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## Phenylisoserine in the gas-phase and water: Ab initio studies on neutral and zwitterion conformers

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Abstract: Phenylisoserine (PhIS) is an active side chain as a part of cytotoxic Paclitaxel medicine. The conformational landscape of phenylisoserine was studied. A trial structures were generated by allowing for all combinations of single-bond rotamers. Based on the B3LYP/aug-cc-pVDZ calculations 54 conformers were found to be stable in the gas phase. The six most stable conformers were further optimized at the B3LYP/auc-pVTZ and MP2/aug-ccpVDZ levels for which characteristic intramolecular hydrogen bond types were classified. To estimate the influence of water on PhIS conformation, the IEF-PCM/B3LYP/aug-cc-pVDZ calculations were carried out and showed 51 neutral and 6 zwitterionic conformers to be stable in water solution. According to DFT calculations, the conformer equilibrium in the gas phase is dominated by one conformer, whereas the MP2 calculations suggest three PhIS structures to be significantly populated. Comparison of DFT and MP2 energies of all 57 structures stable in water indicates that, in practice, one zwitterionic and one neutral conformer determine the equilibrium in water. We found that for the neutral conformers in vacuum and in water,  $d(H...B)$  is linearly correlated with Laplacian.

Response to Reviewers: Dear Dr. Toro-Labbe,

Enclosed please find our revised manuscript " Phenylisoserine in the gas-phase and water: ab initio studies on neutral and zwitterion conformers". We thank the Reviewer for kind and constructive comments.

In the current version we address the following question suggested by the Reviewer :

" What I would like to see is a computation of how much stabilization is provided by each of the hydrogen bonds identified in each of the important conformers, both in vacuum and solvation. This data would make the manuscript of much greater general interest, as it would change the focus of the paper to how intermolecular hydrogen bonds stabilize organic conformers - and how this stabilization might change in aqueous solution."

To answer this question we performed the AIM analysis and added three paragraphs at the end of the Results and Discussion section. One Figure was added to the text too, and one Table to the Supplementary Information file. Also four references are supplied.

We think that the manuscript after corrections fits requirements of the journal.

Sincerely yours,

Joanna

## Phenylisoserine in the gas-phase and water: *ab initio* studies on neutral and zwitterion conformers

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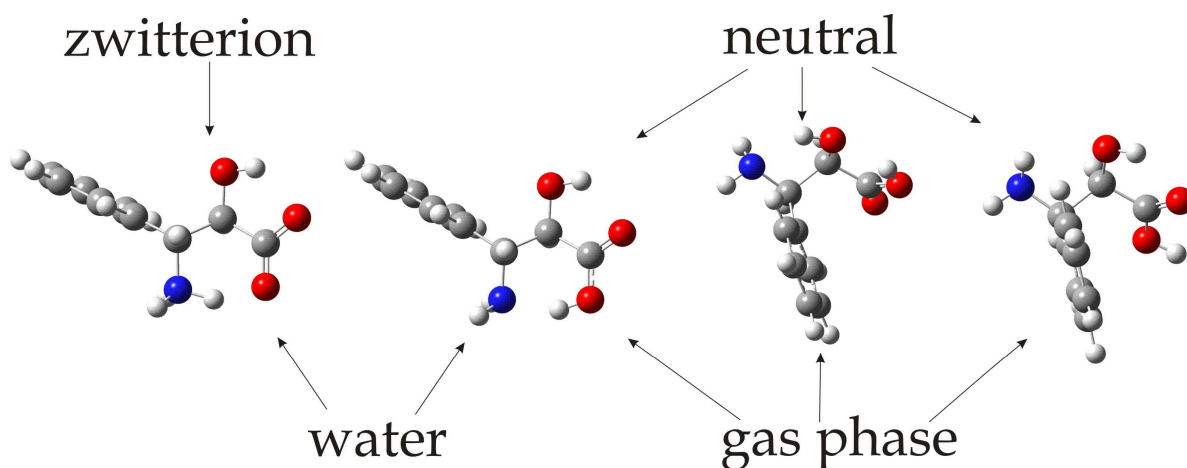
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Phenylisoserine (PhIS) is an active side chain of cytotoxic Paclitaxel medicine. The conformational landscape of phenylisoserine was studied. One zwitterionic and one neutral conformer determine the equilibrium in water whereas in the gas phase the MP2 calculations suggest three PhIS structures to be significantly populated.



# Phenylisoserine: *ab initio* studies of the gas-phase and neutral and zwitterions conformers in water

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## Abstract

The conformational landscape of phenylisoserine (PhIS) was studied. A trial structures were generated by allowing for all combinations of single-bond rotamers. Based on the B3LYP/aug-cc-pVDZ calculations 54 conformers were found to be stable in the gas phase. The six most stable conformers were further optimized at the B3LYP/auc-pVTZ and MP2/aug-ccpVDZ levels for which characteristic intramolecular hydrogen bond types were classified. To estimate the influence of water on PhIS conformation, the IEF-PCM/B3LYP/aug-cc-pVDZ calculations were carried out and showed 51 neutral and 6 zwitterionic conformers to be stable in water solution. According to DFT calculations, the conformer equilibrium in the gas phase is dominated by one conformer, whereas the MP2 calculations suggest three PhIS structures to be significantly populated. Comparison of DFT and MP2 energies of all 57 structures stable in water indicates that, in practice, one zwitterionic and one neutral conformer determine the equilibrium in water. We found that for the neutral conformers in vacuum and in water,  $d(\text{H}\dots\text{B})$  is linearly correlated with Laplacian.

**Keywords** Conformers · DFT · MP2 · Phenylisoserine · Zwitterion

## Introduction

The molecules important in biology are remarkable, considering that they can display wide variety of structures and functions. Most of the interesting functions carried out by these biomolecules are dependent on stable well-defined structures. This factor one can consider in the development of unnatural backbone modified peptides. To such a group belongs  $\beta$ -amino acids [1]. The additional carbon atom incorporated into the backbone structure in natural  $\alpha$ -amino acids results in unnatural oligomers containing side chains, which are significantly different from that found in natural compounds, but that can be recognized by side chain of receptors. The title molecule, phenylisoserine (Scheme 1), is one of such examples.

Among the new families of anticancer agents the natural product paclitaxel (Taxol<sup>®</sup>, Scheme 2) and its derivative docetaxel (Taxotere<sup>®</sup>) are used in the treatment of breast, ovarian cancers and lung carcinomas [2-4]. Paclitaxel is a natural product isolated from the bark of the western pacific yew tree. It contains 10-deacetylbaccatin-III (DBAC, Scheme 3) - a natural substance isolated from the leaves of the *Taxus baccata* species and phenylisoserine side chain [5, 6]. It has been shown that the side chain at C-13 and the diterpene moiety of taxol (DBAC) are both essential for the anticancer activity of the taxoid family. The baccatin III tetracyclic ring system has been shown to be rigid segment. Moreover, the structure-activity studies demonstrated that the presence of the phenylisoserine side chain (as N-benzoyl-(2R,3S)-3-phenylisoserine, Scheme 2) with correct absolute stereochemistry is significant for strong cytotoxicity. The side chain of paclitaxel, as all amino acids, is flexible and can adopt different conformations. The total synthesis of paclitaxel was done in early 70s [7], however, because of complicated multistep synthesis and small yield of the synthesis, the total synthesis is not applied in the pharmaceutical industry. A semisynthetic way of producing paclitaxel seems to be the most promising: it is based on semiproduct (10-deacetylbaccatin-III) extracted from leaves of *Taxus baccata* to condensate it with N-benzoyl-(2R,3S)-3-phenylisoserine [8-10]. Therefore, study on conformational landscape of phenylisoserine may provide insights and support practical efforts to obtain the very valuable medicine.

To study of the conformational landscape of phenylisoserine as one of the  $\beta$ -amino acids is important not only because of paclitaxel and related compounds. It was found that  $\beta$ -amino acids can form stable  $\alpha$ -helix,  $\beta$ -sheet, and hairpin motifs, similar as in  $\alpha$ -peptides. Indeed,

while ca.15-20 residues are required to obtain a stable  $\alpha$ -peptide  $\alpha$ -helix, only six  $\beta$ -amino acids are necessary to form a stable  $\beta$ -peptide-based helix [11-14]. Because of its special importance in so many aspects, it is highly desirable to explore conformations of the  $\beta$ -amino acids thoroughly.

Likewise other amino acids, the phenylisoserine molecule has no symmetry and exhibits a significant internal rotational degree of freedom due to rotations around the three single bonds in the central part of the carbon skeleton. Therefore, it is likely to occur as numerous low energy conformers. Amino acid are known to exist as zwitterions in the solid state and in solution and in the nonionized, neutral form in the gas phase. Study of the conformational behavior of the neutral amino acids is important for understanding the dependence of the peptides and protein backbone.

The gas-phase data are, in general qualitatively consistent with the matrix-isolation results. Several amino acids have been studied experimentally by using the IR inert-matrix-isolation method [15-24]. In the in low-temperature matrices three conformers were found for glycine [15-18], three for valine [19], two for proline [20], four for serine [21], six for phenylalanine [24], and more than three for tryptophane [25]. Tyrosine has been studied only by *ab initio* method [26]. Recently, for cysteine and  $\beta$ -alanine we identified in the low-temperature matrices, 3 and 6 conformers, respectively [22, 23]. Also, in few laboratories, investigations on gaseous amino acids have been carried out by microwave spectroscopy during the past two decades [26-41]. To the best of our knowledge, so far, phenylisoserine has not been studied neither by by matrix-isolation IR spectroscopy. nor microwave spectroscopy.

The conformational characteristic of phenylisoserine has been the subject of only few theoretical studies. In the most detailed theoretical study, the conformation of the side chain (with the glycolate fragment) have been investigated at HF/6-31G(d,p) and PM3 level [42]. Nine conformers have been found and it has been suggested that only in one of them, most stable, the C3 phenyl is accommodated in a favorable position with its  $\pi$  orbital far away from the carbonyl oxygen lone pairs. Onsager continuum approach (SCFR) and supermolecular models with two water molecules have been used for study the conformation in polar solvent. The conformation similar to molecule of the crystal structure of paclitaxel is now the most favorable [42] (and refs. therein). The second part of paclitaxol – DBAC have been also studied by the calculations. The benzoate and acetate are necessary to allow binding to tubulin

in the humane body. The importance of the oxetane was found by ZINDO method, what is consistent with experimental data [43].

The structure-activity relationship in the phenylisoserine moiety of the paclitaxel are dominated by the discussion of its different conformations named as polar and non-polar [42, 44, 45]. If the solvent is non-polar ( $\text{CDCl}_3$ ), than one assume that paclitaxel binding site on microtubules is hydrophobic and the molecule adopt a staggered conformation around the C2-C3 bond. On the other hand, if solvent is polar, the C3 phenyl group is positioned close to C2 benzoyl and C4 acetyl groups [42]. To summarize, the conformation of the phenylisoserine moiety in different solvents depends on several factors.

Continuing our previous study on  $\beta$ -amino acids [22, 23] we undertook a detailed investigation on the conformation behavior of the gas-phase phenylisoserine isolated and in the water solvent. Since there has been no experimental attempt to determine neither microwave and matrix isolation IR spectra of gaseous phenylisoserine nor x-ray structure, the calculated data may be useful in searching of both gas-phase and condensed phases conformers with the spectroscopic methods. Therefore, the goal of this study is twofold: (i) to estimate the conformer population of phenylisoserine in the gas-phase; (ii) to predict the conformer population of phenylisoserine in the water solution considering zwitterionic structures. In this way, a platform for a better distinction of various conformers in future liquid-phase experiments is settled out. To the best of our knowledge, no systematic and accurate study on the conformational behavior of phenylisoserine in gas-phase and in water solution has been reported.

## **Computational details**

### **Modeling the gas phase**

All the calculations were performed by using both the hybrid Becke three-parameter Lee–Yang–Parr DFT B3LYP functional [46, 47] whose reliability in calculations of the ground state geometries has been widely assessed [48]. The aug-cc-pVDZ Dunning's [49, 50] (and for the most stable gas-phase conformers the aug-cc-pVTZ) basis sets were employed. These basis sets are known to be adequate to describe both organic molecules and their hydrogen-



bonded systems. The conformational space of phenylisoserine was explored through a systematic variation of dihedral angles:  $d(O4C1O5H)$ ,  $d(O5C1C2C3)$ ,  $d(C1C2N6H)$ ,  $d(C1C2C3S7)$ ,  $d(C2C3S7H)$  and  $d(C2'C1'C3C2)$  (for atom labeling see Scheme 1). The stationary structures are found by ascertaining that all the harmonic frequencies are real. The relative abundances of the most stable conformations were then estimated by using the Gibbs free energy at 298.15 K,  $\Delta G$ , relative to the most stable conformer. At the B3LYP/aug-cc-pVDZ level, 54 conformers were found to be stable in the gas phase.

All the calculations were performed by using the *Gaussian 03* [51] and *Gaussian 09* [52] programs.

### **Modeling the aqueous phase**

A systematic search for the stable zwitterions within the supermolecule approach goes far beyond this study; therefore, we decided to study the solvent effect by the IEF-PCM model [53, 54], which includes long-range interactions only. Continuum models are widely used nowadays to simulate solvent effects on conformation [55]. Among many methods used, the IEF-PCM method introduced in late 1990s, was shown to simulate the aqueous phase fairly well [55]. Combined supermolecular-continuum approaches would be probably more successful, if they could be applied for phenylisoserine surrounded by hundreds water molecules. To this aim, 54 gas-phase nonionized structures were reoptimized in water solvent at the IEFPCM/B3LYP/aug-cc-pVDZ level to yield 51 nonionized and 6 stable zwitterion structures.

## **Results and discussion**

### **Geometry and energy of the gas-phase phenylisoserine monomers**

The phenylisoserine molecule has six single bonds around which free rotations may lead to as much as ca. 40 000 local minima. To generate the structures of it the relevant torsion angles were varied. Based on semiempirical AM1 search, 158 stable phenylisoserine conformers were appointed and reoptimized at the B3LYP/aug-cc-pVDZ level yielding to 54 stable structures. Each of the phenylisoserine functional groups, carboxyl and alcoholic OH, C=O,

and  $\text{NH}_2$ , may operate as a hydrogen bond donor or acceptor. Thus, because of internal hydrogen bonds some conformers are stabilized more than others. Six low-energy structures of phenylisoserine (Fig. 1, Table 1) were further studied by using the B3LYP/aug-cc-pVTZ and MP2/aug-cc-pVDZ methods. They were found to be in the  $3.5 \text{ kcal mol}^{-1}$  energy range relative to the most stable form. Thermochemical properties at 298.15 K were computed for all the conformers and the relative abundances were estimated for six of them. Figures, energetic and selected dihedral angles of all the fifty four phenylisoserine conformers optimized at the B3LYP/aug-cc-pVDZ level are available in the electronic supplementary materials (Tables 1SI and 2SI, Fig. 1SI). In Table 3SI Cartesian Coordinates are gathered for the six most stable structures calculated at the B3LYP/aug-cc-pVDZ level.

