Chemical Physics 387 (2011) 85–91

Contents lists available at ScienceDirect

Chemical Physics

journal homepage: www.elsevier.com/locate/chemphys

Are hydrogen bonds responsible for glycine conformational preferences?

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ARTICLE INFO

Article history:
Received 18 May 2011
In final form 6 July 2011
Available online 12 July 2011

Keywords:
Conformational analysis
Amino acids
Glycine
Natural bond orbital analysis
Quantum theory of atoms in molecules

ABSTRACT

Glycine conformational preferences have mostly been explained as due to the formation of intramolecular hydrogen bonding, despite other possible relevant intramolecular interactions that may be present in this molecular system. This paper, within the framework of the quantum theory of atoms in molecules and natural bond orbital analysis, at the B3LYP/aug-cc-pVDZ level, shows that hydrogen bonding formally stabilizes just one of the glycine conformers. Indeed, these theoretical calculations suggest that both steric hindrance and hyperconjugative effects rule conformational preferences of this model compound and may not be ignored in discussions of amino acid conformational analyses.

1. Introduction

Knowledge of the stable conformers of glycine, a basic model for more complex α-amino acids in their neutral isolated forms, has gained special attention, being of great interest due to its biological role. The great rotational flexibility of the glycine molecule, the rotation of its three main dihedral angles, as shown in Fig. 1, that is, the ϕ (LP—N—C—C(O)), ψ (N—C—C=O) and θ (O=C—O—H) dihedral angles, leads to various low energy conformers [1]. Such conformers have been extensively studied theoretically [1–17], and the more stable ones predicted (Fig. 2; the notation used for the conformers is described in Ref. [1]) were experimentally recognized [18–24]. Nevertheless, the central discussion is based on the most stable geometry adopted by all possible conformers of glycine and on their corresponding relative energies. The effects which stabilize such conformers, however, are commonly attributed to possible intramolecular hydrogen bond (H-bond) formation and more detailed interpretations encompassing this assumption are scarce.

It has been suggested that the existence of some types of H-bond are responsible for the energy difference between the most stable conformers of glycine [13]. According to this interpretation, a N···H—O interaction stabilizes conformers **IIn** and **VIIp**, two bifurcated N—H···O=C and N—H···O—H interactions stabilize **Ip** and **IIIn** conformers, respectively, N—H···O=C and N—H···O—H stabilize **IVn** and **Vn**, respectively, and a C=O···H—O stabilizes the **Ip**, **IIIn**, **IVn** and **Vn** conformers, which have a *Z* carboxyl functional group conformation Fig. 3. Such assumptions diverge from earlier papers that used the quantum theory of atoms in molecules (QTAIM) to characterize these intramolecular interactions [25–27]. Pacios et al. found evidence of a stabilizing H-bond only in the **IIn** conformer and, surprisingly, suggested that the origin of the glycine conformational preferences is due to possible residuals of H-bond present in the remaining conformers [25,26]. Accordingly, Wang et al. [27] found that a H-bond only exists in the **IIn** conformer, and concluded that hyperconjugative effects rule the conformational preferences of neutral glycine, based on their natural bond orbital (NBO) analysis. Thus, no consensus is observed between these authors and additional papers concerning the effects that govern glycine conformational preferences cannot be found in the literature.

Classic (steric and electrostatic) and quantum (hyperconjugative) effects have been invoked to explain the energy difference of conformers of several molecular systems, even some simpler than glycine [28–33]. Surprisingly, these effects have been ignored in the study of amino acids and, although there is no evidence of H-bonds in most conformers of glycine, its stabilization is actually attributed to this intramolecular interaction [1–24]. Such arbitrary interpretation makes a reliable understanding of the amino acids rotational isomerism impossible and, hence, protein folding pathway rationalization.

Thus, B3LYP/aug-cc-pVDZ, a theory level which has shown results in excellent agreement with MP2/aug-cc-pVDZ and with matrix-isolation infrared experimental data for the glycine molecule [24], was performed on the glycine conformers of Fig. 2. QTAIM and NBO analysis have been also carried out, in order to understand the classical and quantum effects and H-bond contributions to their relative stabilities.

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doi:10.1016/j.chemphys.2011.07.006

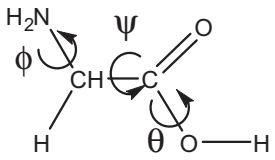

Fig. 1. The rotation of σ bonds, which gives origin to the various possible conformers of glycine. The N—C bond rotation is associated with the ϕ dihedral angle, the C—C(O) with the ψ dihedral angle and the C—O(H) with the θ dihedral angle.

