and hyperconjugative energies of these compounds are about the same, one can conclude that steric and hyperconjugative effect contributions for sarcosine conformational preferences are in balance.

The higher steric effect contributions with sarcosine have significant consequences in its conformational geometries. Indeed, in order to decrease the steric effects by keeping the CH_3 and COOH groups apart from one another, all sarcosine conformers bend their ψ and ϕ dihedral angles in comparison to glycine conformers (dihedral angle values in Table 1). As a consequence of these dihedral angle distortions the steric effects are minimized, but hyperconjugative interactions are committed, i.e., due to the dihedral angle bending the molecular orbitals involved in hyperconjugative interactions have overlap alignments that are not optimal (here highlighted by the NBO analysis).

A question that then arises is: if steric effects have higher contributions for sarcosine conformational preferences in comparison to glycine, which has about the same contribution of hyperconjugative effects as the former compound, what should occur with DMG that has two bulky CH_3 groups? We might expect that steric effects should have higher contributions in DMG than in sarcosine, possibly with higher contributions than hyperconjugative effects, and this is indeed the case. In comparison to glycine, DMG shows a severe increase of steric effects due to exchanging two hydrogen atoms by two CH_3 groups. However, as shown in Table 1 and Fig. 2, DMG conformers are analogous to glycine conformers and, due to this, are also analogous to sarcosine, as well. C—H···O IHB formations have been arbitrarily indicated in the literature as the main force which rules the conformational energies of this amino acid (e.g., see reference **13**). Actually, the DMG **Ip** conformer (**Ip_{DMG}**), unlike glycine and sarcosine, is not the global minimum, while conformer **II** is.

Popelier criteria applied to DMG conformers (Table 2 and Fig. 3) indicate that only conformer **II** forms an N···H—O IHB, while conformer **III** shows C—H···O interactions that do not satisfy Popelier criteria and conformer **IV** has a stable C—H···O IHB. Nevertheless, the DMG conformer **II** N···H—O IHB is weaker than in glycine and sarcosine conformer **II** (ρ values; Table 2) and, even so, DMG conformer **II** is more stable than conformer **Ip_{DMG}**. In other words, the DMG conformer **II** NH–O IHB is the responsible force for its stabilization, but it is weaker than for both conformer **IIn** of glycine and conformer **II** of sarcosine. Thus, although N···H—O IHB is weaker for the DMG conformer **II** than for both glycine conformer **IIn** and sarcosine conformer **II**, surprisingly the former is the global minimum, while the later are less stable than glycine conformer **Ip** and sarcosine conformer **I**, respectively. In this sense, the fact that DMG conformer **II** forms a weaker IHB than glycine and sarcosine conformer **II** and, unlike these last ones, is more stable than **Ip_{DMG}**, must have origin in other intramolecular effects than IHB.

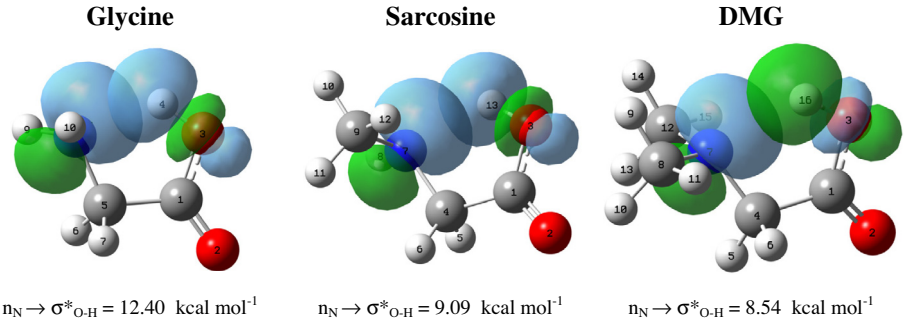

Fig. 4. NBO orbital plots for $n_N \rightarrow \sigma^*_{O-H}$ interactions. The $n_N \rightarrow \sigma^*_{O-H}$ hyperconjugative interaction values are indicated.