Now let us compare the energetic results generated by using different methods and basis sets. The conformers are ordered according to the increasing total energy obtained at the B3LYP/aug-cc-pVDZ level (Table 1, Table 1SI). First and foremost, at the B3LYP/aug-cc-pVDZ level the most stable conformer **1** is more stable than the next one by as much as  $2.3 \text{ kcal mol}^{-1}$ . Upon the thermochemical corrections, the energetic order changes but only slightly: conformer **3** is located at 2nd position and conformer **5** at the 4th place (Table 1). However, the order of the conformers **4**, **5**, and **6** is slightly perturbed (Table 1). Conformer **1** is found to be still the global minimum when the basis set is increased to aug-cc-pVTZ and is still separated from the next one by more than  $2.3 \text{ kcal mol}^{-1}$  (Table 1). The energetical picture undergo significant change at the MP2/aug-cc-pVDZ level. First, conformer **2** becomes global minimum, separated from the next one, **1**, by only  $0.13 \text{ kcal mol}^{-1}$ . Moreover, the third stable conformer **3** is only  $0.86 \text{ kcal mol}^{-1}$  less stable than **2**, and should be seriously taken into account if equilibrium conformer mixture in the gas phase is considered (Table 1).

The conformers may be characterized by the intramolecular hydrogen bonds (IHB). The presence of three hydrogen bond donors ( $\text{NH}_2$ ,  $\text{OH}_c$ ,  $\text{OH}_a$ ) and four hydrogen bond acceptors ( $\text{O}=\text{C}$ ,  $\text{OH}_a$ ,  $\text{NH}_2$ ,  $\text{OH}_c$ ) allows for a wide range of hydrogen bond combinations and large number of stable forms. Let us now discuss the six lowest energy conformers. All the most stable six structures, exhibit the presence of the intramolecular hydrogen bonds (Fig. 1, Table 2). Two of them, **1** and **4**, exhibit the  $\text{OH}_c \dots \text{NH}_2$  hydrogen bond, in which the  $\text{OH}_c$  carboxylic group, as a proton donor, is in trans position to the  $\text{C}=\text{O}$  group. This IHB forms a six-membered ring (Fig. 1). In conformers **1** and **4** this intramolecular H-bond is quite short i.e. ca.  $1.74 \text{ \AA}$  (Table 2). This type of hydrogen bond  $\text{OH}_c \dots \text{NH}_2$  is the same as that of phenylalanine [24], tyrosine [26] and tryptophan [56] global minimum. In the structures **2** and

**3**, the OH<sub>a</sub> alcoholic hydroxyl group is the proton donor and proton acceptor in the same time. In the conformer **2** it is proton donor to the NH<sub>2</sub> group and proton acceptor from the OH<sub>c</sub> group forming the OH<sub>a</sub>...NH<sub>2</sub> and OH<sub>c</sub>...OH<sub>a</sub> IHB, respectively. In the conformer **3** the situation is different: the OH<sub>a</sub> group is the proton acceptor from the NH<sub>2</sub> group and the proton donor to the C=O group, forming NH<sub>2</sub>...OH<sub>a</sub> and OH<sub>a</sub>...O=C IHB, respectively. The other very important IHB is the OH<sub>a</sub>...O=C bond (ca. 2.0 Å) stabilizing the **1**, **3**, and **6** conformers by forming a five-membered ring (Fig. 1). The next IHB, OH<sub>c</sub>...OH<sub>a</sub> is quite a short (ca. 1.9 Å) and it is present in two conformers **2** and **5**. In case of conformers **3**, **4**, **5**, and **6**, there is also an IHB in which NH<sub>2</sub> group is a proton donor to either OH<sub>a</sub> or O=C groups (Table 2).

The population of conformers at room temperature are shown in Table 1. In the gas phase the distribution has a peak: the most stable form **1** is at the DFT level populated in at least 93 % (X(G) in terms of ΔG/B3LYP) (Table 1). On the other hand, the populations based on total energies calculated at the MP2/aug-cc-pVDZ level indicate three conformers: **1**, **2**, and **3** to be stable in significant amounts of ca. 37%, 46%, and 11%, respectively. Thus the population analysis is definitely dependent on energy correlation factor, however, to go far beyond the level applied here seems now to be quite a difficult task for so many conformers.

### **Energy of the aqueous-phase phenylisoserine conformers**

#### *Neutral forms*

To estimate the influence of water on phenylisoserine molecule conformations, all the 54 conformers stable in the gas phase were reoptimized by using the IEF-PCM/B3LYP/aug-cc-pVDZ method. The aqueous surrounding affects both the shape of the conformer distribution curve and the energetic differences between PhIS conformers. It is noticeable that in the first six stable conformations there are four conformers stable in the gas phase, yet, in a different order. Conformer 1w (1 stands for number of the conformer in the gas phase, w denotes water) remains still the most stable one and is still separated from the next one by 2.4 kcal mol<sup>-1</sup> (in terms of ΔG, Table 1). Furthermore, the conformers are ordered differently (Table 1); in particular, the energy differences between them are larger. Additionally, among the most stable conformers there are forms denoted as 29w and 10w, that have been much less populated in the gas phase. This confirms a significant effect of solvation on geometrical parameters and solvation energies of solutes.

All the most stable six neutral structures exhibit the presence of the intramolecular hydrogen bonds (IHB, Fig. 2, Table 2). Out of these six neutral conformers, three exhibit the  $\text{OH}_c \dots \text{NH}_2$  and two  $\text{OH}_a \dots \text{NH}_2$  internal hydrogen bonds (Fig. 2, Table 2). The shortest  $\text{OH}_c \dots \text{NH}_2$  hydrogen bond is found for **1w**, which is the most stable neutral form in water. It is noticeable, that all structures with the  $\text{OH}_c \dots \text{NH}_2$  IHB (**1w**, **29w**, **4w**) are the most stable in water. The longest  $\text{OH}_c \dots \text{NH}_2$  hydrogen bond is detected for the **2w** conformer, which is the fourth stable neutral form in water. Thus, the presence of the internal  $\text{OH}_c \dots \text{NH}_2$  hydrogen bond is probably the main factor controlling conformer stability in water. Additionally, the distance of  $\text{OH}_a \dots \text{C1}'(\text{Phe})$  is shorter in **29w** than in the other conformers. This suggests that the interaction with the ring  $\pi$ -electrons may be also be an important factor. Figures, energies and selected dihedral angles of all 51 neutral PhIS conformers in water optimized at the IEF-PCM/B3LYP/aug-cc-pVDZ level are available in the electronic supplementary materials (Tables 4SI and 5SI, Fig. 2SI). Additionally, Table 3SI lists Cartesian coordinates of the six most stable neutral forms in water.

### *Zwitterionic forms*

The zwitterionic phenylisoserine conformers are unstable in the gas phase and thus, there are no such minima on the potential energy surface of an isolated monomer. Yet, in the water medium they become quite populated. Therefore, we carried out calculations for the zwitterion form of PhIS in the water phase. Out of 51 neutral structures stable in water only 6 appeared to exist as zwitterions (**z**) (Fig. 3, Table 1). Moreover, the zwitterionic **1z** conformer came out to be the most stable, and definitely dominating, conformer in water. Energies and selected dihedral angles of the 6 zwitterion PhIS conformers in water, optimized at the IEF-PCM/B3LYP/aug-cc-pVDZ level, are available in the electronic supplementary materials (Tables 6SI and 7SI). Additionally, in Table 3SI Cartesian coordinates these zwitterion structures are listed.

According to energetic  $\Delta G$  results (Table 1), the most stable five zwitterion forms are those where the internal hydrogen bond is formed between the protonated amino group,  $\text{NH}_3^+$ , and the carboxylic  $\text{COO}^-$  moiety. For example, in **1z** this distance is equal to 1.565 Å and is shorter by 0.056 Å than  $\text{OH}_c \dots \text{NH}_2$  in neutral **1w** form and shorter by 0.178 Å than  $\text{OH}_c \dots \text{NH}_2$  in **1** in the gas phase. Additionally, the interaction of the  $\text{NH}_3^+$  group with the  $\text{OH}_a$  group stabilizes conformer **6z**. Moreover, the interaction of  $\text{OH}_a$  with the ring,  $\text{OH}_a \dots \text{C1}'(\text{Phe})$ , seems to stabilize all zwitterionic conformers.

Let us now discuss conformer population in water solution. For water phase it is necessary to consider both the neutral and zwitterionic forms because for all aminoacids there are equilibria of these forms in solution. However, first let us focus on each type separately. The population of neutral conformers in water (Table 1) shows the maximum peak for conformer 1w, which is populated in at least 98 % (X(G) in terms of  $\Delta G/B3LYP$ ). In contrast to the gas phase population, the MP2 level does not change the quantitative population picture. Indeed, according to MP2/aug-cc-pVDZ total energies conformer 1w is populated in ca. 87% (Table 1). Similarly, the population of zwitterionic conformers in water (Table 1) shows the maximum peak for conformer 1z, which is populated in ca. 99 % (X(G) in terms of  $\Delta G/B3LYP$  and 98% at the MP2 level (Table 1). Now, when the most stable 6 neutral and 6 zwitterionic conformers are considered all together (Table 8SI) it appears that, at the DFT level, only the most stable neutral conformer 1w and the most stable zwitterionic conformer 1z are present in amounts of ca. 86% and 12 %, respectively. Qualitatively, the MP2 calculations yield a similar result: in practice only the most stable neutral conformer 1w and the most stable zwitterionic conformer 1z are present. However, the MP2 level indicate that the zwitterions can be populated much more (ca. 36%) than predicted by the DFT calculations. Thus we expect both forms to be detected in equilibrium in water.

At the end let us comment on question of how much stabilization is provided by each of the hydrogen bonds identified in each of the important conformers, both in vacuum and in water. Notice, that the studied conformers are stabilized by variety of different hydrogen bonds and close contacts (see Table 2). Moreover, the repulsive interactions are also important for conformer diversification.

A more detailed inspection into the influence of intramolecular hydrogen bonds can be obtained by AIM analysis [57]. It was shown that Laplacian value of the electron density as well as electron density in bond and ring critical points of the hydrogen bonds correlates with hydrogen bond strength [58-61]. Also, the hydrogen bond length correlates with its strength. Therefore, an interdependence between intramolecular hydrogen bond length and the Laplacian in its critical point is presented for all the most stable conformers in Fig. 4 (the values are listed in Table 9SI in Supplementary Information file). It is clear that the stronger is the hydrogen bond the shorter it is and the more negative is the Laplacian value. We found that for the neutral conformers in vacuum and in water,  $d(H...B)$  is linearly correlated with  $\nabla^2\rho$  ( $R=0.930$ , Fig. 4), whereas the points corresponding to the zwitterions are spread out.

Thus, the weak CH...OH<sub>a</sub> bond is placed in top right of Fig. 4, the medium strong OH<sub>a</sub>...NH<sub>2</sub> and OH<sub>a</sub>...O=C bonds are located in the center, whereas the strongest OH<sub>c</sub>...NH<sub>2</sub> bonds are concentrated in bottom left of the Fig. 4. We found that for zwitterions the hydrogen bond length is not correlated with  $\nabla^2\rho$  value (Fig. 4), which is not surprising because of strong localization of the charges at the ends of the H-bonds.

As we stress above, the hydrogen bond strength is not an unique factor ordering the conformers stability. Thus, despite the fact that one is able to scale the intramolecular H-bond strength in the studied conformers, the other factors are hidden yet not negligible.

## Summary

Continuing our earlier studies on  $\beta$ -amino-acid conformations we found 54 conformers of penylisoserine to be stable in the gas phase, and 51 neutral and 6 zwitterionic conformers to be stable in water. The calculations were performed at the B3LYP/aug-cc-pVDZ, B3LYP/aug-cc-pVTZ and MP2/aug-cc-pVDZ levels. In the gas phase, in the most stable six conformers the following intramolecular hydrogen bonds are present: OH<sub>a</sub>...O=C, OH<sub>c</sub>...NH<sub>2</sub>, OH<sub>a</sub>...NH<sub>2</sub>, OH<sub>c</sub>...OH<sub>a</sub>, HNH...O=C, and HNH...OH<sub>a</sub>. The most stable conformer in the gas phase and in water phase is stabilized due to strong OH<sub>c</sub>...NH<sub>2</sub> and OH<sub>a</sub>...O=C intramolecular hydrogen bonds. On the other hand, the zwitterionic forms in water are stabilized not only by interaction by NH<sub>3</sub><sup>+</sup> and COO<sup>-</sup> groups but also by interaction between H<sub>2</sub>NH and phenyl ring. In the gas phase, at the DFT level, the most stable conformer is populated in at least 93%, whereas at the MP2/aug-cc-pVDZ level three conformers seems to be present in significant amounts of ca. 37%, 46%, and 11%. This shows that the population analysis is strongly dependent on electron correlation. Population analysis of the conformers in water (6 neutral and 6 zwitterionic conformers) performed at the DFT and MP2 levels show concordantly that only the most stable neutral conformer and the most stable zwitterionic conformer are present. However, conformer ratio is again strongly dependent on electron correlation. Thus we expect both forms to be detected in equilibrium in water.