2. Computational details

In general, the relative energies and geometries obtained from the functional B3LYP of density functional theory (DFT) are in good agreement with those obtained from MP2, both for glycine and for other amino acids [18–24]. Therefore, in order to find the conformational minima, the GAUSSIAN 03 program [34] was used to build the potential energy surfaces (PES) at the B3LYP/cc-pVDZ level, scanning the ϕ and ψ torsional angles simultaneously, e.g., scanning ψ from 0° to 360° in steps of 10° and then holding ϕ fixed at 0°, 10°, etc. This procedure led to the results that are plotted in Fig. 4(a) and (b). The same procedure was done with ϕ and θ dihedral angles giving the plots shown in Fig. 4(c) and (d). Moreover, the six conformers found by the above procedure were optimized at the B3LYP/aug-cc-pVDZ level, with no constraints of dihedral angles and with correction of the zero point energy (ZPE). Furthermore, NBO analysis was carried out for the optimized conformers at the same level of theory [35]. Topological analyses, evaluation of local properties and integral properties over the atomic basins (Ω) were carried out with the AIMALL [36] program, using wave functions calculated at the B3LYP/aug-cc-pVDZ level. The quality of the integral properties were confirmed by the integrated values of the Laplacian of the charge density in each atom (that should be zero for an ideal integration), which were always lower than 10^{-3} au.

3. Results and discussion

Five relatively stable conformers (**In** to **Vn**) and a sixth conformer (**VIIp**) that is relatively unstable, found in the PES constructed at the B3LYP/cc-pVDZ level, were used for the present glycine conformational analysis study, which was optimized at

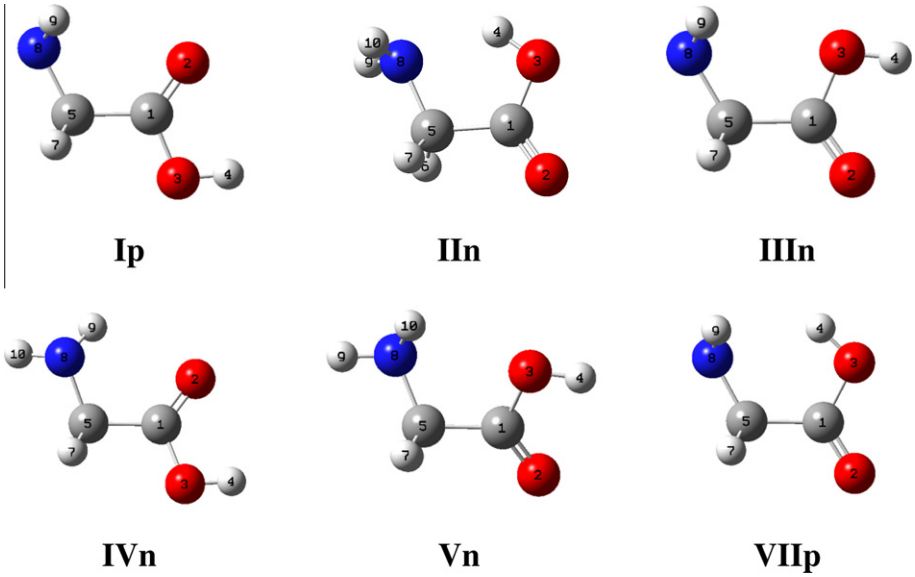

Fig. 2. The most stable conformers of glycine (**Ip**–**Vn**) and a suitable model conformer (**VIIp**). The nomenclature used was adapted from Császár [1] where the roman numerals indicate the stability order and **p** and **n** designate planar and non-planar heavy-atom arrangements, respectively.

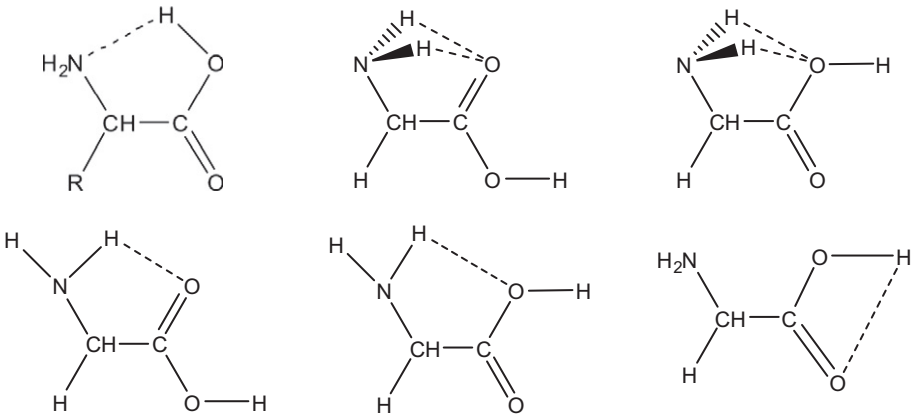

Fig. 3. Possible H-bond formations that are responsible for the glycine conformational preferences.