Indeed, DMG has a different conformer that is not present in either glycine or sarcosine (and, to the best of our knowledge, not before studied), here called conformer **Z**. Conformer **Z** has $N(CH_3)_2$ and COOH groups with an approximately perpendicular relationship ($\psi = 81.2°$; Table 1). Since DMG shows a minimum that has a quasi perpendicular ψ dihedral angle as a stable conformer, the steric effect should have a great increase in DMG conformational preferences in comparison to glycine. In fact, in order to decreases steric effects between the $N(CH_3)_2$ and COOH groups, DMG conformer **Z** adopts a perpendicular ψ dihedral angle geometry, which decreases steric effects in this conformer, but, probably, should also decrease hyperconjugative stabilization energy. NBO analysis (Table 2) confirms these assumptions, showing that conformer **Z** is the DMG conformer that suffers lesser steric effects, but, as due to poor orbital alignment, it is also the conformer less stabilized by hyperconjugation.

Another example that shows that steric effects are the principal responsible force for DMG conformational preferences can be seen by comparing the conformer **II** and $\mathbf{Ip_{DMG}}$ ΔE_{hyper} and ΔE_{Lewis} values in Table 2. If we subtract the conformer **II** $n_N \rightarrow \sigma^*_{O-H}$ hyperconjugative interaction energy value (8.54 kcal mol^{-1}; Fig. 4), which refers to the N···H—O IHB, from ΔE_{hyper} value in Table 2, conformer $\mathbf{Ip_{DMG}}$ would be ca. 4.70 kcal mol^{-1} more stabilized by hyperconjugative interactions. In this way, both hyperconjugation and steric effects favor conformer $\mathbf{Ip_{DMG}}$ in relation to conformer **II**. Also, both the ρ_{HBCP} and $n_N \rightarrow \sigma^*_{O-H}$ values indicate that the DMG N···H—O IHB is weaker than in glycine. Notwithstanding, unlike glycine conformer **IIn**, DMG conformer **II** is the global minimum. One can understand this behavior by observing that the difference between glycine **Ip** and **IIn** ΔE_{Lewis} values (6.76 kcal mol^{-1}; Table 2) is much higher than that between the DMG conformers $\mathbf{Ip_{DMG}}$ and **II** (2.75 kcal mol^{-1}). Therefore, NBO analysis indicates that the source of energy inversion between conformers **I** and **II** of glycine and DMG is due to the higher steric effect contributions to DMG conformational preferences, in comparison with those of glycine. Thus, although the N···H—O IHB, which is the source of stabilization of conformer **II**, is weaker than that of glycine conformer **IIn**, the $\mathbf{Ip_{DMG}}$ conformer, which has two CH_3 groups oriented toward the bulky COOH group, experiences an increase of steric effects in relation to DMG conformer **II**, which has the two CH_3 groups far from the COOH group. Consequently, DMG conformer **II** is the global minimum.

Ultimately, unlike glycine and sarcosine, DMG conformational preferences show an increase of steric effects, which indeed overcome hyperconjugative contributions and, due to this fact, the $\mathbf{Ip_{DMG}}$ conformer is not the global minimum. Therefore, similar to glycine and sarcosine **I** conformers, $\mathbf{Ip_{DMG}}$ does not form an IHB and, consequently, in contrast to literature assumptions, steric/hyperconjugative effects rule these amino acid conformational preferences.

4. Conclusions

Sarcosine and DMG conformational behaviors emphasize that IHB have minor contributions to glycine conformational preferences in comparison to steric and hyperconjugative effects. Indeed, the most stable glycine **Ip** conformer does not form IHB and its conformational energies are governed by steric and hyperconjugative effects, with higher contributions from the latter effects. Moreover, hyperconjugation gives smaller contributions to the glycine analogs sarcosine and DMG, due to the increasing steric effects provided by one and by two CH_3 groups attached to the nitrogen atom, respectively. In fact, steric effect contributions have about the same contributions as hyperconjugative effects in sarcosine and are the major contribution to DMG conformational behavior.

Actually, our results show that glycine conformational preferences can be disturbed by inclusion of CH_3 groups, which increases steric effects in the molecule, but, in contrast with common literature assumptions, IHB are not the responsible force that govern the conformational preferences of glycine and its analogs. Thus, we emphasize that IHB should not be arbitrarily invoked to explain small amino acid conformational behaviors.

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