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## Tables

**Table 1** The B3LYP/aug-cc-pVDZ, B3LYP/aug-cc-pVTZ and MP2/aug-cc-pVDZ optimized for 6 most stable structures of phenylisoserine (PhIS) in gas phase, in water as neutral and zwitterion forms. The relative total energies ( $\Delta E$ , kcal mol<sup>-1</sup>) and free Gibbs energies ( $\Delta G$ , kcal mol<sup>-1</sup>) referred to the most stable conformer. The populations X(G) were calculated based on  $\Delta G$  values (DFT) and  $\Delta E$  values (MP2) separately for the 6 structures of each type

gas phase	B3LYP/aug-cc-pVDZ				B3LYP/aug-cc-pVTZ				MP2/aug-cc-pVDZ	
	$\Delta E$	$\Delta E_0$	$\Delta G$	X(G)	$\Delta E$	$\Delta E_0$	$\Delta G$	X(G)	$\Delta E$	X(G)
<b>1</b>	0.00	0.00	0.00	93.61	0.00	0.00	0.00	94.83	0.13	37.29
<b>2</b>	2.47	2.36	2.35	1.77	2.33	2.36	2.52	1.34	0.00	46.07
<b>3</b>	2.99	2.52	2.32	1.86	2.65	2.35	2.34	1.84	0.86	10.77
<b>4</b>	3.08	3.10	2.76	0.89	3.21	3.34	3.33	0.34	1.61	3.05
<b>5</b>	3.22	2.85	2.65	1.07	2.97	2.77	2.78	0.87	2.04	1.48
<b>6</b>	3.42	2.96	2.83	0.79	3.13	2.83	2.85	0.77	2.09	1.35
neutral in water	$\Delta E$	$\Delta E_0$	$\Delta G$	X(G)	$\Delta E$	$\Delta E_0$	$\Delta G$	X(G)	$\Delta E$	X(G)
<b>1w</b>	0.00	0.00	0.00	97.86	0.00	0.00	0.00	98.20	0.00	86.60
<b>29w</b>	2.51	2.52	2.39	1.74	2.59	2.54	2.48	1.50	1.96	3.18
<b>4w</b>	3.52	3.64	3.43	0.30	3.69	3.80	3.68	0.20	1.65	5.35
<b>2w</b>	4.46	4.62	4.23	0.08	4.28	4.46	4.20	0.08	1.74	4.61
<b>10w</b>	5.77	6.10	5.64	0.01	5.42	5.75	5.27	0.01	4.38	0.05
<b>3w</b>	6.26	5.95	5.23	0.01	5.88	5.65	5.18	0.02	3.57	0.21
zwitterion in water	$\Delta E$	$\Delta E_0$	$\Delta G$	X(G)	$\Delta E$	$\Delta E_0$	$\Delta G$	X(G)	$\Delta E$	X(G)
<b>1z</b>	0.00	0.00	0.00	99.76	0.00	0.00	0.00	99.78	0.00	98.59
<b>2z</b>	4.62	3.80	3.75	0.18	4.77	3.93	3.87	0.14	4.38	0.06
<b>3z</b>	4.75	5.13	5.09	0.02	4.73	5.18	5.04	0.02	4.23	0.08
<b>4z</b>	4.83	4.65	4.62	0.04	4.99	4.84	4.52	0.05	3.13	0.50
<b>5z</b>	5.79	5.98	5.89	0.00	5.82	6.04	5.81	0.01	3.13	0.50
<b>6z</b>	6.11	6.81	6.75	0.00	5.89	6.70	6.59	0.00	3.48	0.28

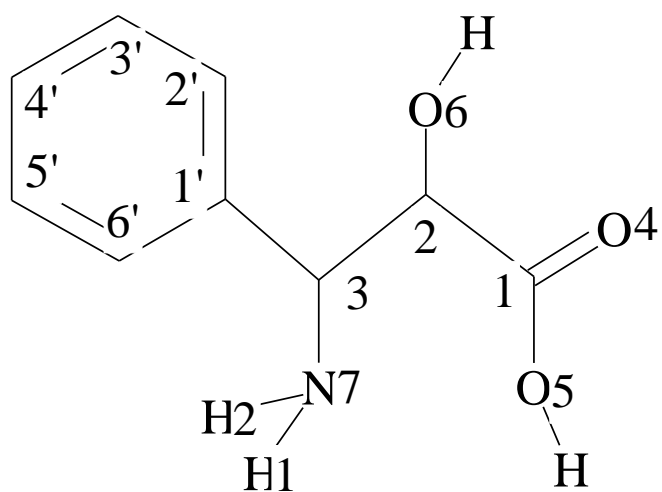


## Figure captions

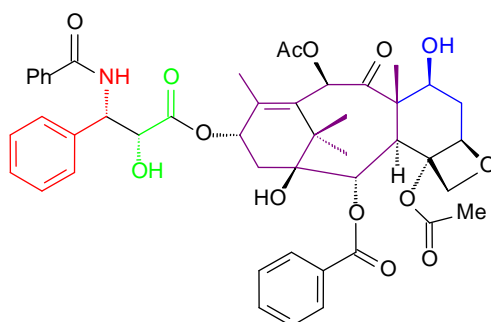
- Fig. 1** The B3LYP/aug-cc-pVDZ optimized the most stable six structures of phenylisoserine in the gas phase. The relative total energies ( $\Delta E$ , kcal mol<sup>-1</sup>) and free Gibbs energies ( $\Delta G$ , kcal mol<sup>-1</sup>) referred to the most stable conformer are given in parentheses and square brackets, respectively
- Fig. 2** The B3LYP/aug-cc-pVDZ optimized the most stable six neutral structures of phenylisoserine in water modeled by IEF-PCM method. The relative total energies ( $\Delta E$ , kcal mol<sup>-1</sup>) and free Gibbs energies ( $\Delta G$ , kcal mol<sup>-1</sup>) referred to the most stable conformer are given in parentheses and square brackets, respectively
- Fig. 3** The B3LYP/aug-cc-pVDZ optimized the most stable six structures of phenylisoserine zwitterions in water modeled by IEF-PCM method. The relative total energies ( $\Delta E$ , kcal mol<sup>-1</sup>) and free Gibbs energies ( $\Delta G$ , kcal mol<sup>-1</sup>) referred to the most stable conformer are given in parentheses and square brackets, respectively
- Fig. 4** The hydrogen bond lengths  $d(\text{H}\dots\text{B})$  vs Laplacians  $\nabla^2\rho$  in the hydrogen bond BCPs calculated for the most stable neutral conformers in vacuum (V) and in water (W) and for zwitterionic forms in water (Z) based on B3LYP/aug-cc-pVDZ optimized structures

## Schemes

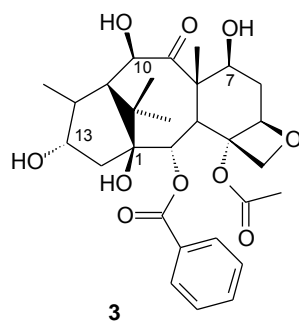
### Scheme 1



### Scheme 2



### Scheme 3





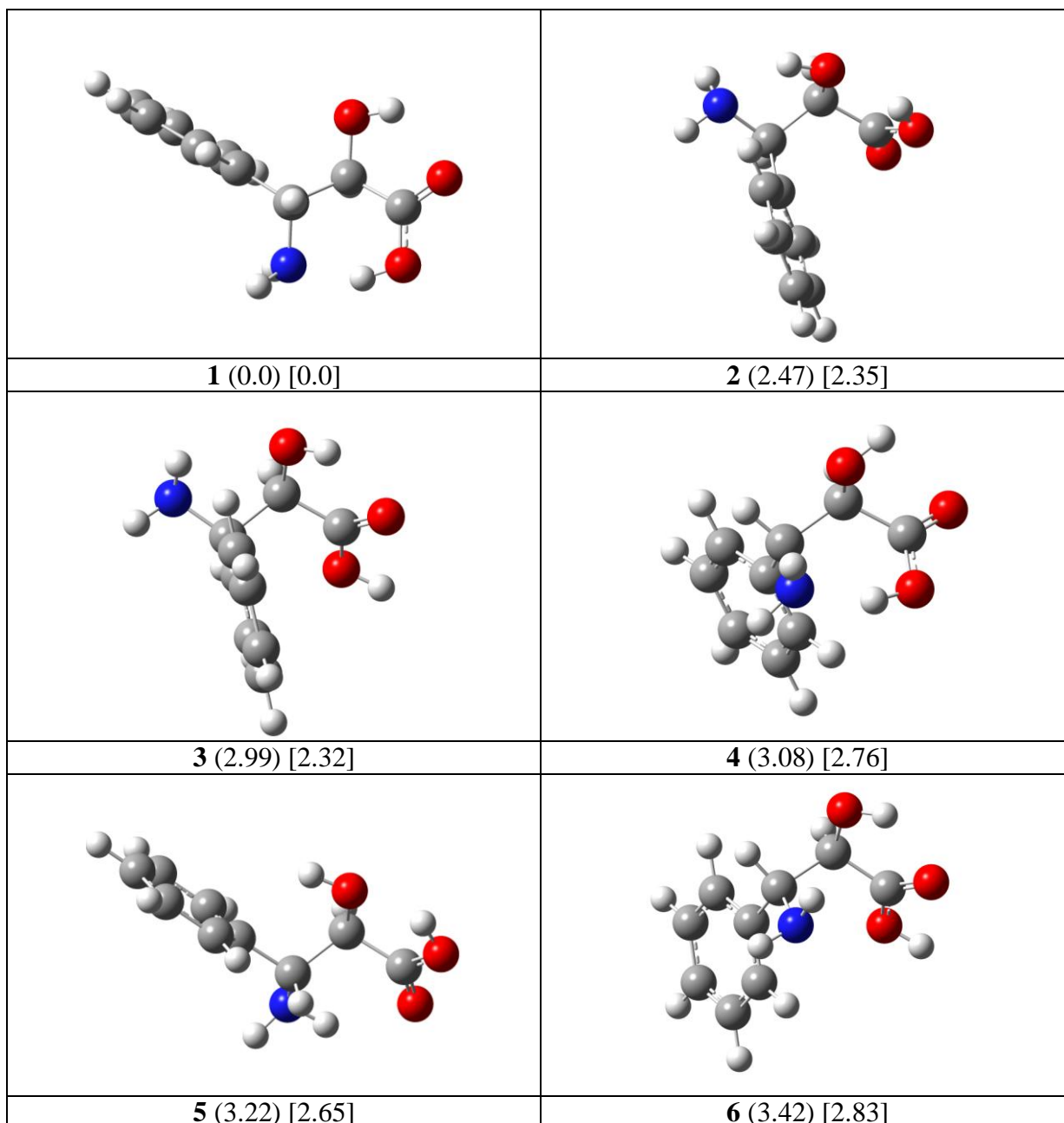
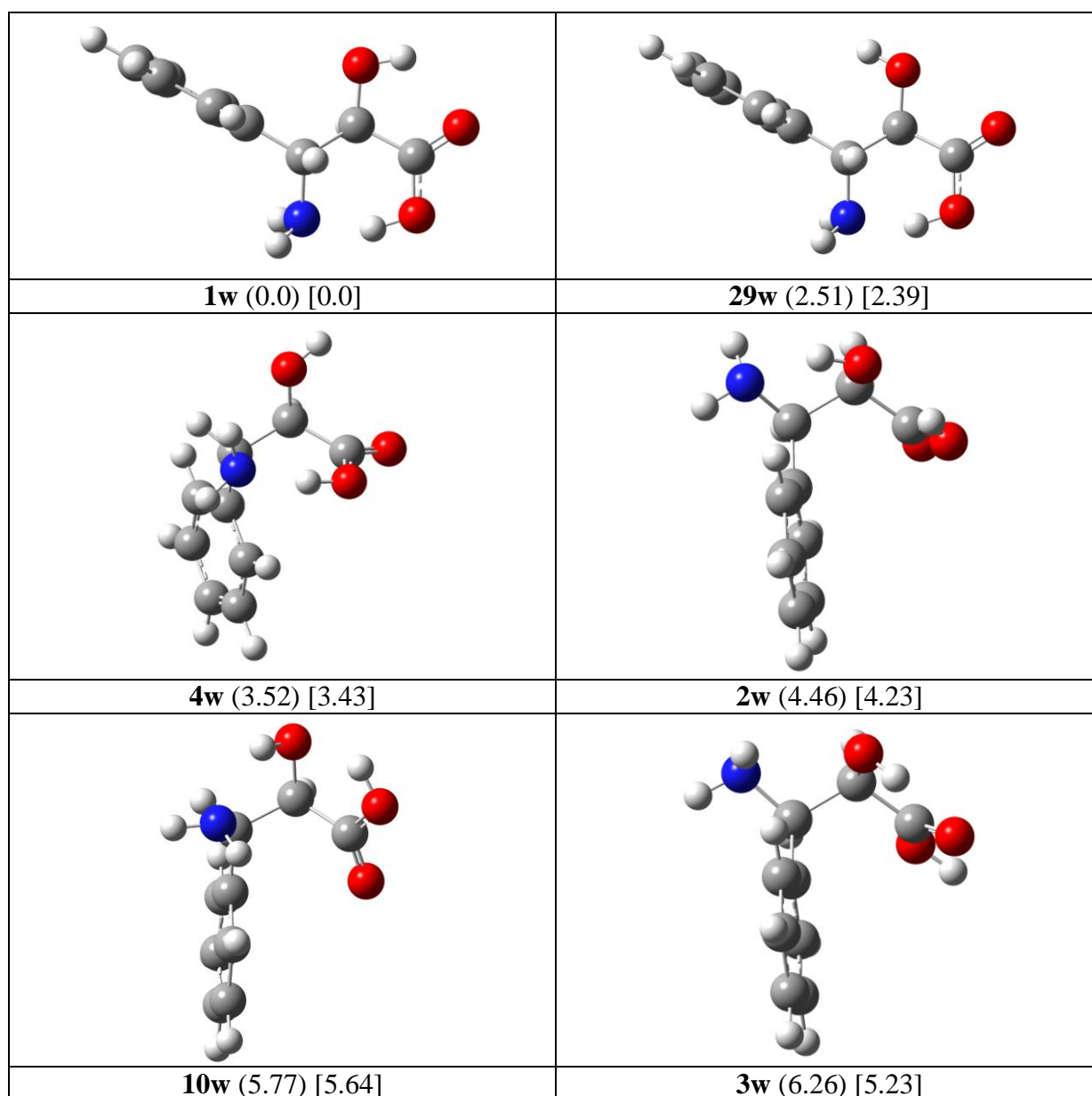


Figure 2  
[Click here to download colour figure: Figure2.doc](#)



**Figure 3**  
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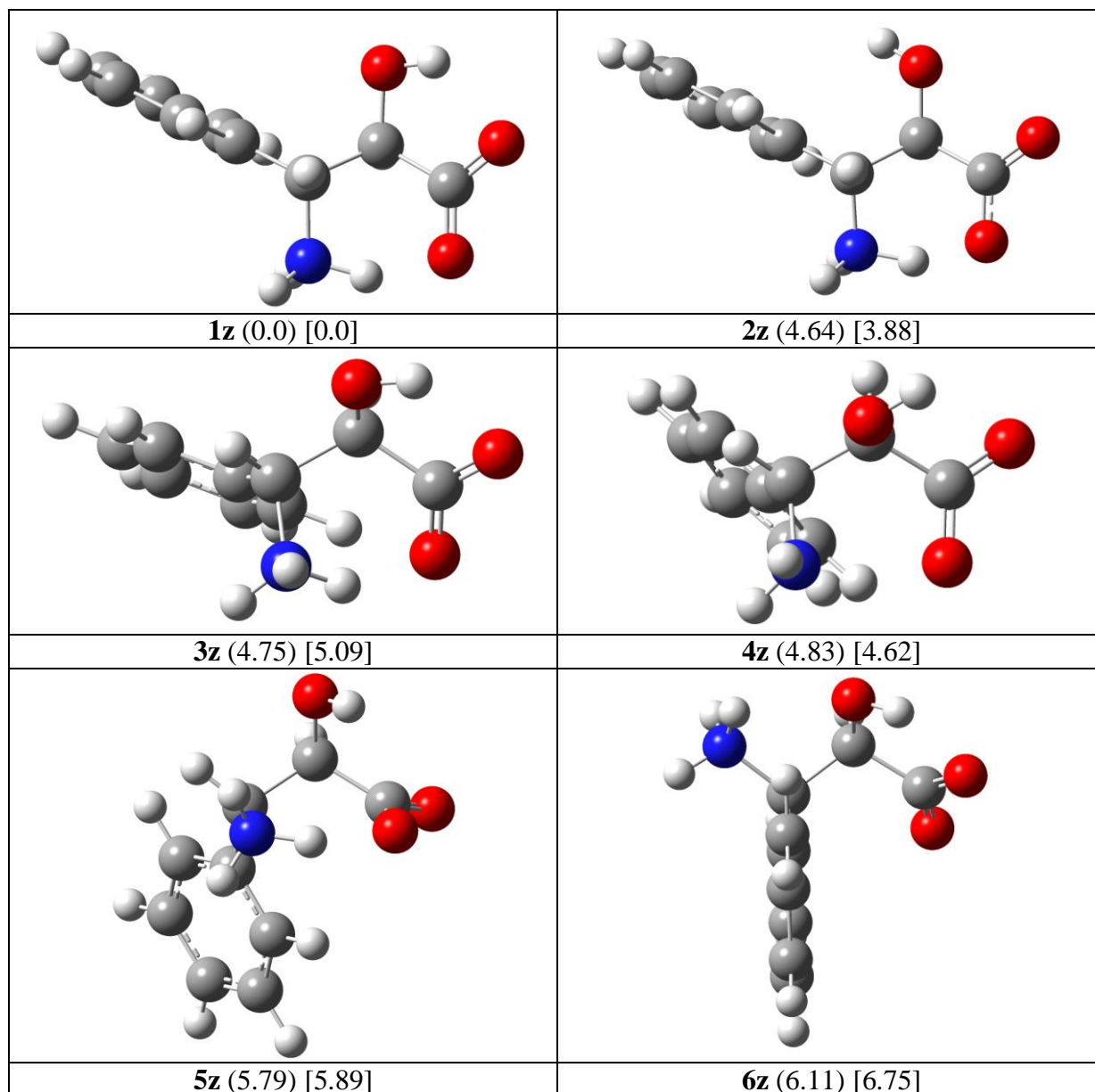


Figure 4

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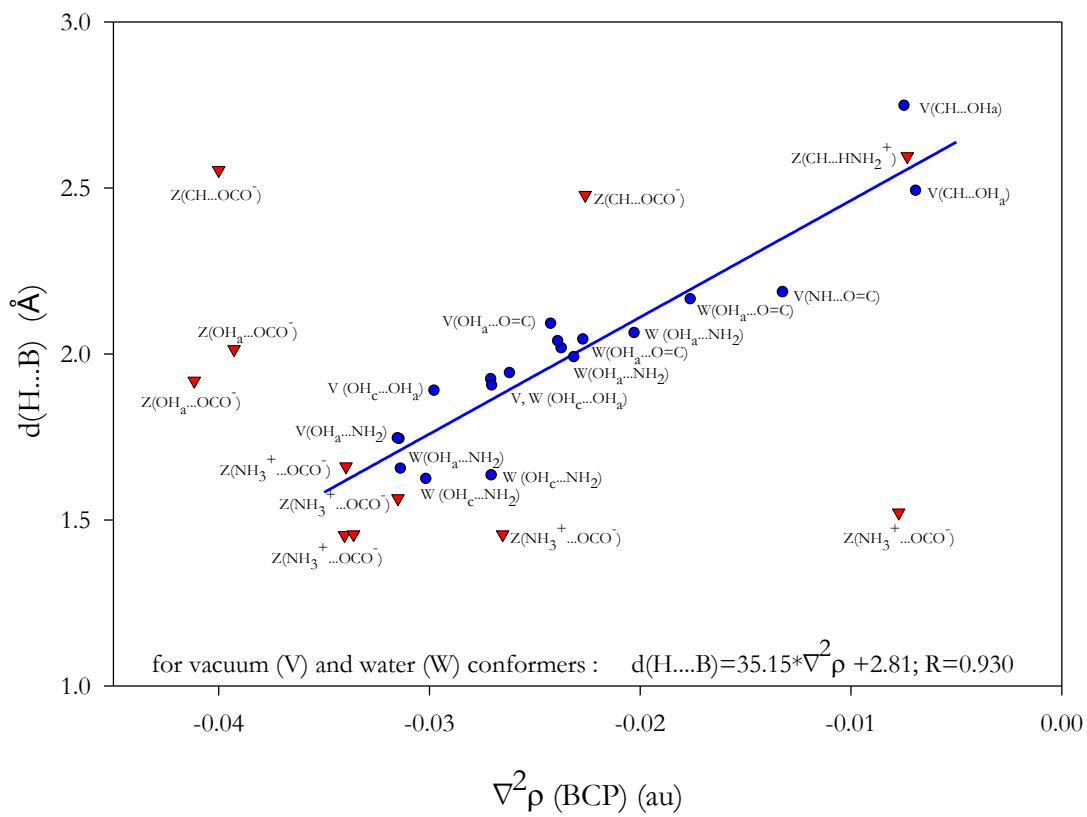


Fig. 4.

**Supplementary Information to**

**Phenylisoserine: ab initio studies of  
the gas-phase and neutral and zwitterions  
conformers in water**

Joanna E. Rode,<sup>[a]</sup> Jan Cz. Dobrowolski,<sup>\*,[a,b]</sup> Joanna Sadlej<sup>\*,[b,c]</sup>

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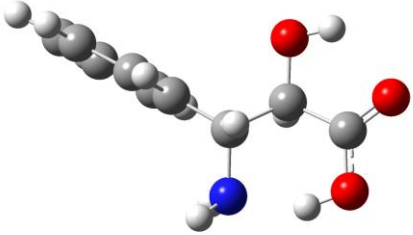
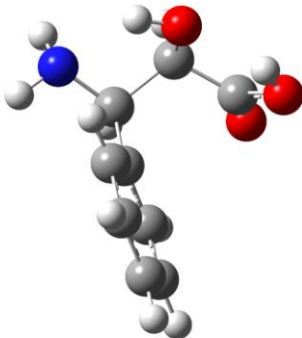
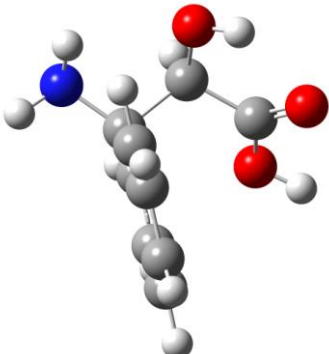
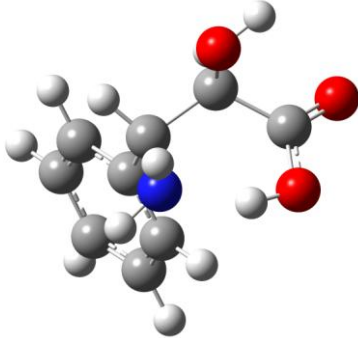
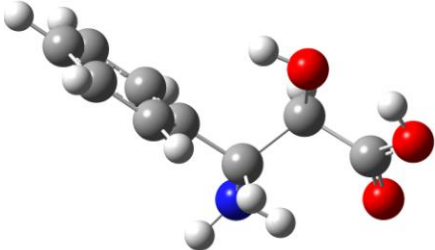
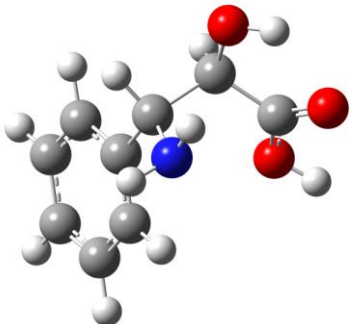
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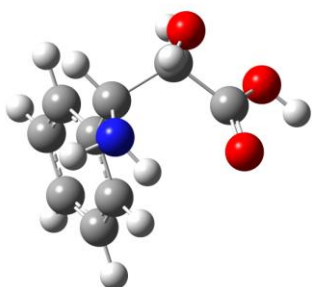
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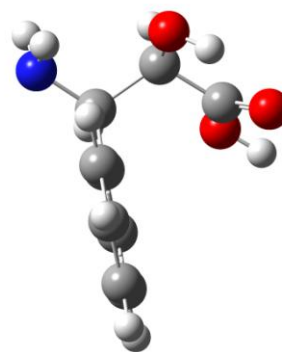
*E-mail: sadlej@chem.uw.edu.pl;*

Fig. 1SI. The B3LYP/aug-cc-pVDZ optimized 54 stable structures of phenylisoserine (PhIS) in the gas phase. The relative total energies ( $\Delta E$ , kcal/mol) and free Gibbs energies ( $\Delta G$ , kcal/mol) referred to the most stable conformer are given in parentheses and square brackets, respectively.

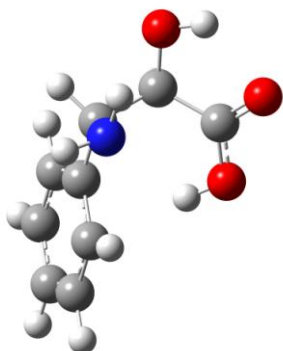
	
<p><b>1</b> (0.0) [0.0]</p>	<p><b>2</b> (2.47) [2.35]</p>
	
<p><b>3</b> (2.99) [2.32]</p>	<p><b>4</b> (3.08) [2.76]</p>
	
<p><b>5</b> (3.22) [2.65]</p>	<p><b>6</b> (3.42) [2.83]</p>



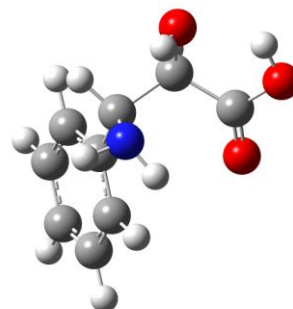
**7** (3.53) [3.12]



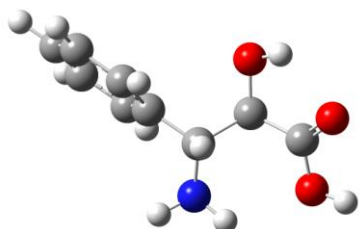
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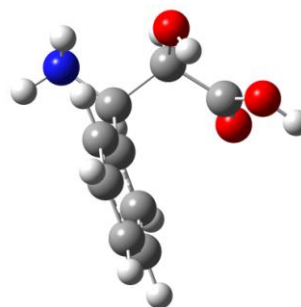
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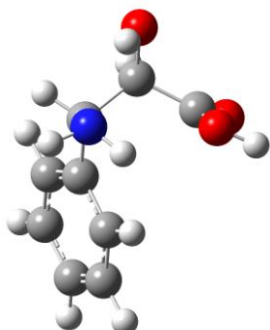
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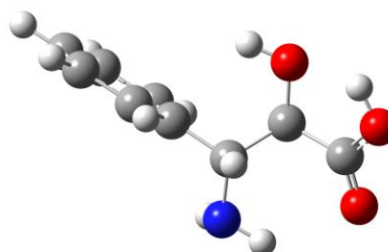
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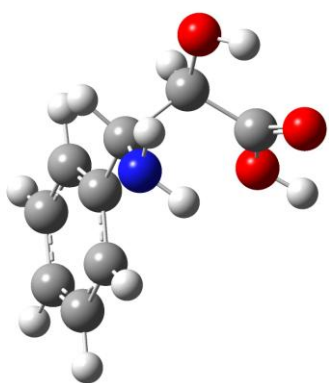
**12** (4.88) [4.02]



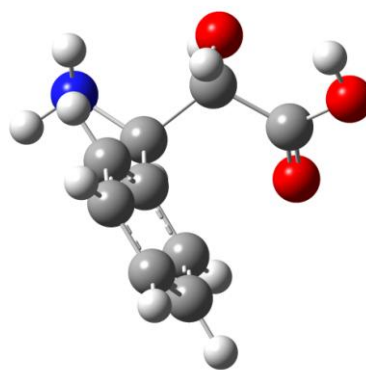
**13** (4.88) [4.28]



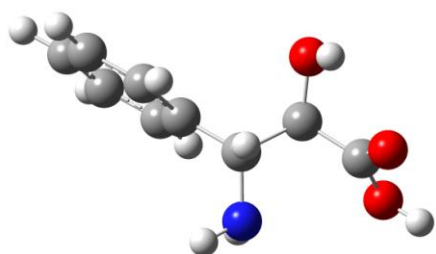
**14** (5.04) [4.13]



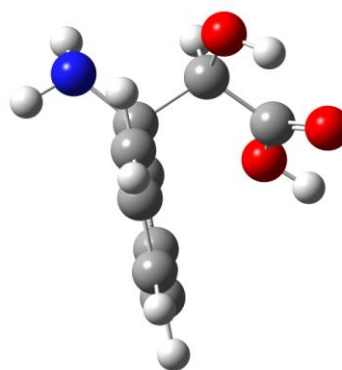
**15** (5.05) [3.64]



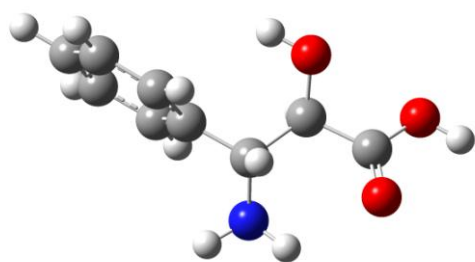
**16** (5.13) [4.99]



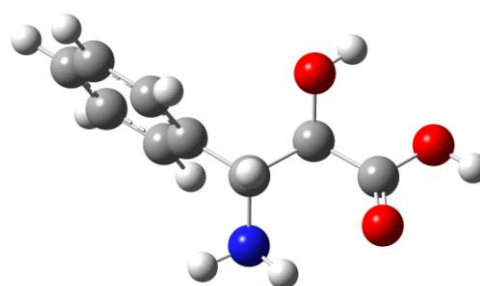
**17** (5.26) [3.92]



**18** (5.31) [4.02]

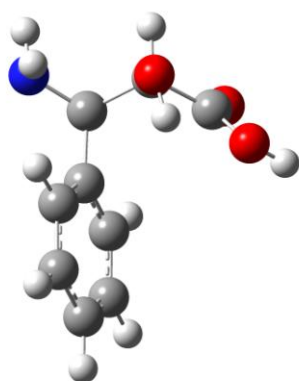


**19** (5.48) [4.23]

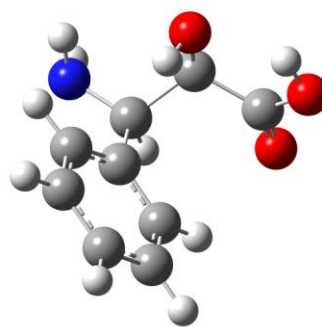


**20** (5.51) [4.22]

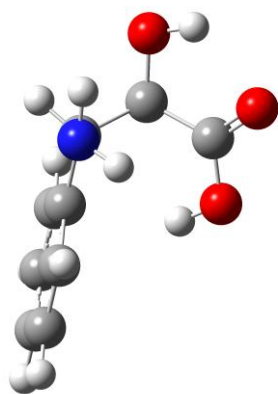




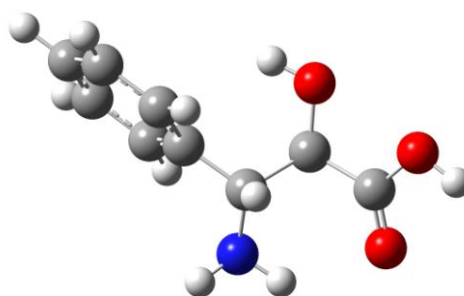
**21** (5.74) [4.91]



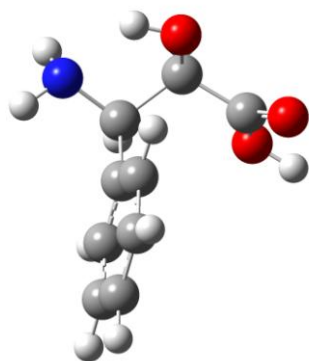
**22** (5.93) [5.72]



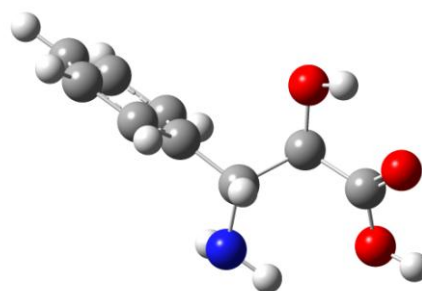
**23** (5.97) [5.29]



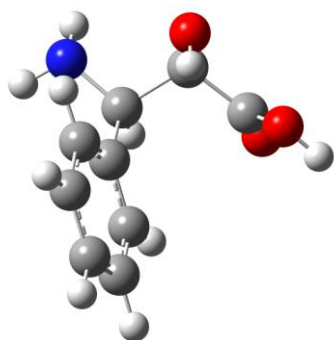
**24** (6.06) [4.11]



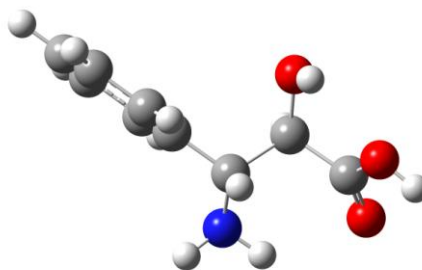
**25** (6.06) [4.98]



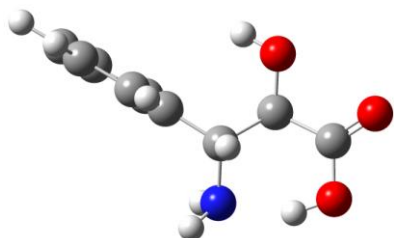
**26** (6.22) [4.91]



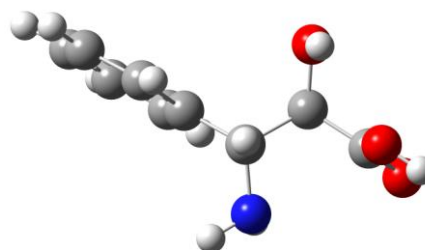
**27** (6.44) [5.33]



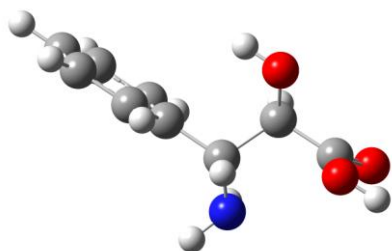
**28** (6.57) [4.79]



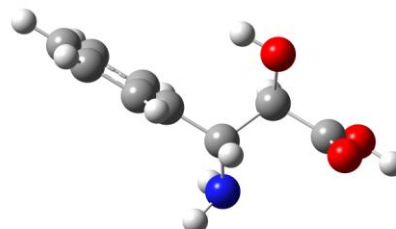
**29** (6.58) [5.94]



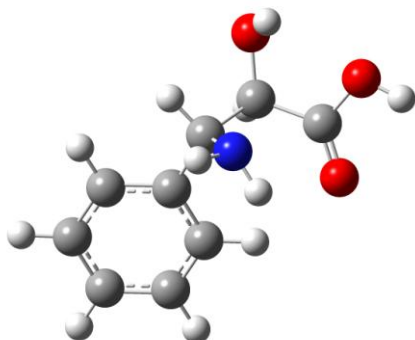
**30** (6.76) [4.99]



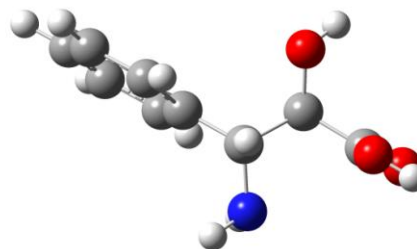
**31** (7.25) [5.35]



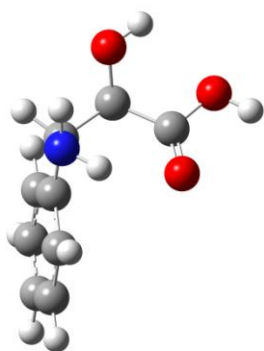
**32** (7.28) [5.29]



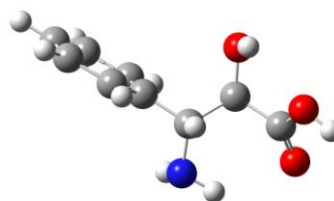
**33** (7.32) [6.19]



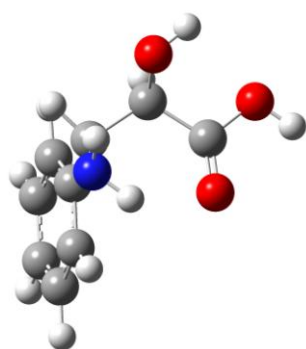
**34** (7.50) [5.59]



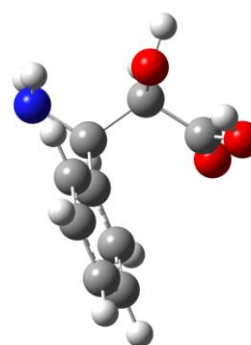
**35** (7.58) [6.28]



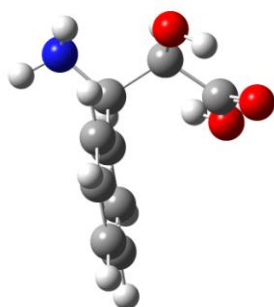
**36** (7.59) [5.85]



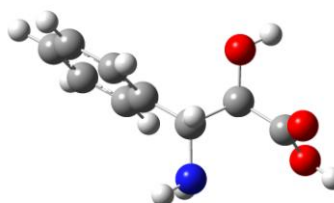
**37** (7.63) [5.92]



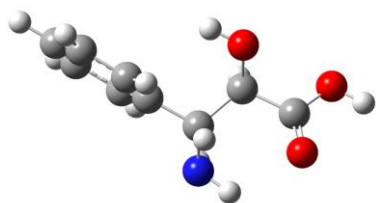
**38** (7.75) [6.74]



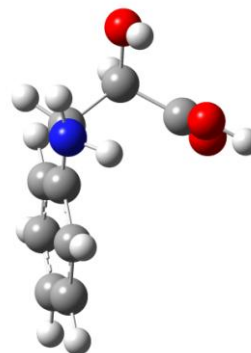
**39** (7.86) [6.75]



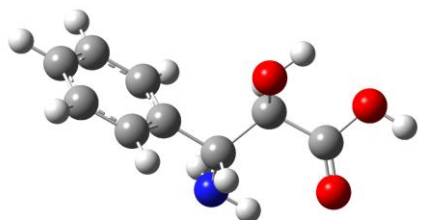
**40** (7.88) [5.36]



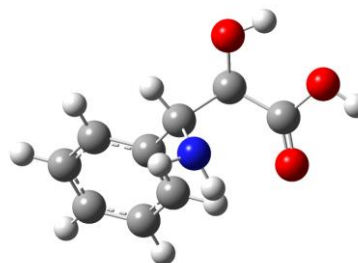
**41** (7.88) [5.77]



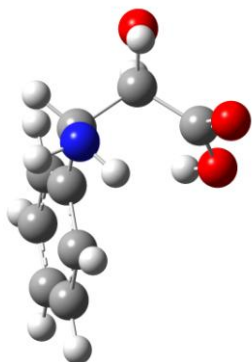
**42** (7.89) [6.50]



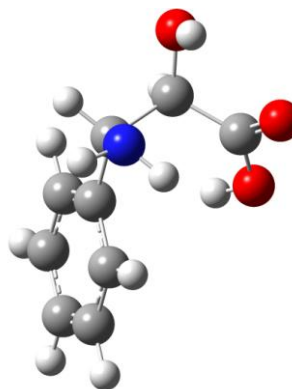
**43** (8.03) [6.05]



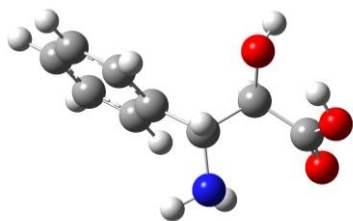
**44** (8.03) [6.77]



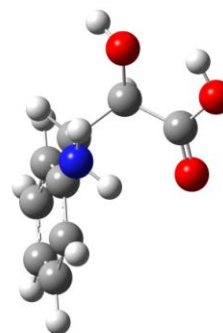
**45** (8.51) [8.13]



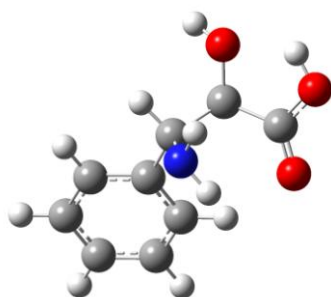
**46** (8.52) [8.20]



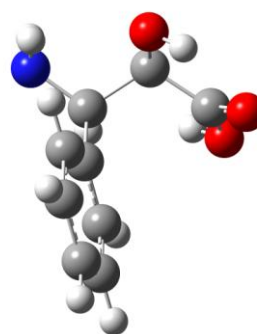
**47** (8.63) [6.94]



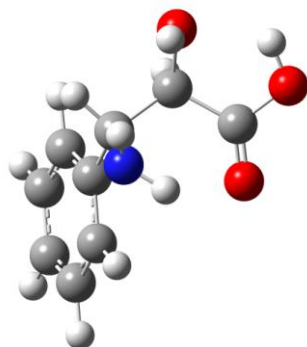
**48** (8.86) [7.28]



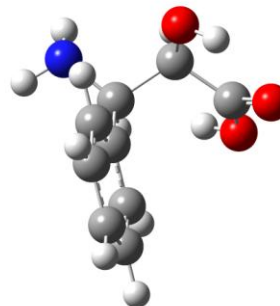
**49** (9.04) [7.66]



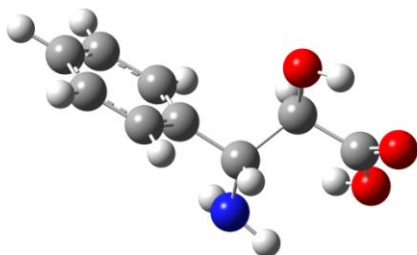
**50** (9.73) [8.22]



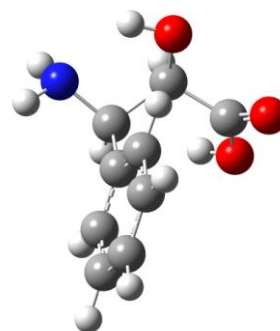
**51** (9.91) [8.47]



**52** (10.47) [9.05]

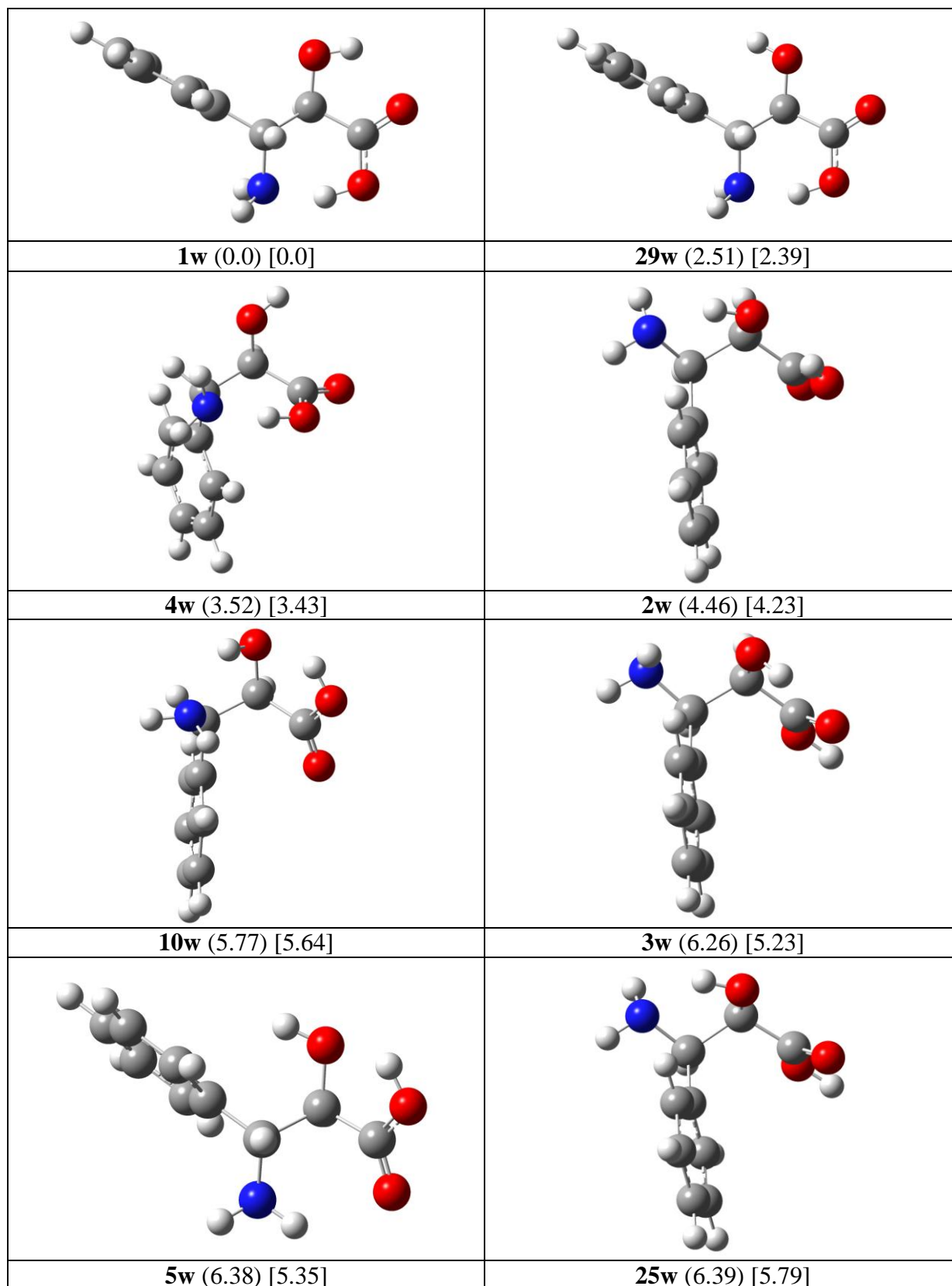


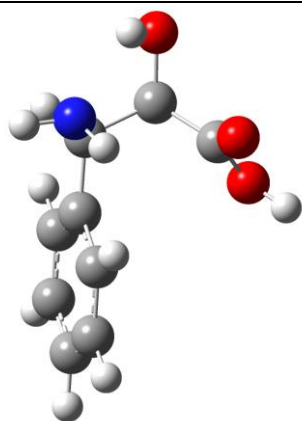
**53** (10.86) [9.10]



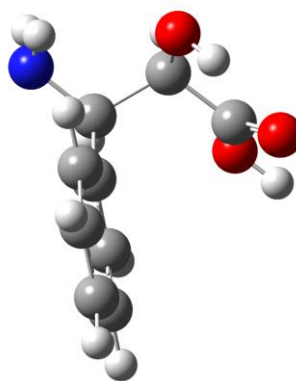
**54** (12.56) [11.04]

Fig. 2SI. The B3LYP/aug-cc-pVDZ optimized 51 stable structures of phenylisoserine (PhIS) in water. The relative total energies ( $\Delta E$ , kcal/mol) and free Gibbs energies ( $\Delta G$ , kcal/mol) referred to the most stable conformer are given in parentheses and square brackets, respectively.

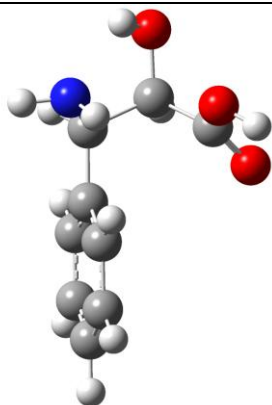




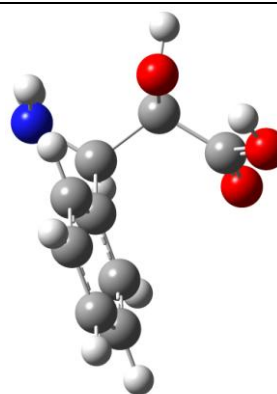
**7w** (6.46) [5.71]



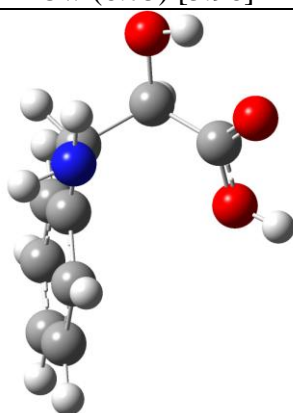
**8w** (6.62) [5.44]



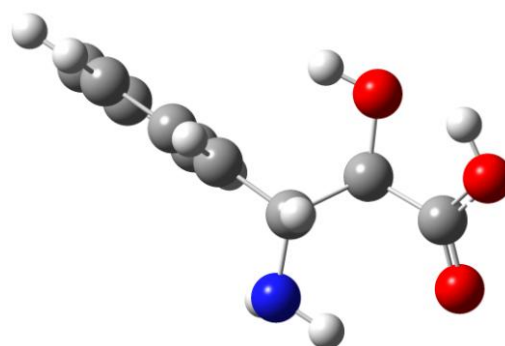
**13w** (6.75) [5.96]



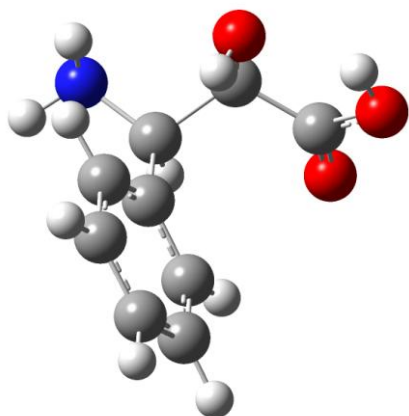
**38w** (6.79) [5.84]



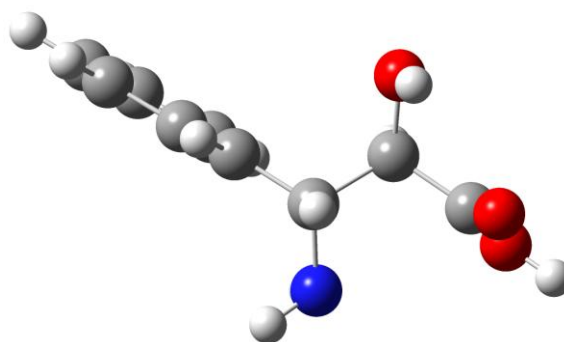
**6w** (6.86) [6.04]



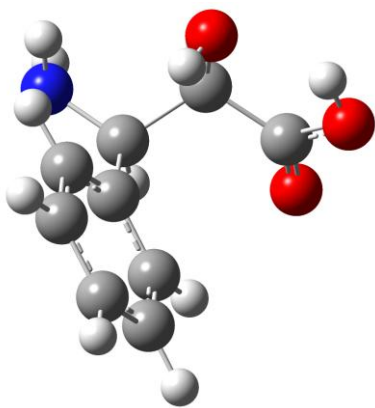
**14w** (6.87) [5.79]



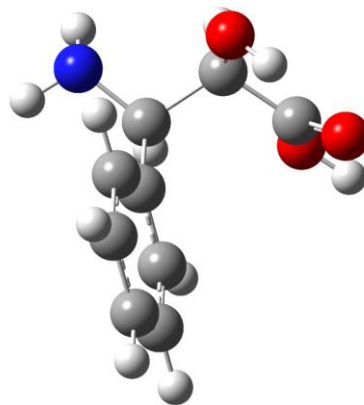
**16w** (6.95) [6.88]



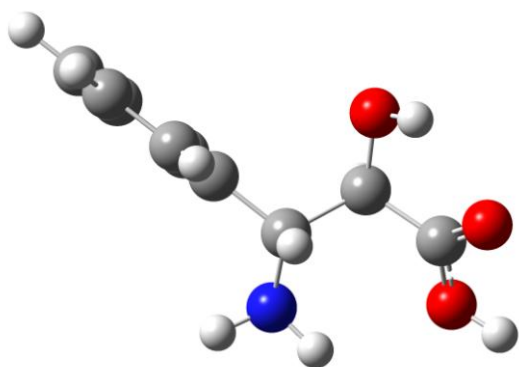
**17w** (7.24) [5.97]



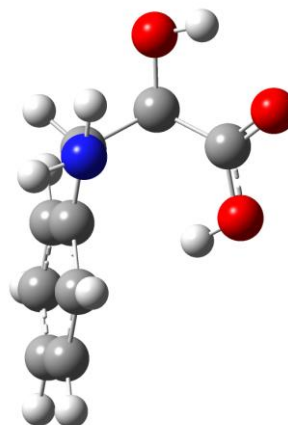
**22w** (7.30) [7.36]



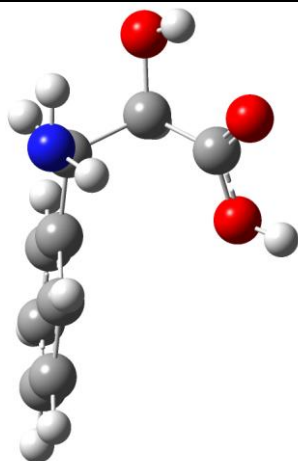
**18w** (7.35) [6.14]



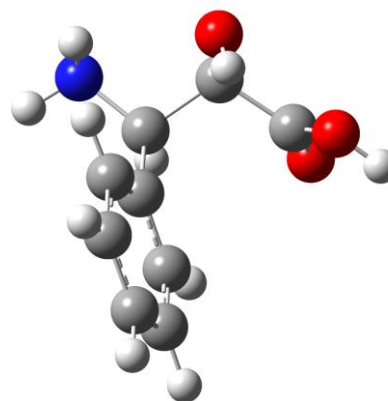
**11w** (7.38) [6.10]



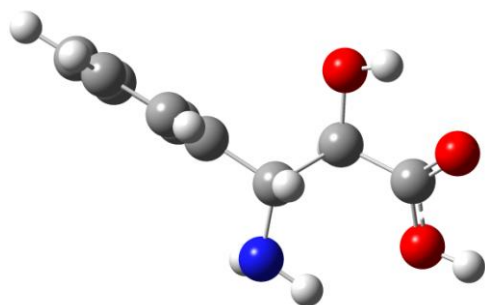
**9w** (7.50) [7.09]



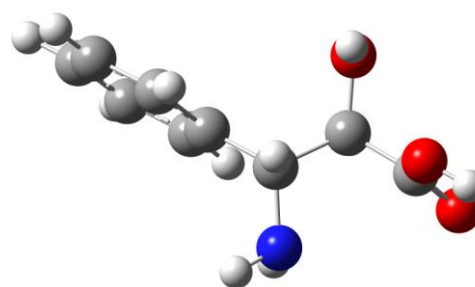
**15w** (7.65) [6.77]



**12w** (7.73) [6.88]

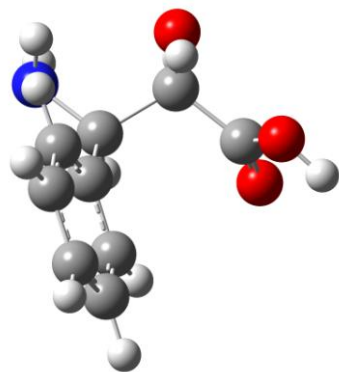


**26w** (7.80) [6.61]

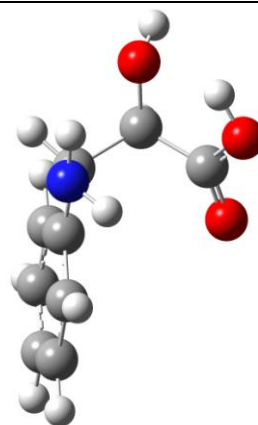


**30w** (7.90) [6.49]

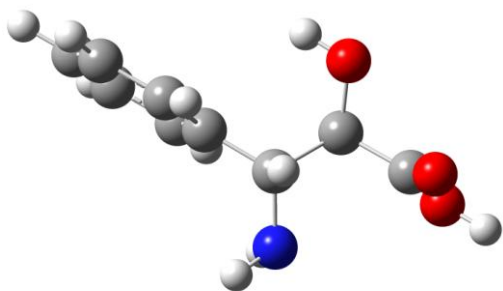




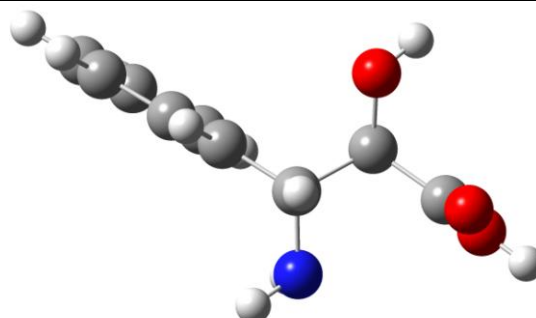
**21w** (8.00) [7.14]



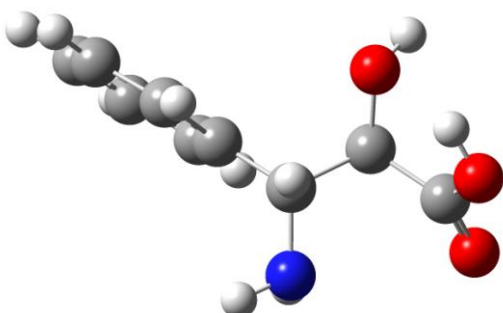
**48w, 49w** (8.04) [6.71]



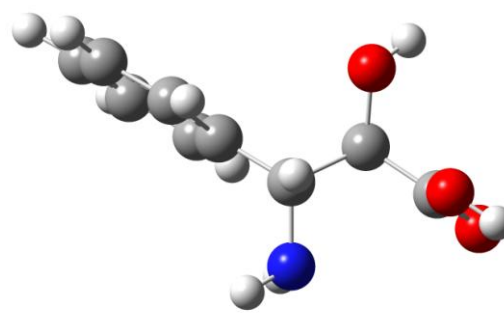
**32w** (8.04) [6.47]



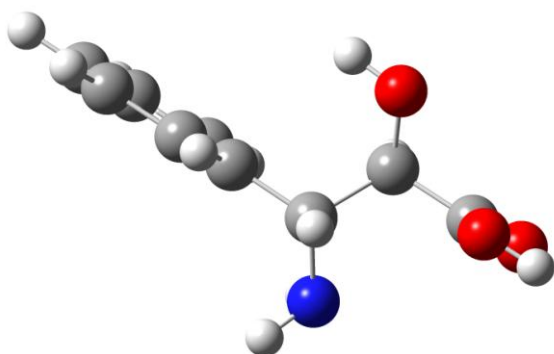
**40w** (8.08) [6.52]



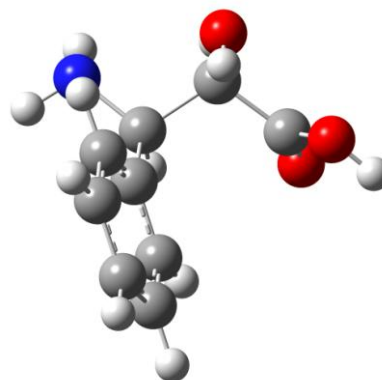
**47w** (8.11) [7.17]



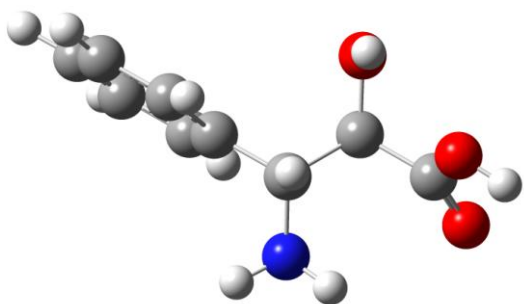
**34w** (8.15) [6.83]



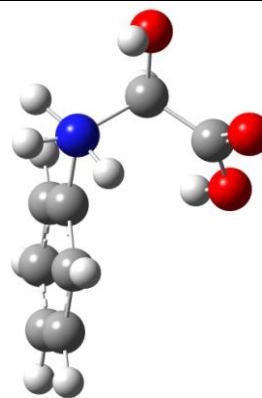
**31w** (8.28) [6.77]



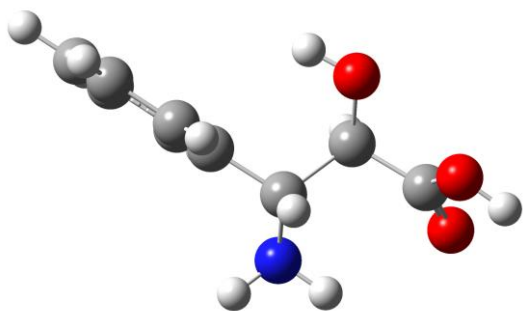
**27w** (8.48) [7.38]



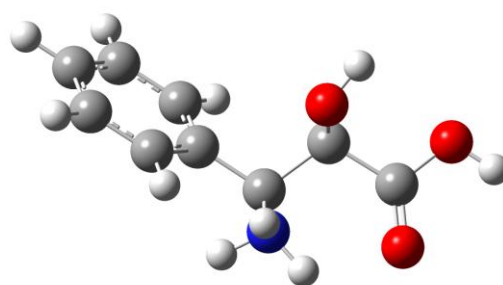
**28w** (8.55) [6.81]



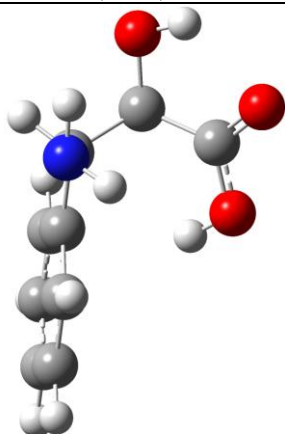
**45w, 46w** (8.66) [7.94]



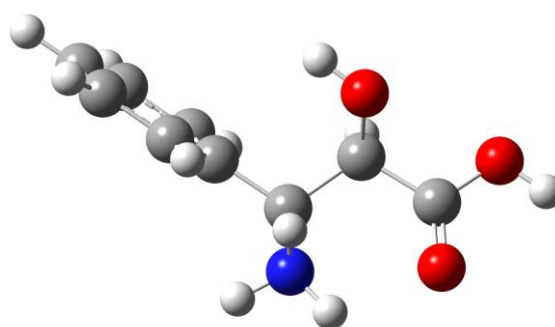
**24w** (8.69) [7.07]



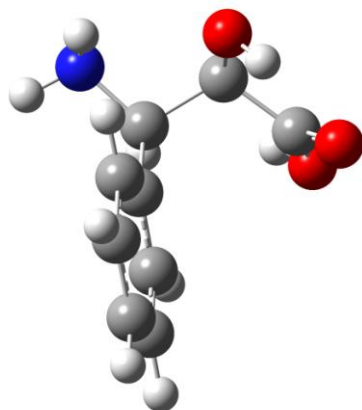
**20w** (8.71) [7.17]



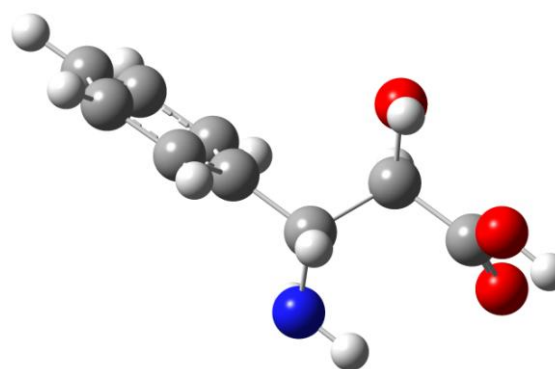
**23w** (8.73) [8.78]



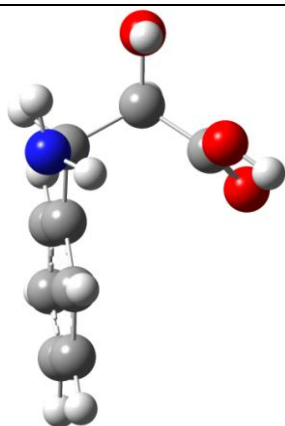
**19w** (8.81) [6.98]



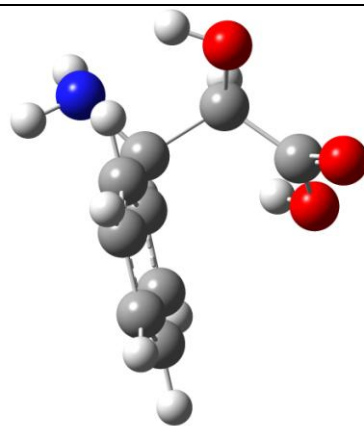
**39w** (8.90) [7.68]



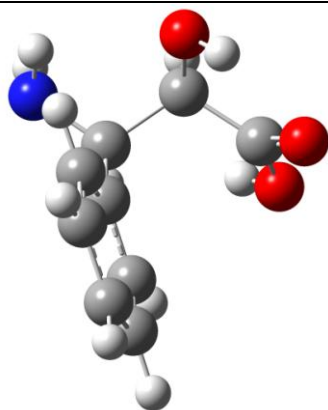
**36w** (9.02) [7.26]



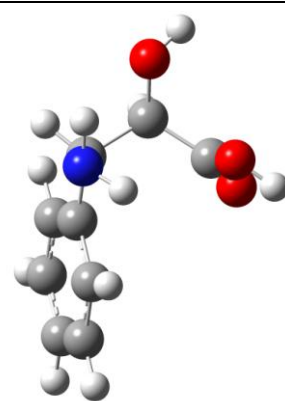
**42w** (9.19) [8.13]



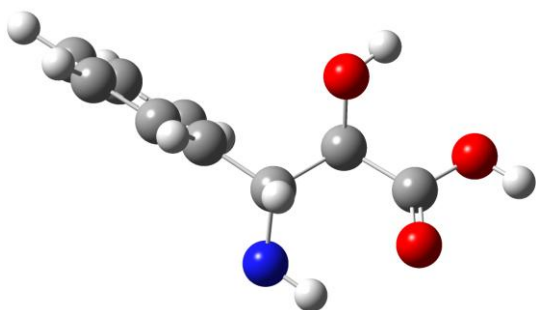
**54w** (9.28) [8.81]



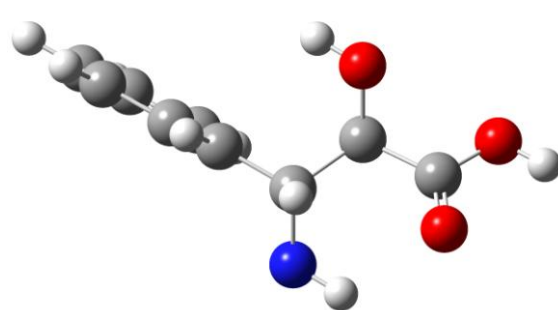
**50w** (9.29) [8.46]



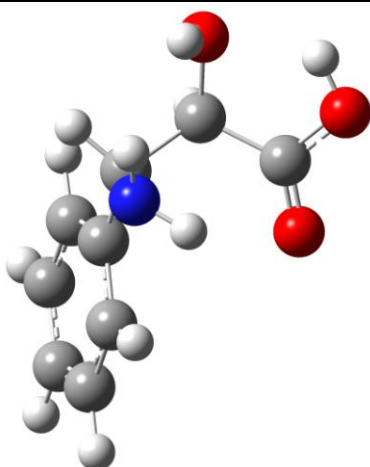
**35w, 37w** (9.42) [8.27]



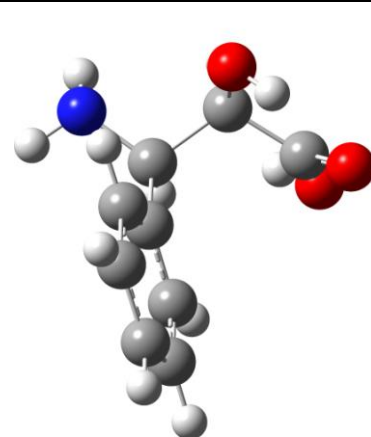
**43w** (9.47) [7.83]



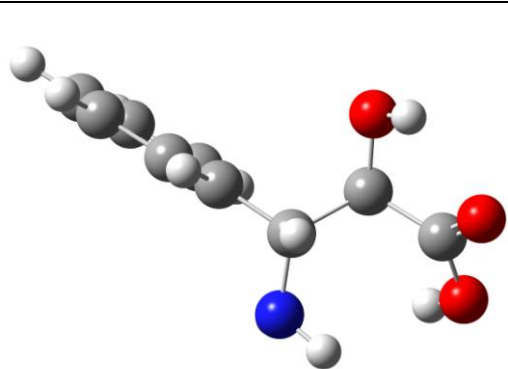
**41w** (9.60) [8.58]



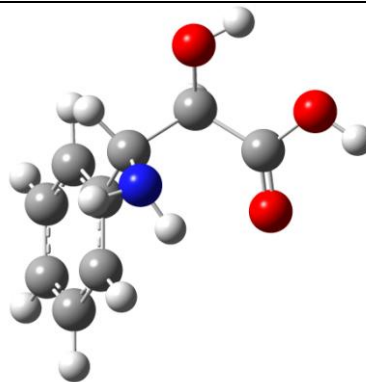
**51w** (9.64) [8.29]



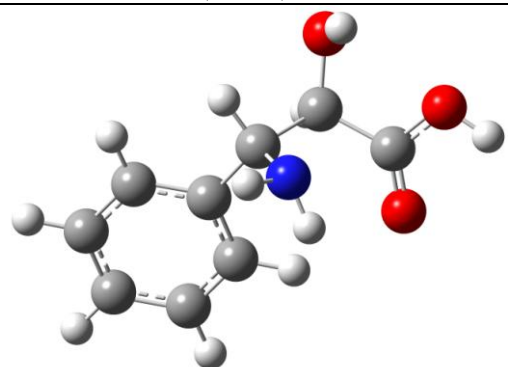
**52w** (9.92) [8.70]



**53w** (10.34) [8.77]



**44w** (10.47) [9.04]

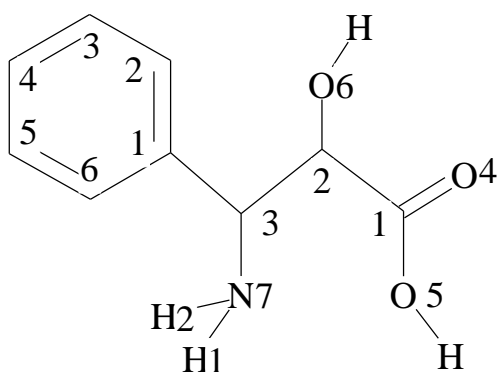


**33w** (10.66) [10.71]

Table 1SI. The total energies (E, hartree), the total energies corrected for zero-point energies ( $E_0$ , hartree), the Gibbs free energies in 298.15 K (G, hartree), relative total energies ( $\Delta E$ , kcal/mol), and corresponding relative energies referred to the most stable conformer (kcal/mol) for the B3LYP/aug-cc-pVDZ optimized 54 stable structures of phenylisoserine (PhIS) in the gas phase (Fig 1SI).

Conformer number	E	$\Delta E$	$E_0$	$\Delta E_0$	G	$\Delta G$
1	-630.1106344	0.00	-629.916669	0.00	-629.955374	0.00
2	-630.1066909	2.47	-629.912906	2.36	-629.951632	2.35
3	-630.1058767	2.99	-629.912657	2.52	-629.951677	2.32
4	-630.1057309	3.08	-629.911726	3.10	-629.950976	2.76
5	-630.1055081	3.22	-629.91213	2.85	-629.951154	2.65
6	-630.1051916	3.42	-629.911953	2.96	-629.950866	2.83
7	-630.1050081	3.53	-629.91113	3.48	-629.950402	3.12
8	-630.1038614	4.25	-629.910941	3.59	-629.950269	3.20
9	-630.1032139	4.66	-629.909905	4.24	-629.948363	4.40
10	-630.1030781	4.74	-629.909361	4.59	-629.950418	3.11
11	-630.1029007	4.85	-629.910008	4.18	-629.949907	3.43
12	-630.1028648	4.88	-629.90979	4.32	-629.948964	4.02
13	-630.1028523	4.88	-629.909223	4.67	-629.948555	4.28
14	-630.1026009	5.04	-629.909427	4.54	-629.948796	4.13
15	-630.1025839	5.05	-629.909674	4.39	-629.949572	3.64
16	-630.1024669	5.13	-629.908706	5.00	-629.947417	4.99
17	-630.1022594	5.26	-629.909324	4.61	-629.949135	3.92
18	-630.1021694	5.31	-629.909476	4.51	-629.948969	4.02
19	-630.1018959	5.48	-629.908894	4.88	-629.948626	4.23
20	-630.1018543	5.51	-629.908868	4.90	-629.948651	4.22
21	-630.1014821	5.74	-629.908455	5.15	-629.947557	4.91
22	-630.1011816	5.93	-629.907505	5.75	-629.946254	5.72
23	-630.1011206	5.97	-629.908001	5.44	-629.946951	5.29
24	-630.1009758	6.06	-629.907868	5.52	-629.948818	4.11
25	-630.1009731	6.06	-629.907599	5.69	-629.947432	4.98
26	-630.1007271	6.22	-629.907898	5.50	-629.947552	4.91
27	-630.1003724	6.44	-629.90749	5.76	-629.946887	5.33
28	-630.1001595	6.57	-629.907573	5.71	-629.947734	4.79
29	-630.1001414	6.58	-629.906708	6.25	-629.945901	5.94
30	-630.0998583	6.76	-629.907173	5.96	-629.947423	4.99
31	-630.0990831	7.25	-629.906518	6.37	-629.946851	5.35
32	-630.0990381	7.28	-629.906404	6.44	-629.946942	5.29
33	-630.0989673	7.32	-629.905625	6.93	-629.94551	6.19
34	-630.0986856	7.50	-629.905999	6.70	-629.946462	5.59
35	-630.0985616	7.58	-629.90557	6.96	-629.945359	6.28
36	-630.098537	7.59	-629.905981	6.71	-629.946045	5.85
37	-630.098482	7.63	-629.905517	7.00	-629.945944	5.92
38	-630.0982798	7.75	-629.905221	7.18	-629.944627	6.74
39	-630.098112	7.86	-629.905287	7.14	-629.944611	6.75
40	-630.0980809	7.88	-629.905654	6.91	-629.946827	5.36
41	-630.098079	7.88	-629.90548	7.02	-629.946178	5.77
42	-630.0980646	7.89	-629.905274	7.15	-629.945022	6.50
43	-630.097839	8.03	-629.905296	7.14	-629.945734	6.05
44	-630.0978363	8.03	-629.904817	7.44	-629.944593	6.77

<b>45</b>	-630.0970777	8.51	-629.904505	7.63	-629.942415	8.13
<b>46</b>	-630.0970608	8.52	-629.904475	7.65	-629.942313	8.20
<b>47</b>	-630.0968834	8.63	-629.904065	7.91	-629.944312	6.94
<b>48</b>	-630.0965157	8.86	-629.903732	8.12	-629.943774	7.28
<b>49</b>	-630.0962329	9.04	-629.90332	8.38	-629.94316	7.66
<b>50</b>	-630.0951326	9.73	-629.902648	8.80	-629.94228	8.22
<b>51</b>	-630.0948375	9.91	-629.901972	9.22	-629.941871	8.47
<b>52</b>	-630.0939559	10.47	-629.901618	9.44	-629.940958	9.05
<b>53</b>	-630.0933245	10.86	-629.901072	9.79	-629.940867	9.10
<b>54</b>	-630.0906214	12.56	-629.897789	11.85	-629.937783	11.04



Scheme 1SI.

Table 2SI. The selected dihedral angles (deg) for the B3LYP/aug-cc-pVDZ optimized 54 stable structures of phenylisoserine (PhIS) in the gas phase (Fig 1SI). Atom numbering as in Scheme 1SI.

	d(H1N7C3C2)	d(H2N7C3C2)	d(N7C3C2C1)= =(Ph1C3C2C1)	d(O4C1C2C3)	d(HO5C1C2)	d(HO6C2C1)	d(Ph2Ph1C3C2)
	f1	f2	f3	f4	f5	f6	f7
<b>1</b>	162.3	-81.1	-61.4	-135.2	-10	11.2	55.9
<b>2</b>	-167.6	73.4	175	64.2	-0.3	-157.8	-94.1
<b>3</b>	-56.9	-175.2	-176.5	-120.2	-179.9	-8.7	-105.7
<b>4</b>	71	-170.1	55.6	147.9	5.4	55.6	-94.4
<b>5</b>	53.9	173.4	-71.6	58.6	-0.5	-165.5	79.2
<b>6</b>	56.5	173.8	50	-116.9	179.8	1.9	-77.4
<b>7</b>	-69.2	168.7	71.5	-53.6	178.5	-86.9	-86.7
<b>8</b>	-52.8	64.4	179.5	-117.3	-178.8	-11.3	-102.2
<b>9</b>	51.6	169	53.7	-127.4	-11.4	8.6	-74
<b>10</b>	-77.3	163.3	62.4	43.1	3.98	-88.8	-78.5
<b>11</b>	64.1	-175.6	-70.8	-113.3	180	-6.9	76.9
<b>12</b>	168.9	-174	-168.9	63.5	178.1	-45.6	52.3
<b>13</b>	-74	164.5	77.6	115.5	-177.5	-92.6	-84.2
<b>14</b>	45.4	-73.4	-64.4	66	-3.4	-162.7	60.3
<b>15</b>	58.5	-59.8	61.1	-101	-177.9	-14.4	-63.3
<b>16</b>	-177.2	-57.3	-159.1	42.1	2.2	-88	-87.3
<b>17</b>	-66.2	176.3	-49.7	-82.1	-177.5	-36.8	67.1
<b>18</b>	62.1	-179.1	-172.9	-118.5	-180	-12.9	-102.3
<b>19</b>	73.5	-168.6	-62.3	-6.8	178.8	178.9	76.1
<b>20</b>	74.2	-167.4	-59.6	-3.1	177.6	63.9	76.2
<b>21</b>	-46	71.3	-171.2	66	177.2	-49.5	-91.3
<b>22</b>	-45.6	72.5	-161	47.1	0.8	-93	-79.4
<b>23</b>	57.7	-59.8	58.8	-121.2	-5.2	3.5	-58.8
<b>24</b>	54	173.8	-70.1	60.5	179.7	-174.9	79.4
<b>25</b>	-157.7	82.4	169.3	-116.5	-178.7	-159.6	-133.9
<b>26</b>	44	-77	-65.7	-108	-178.8	-12.1	58.8
<b>27</b>	177.8	59.3	-166.9	65.5	178.4	-60.9	-96.5
<b>28</b>	54.2	175.4	-66.5	78.5	177.5	-46.8	75.8
<b>29</b>	163.2	-79.1	-63.1	-136.8	-9.5	176.1	61.4
<b>30</b>	179.7	-62.1	-44.2	108.6	-179.9	-55.6	66.9
<b>31</b>	177.4	-63.4	-52	116.4	179.7	179.2	71

<b>32</b>	168.4	-73	-59.8	-60	-178.9	-174.9	68.2
<b>33</b>	160	-83.1	33.9	60	178.3	-52.4	-123.5
<b>34</b>	170.8	-71.3	-48.9	124.1	-179.5	71.1	68.9
<b>35</b>	60.3	-57.1	58.1	2.3	178.7	55.5	-63.9
<b>36</b>	40.8	-79	-59.8	80.2	177.2	-50.3	54.9
<b>37</b>	-55.7	61.5	59.7	-6.6	177.3	60.9	-65.6
<b>38</b>	-53.2	65.9	-172.8	67.5	1.01	95.9	-91.9
<b>39</b>	-54.9	-173.1	-174.4	-116	1.9	-10.7	-102.9
<b>40</b>	170.7	-71.8	-51	-74.1	-176.8	57.1	67.6
<b>41</b>	66.5	-53.1	-61.6	-15.6	177.2	-176.8	84.4
<b>42</b>	-52.2	68.5	72.6	103.2	-179.1	-53.3	-64.6
<b>43</b>	52.5	-69.8	-60.1	11.5	179.5	52.7	62.4
<b>44</b>	161.3	-80.6	32.8	46.5	-178	29.1	-117.8
<b>45</b>	167.1	-70.2	63.2	-96.3	-3.9	-61.9	-70.8
<b>46</b>	-69.6	168	61.1	-99.1	-3.7	-54.4	-71.2
<b>47</b>	-165	-43.2	-32.3	85.6	-4.9	88.7	76.8
<b>48</b>	56.6	-62.6	49.9	50.5	0.9	155.7	-63.6
<b>49</b>	52.1	-68.6	32.4	54.9	-0.9	160.5	-130.2
<b>50</b>	-53.9	63.2	-179.6	-115	1.9	-10.7	-98.9
<b>51</b>	74.4	-51.4	50.2	32.5	4.2	44.8	-66.1
<b>52</b>	179.8	59.5	-173	-118.5	-0.5	-9.3	-100.2
<b>53</b>	59.9	-72.2	-57.9	-104.3	1	-12.6	60.1
<b>54</b>	-158.2	81.4	169	-109.5	4.4	-158.7	-134.5



Table 3SI. The B3LYP/aug-cc-pVDZ Cartesian Coordinates of the six most stable PhIS conformers in the gas phase, and neutral (**w**) and zwitterion (**z**) forms in water.

C	-2.83728700	-0.21755300	-0.02556900	C	1.83493600	-1.13867800	0.07994100
O	-3.54997900	-1.17356000	0.20644000	O	1.99459000	-1.85834700	-0.87826000
O	-3.28466100	1.03672800	-0.02571200	O	1.64122700	-1.61627400	1.31978100
H	-2.48784700	1.64075000	-0.10299900	H	1.54317500	-0.84869800	1.91518500
C	-1.34943600	-0.43248000	-0.37245700	C	1.83760700	0.38424000	-0.03838100
H	-1.25705500	-0.23849100	-1.46013000	H	2.77546100	0.65398600	-0.55416600
C	-0.40820500	0.54433600	0.37423900	C	0.65259300	0.90453900	-0.90795600
H	-0.63650200	0.46673600	1.44555300	H	0.82913000	0.52378100	-1.92521300
O	-0.99530100	-1.76219100	-0.08623200	O	1.81224100	0.95771100	1.26117900
H	-1.83618800	-2.22493400	0.08139700	H	1.46013000	1.85780100	1.14520100
N	-0.77156600	1.92818800	-0.04275100	N	0.72673100	2.37590700	-0.82123100
H	-0.39532300	2.60228300	0.62021800	H	1.50669200	2.72876900	-1.37156800
H	-0.34395400	2.14642500	-0.94169400	H	-0.12042800	2.80214700	-1.18750200
C	1.06391000	0.22014100	0.17752600	C	-0.70783400	0.40158200	-0.44977200
C	3.81316600	-0.29097100	-0.15767300	C	-3.20532900	-0.60602000	0.37885900
C	1.89882300	0.04183300	1.28768000	C	-1.43937900	1.04538000	0.56103000
C	1.62437800	0.13275800	-1.10640000	C	-1.24805600	-0.75092600	-1.04174800
C	2.98748100	-0.11909600	-1.27431900	C	-2.48471600	-1.25331600	-0.62928100
C	3.26462700	-0.21226300	1.12472100	C	-2.67930300	0.54566400	0.97089800
H	1.47629200	0.09229900	2.29253700	H	-1.04527000	1.94510300	1.03094900
H	0.99522100	0.24393400	-1.99122300	H	-0.68980300	-1.26584600	-1.82377400
H	3.40590500	-0.18994500	-2.27878700	H	-2.88663100	-2.15112300	-1.09957400
H	3.89848200	-0.35261400	2.00077700	H	-3.23505100	1.05864300	1.75658500
H	4.87671400	-0.49180500	-0.28885400	H	-4.17208300	-0.99542300	0.69935800
<b>1</b>				<b>2</b>			
C	1.87573200	-1.01974300	0.26454600	C	-1.90059200	0.94133100	-0.46798200
O	1.79036000	-1.51802300	1.36691600	O	-2.19636200	1.60335700	-1.43921500
O	2.06529300	-1.73621000	-0.86267000	O	-1.98966700	1.41827800	0.77944300
H	2.09869700	-2.67309600	-0.60774800	H	-1.67375600	0.70508100	1.40634900
C	1.80001700	0.47697700	0.01542900	C	-1.49016600	-0.54163900	-0.62306500
H	2.72664600	0.78298500	-0.49641200	H	-1.08674500	-0.65042400	-1.63909000
C	0.62715100	0.87377500	-0.92347900	C	-0.45907000	-1.08428100	0.38681200
H	0.83320300	0.38988900	-1.88874600	H	-0.39141200	-2.16242800	0.17111600
O	1.72269300	1.15529300	1.25375800	O	-2.66152500	-1.35776600	-0.45523500
H	1.59755000	0.48041000	1.94067200	H	-3.33286500	-1.06786300	-1.08656400
N	0.74142300	2.32159700	-1.13113200	N	-0.97179000	-0.85087900	1.75848900
H	-0.04600100	2.66253900	-1.67680200	H	-0.25195100	-1.04568800	2.44958800
H	0.72328600	2.80844800	-0.23742000	H	-1.75609100	-1.47403700	1.93787300
C	-0.72865200	0.36795200	-0.43520600	C	0.92503900	-0.48790400	0.18433000
C	-3.22862700	-0.61324900	0.42981700	C	3.49959500	0.55921700	-0.28147900
C	-1.39380600	0.95828300	0.65205700	C	1.85181800	-1.18362400	-0.60776200
C	-1.34055400	-0.71609100	-1.08275000	C	1.30823500	0.74105900	0.74376300
C	-2.58019700	-1.20496400	-0.65723200	C	2.58720500	1.25796400	0.51355100
C	-2.63038600	0.47040700	1.08213400	C	3.12732700	-0.66544700	-0.84400900
H	-0.94321000	1.80400400	1.16946500	H	1.57358400	-2.14545000	-1.04209200
H	-0.84297900	-1.18042500	-1.93605300	H	0.60999400	1.30780300	1.35664200
H	-3.04132700	-2.04415000	-1.17947700	H	2.86776900	2.21479000	0.95442700
H	-3.13063400	0.93908700	1.93050700	H	3.83263100	-1.22192600	-1.46192200
H	-4.19602200	-0.98943100	0.76402100	H	4.49546200	0.96529500	-0.46064400
<b>3</b>				<b>4</b>			
C	-2.79611600	-0.11061500	-0.12207100	C	-1.97552800	0.87290500	-0.45305800
O	-3.39925300	0.91521600	0.10130800	O	-3.12449900	1.18601400	-0.21357500
O	-3.38308200	-1.31365100	-0.01591200	O	-1.00082000	1.76407100	-0.69632500
H	-2.71304000	-1.98788400	-0.23772100	H	-1.38922400	2.64986500	-0.60313900
C	-1.31689200	-0.12938300	-0.52803500	C	-1.52633200	-0.58088300	-0.56517200
H	-1.22145100	0.45688600	-1.45557500	H	-1.07575800	-0.71804900	-1.56137200

C	-0.43311300	0.55399500	0.55964800	C	-0.48553600	-1.00808100	0.50782200
H	-0.69985200	0.09116800	1.52833800	H	-0.44889700	-2.10668000	0.39110900
O	-0.96648100	-1.49451200	-0.75175100	O	-2.66819400	-1.41170600	-0.43603800
H	-0.00347200	-1.57771800	-0.78519100	H	-3.43476100	-0.82195600	-0.34034400
N	-0.68733800	1.99463900	0.50969000	N	-0.99253500	-0.60309100	1.82189500
H	-1.68616600	2.17674000	0.59359300	H	-1.91056800	-1.01746000	1.96697400
H	-0.21077300	2.46356400	1.27571000	H	-0.38770000	-0.95662900	2.55965600
C	1.03927700	0.25750100	0.30154500	C	0.92010800	-0.48801100	0.24697800
C	3.74258100	-0.34695400	-0.21310500	C	3.53633100	0.41174900	-0.29072700
C	1.69683800	-0.75465900	1.01817100	C	1.46089000	0.59499300	0.95258200
C	1.75634300	0.96747300	-0.67629200	C	1.71178800	-1.11936500	-0.72522500
C	3.09647900	0.66673800	-0.93061800	C	3.00637700	-0.67198300	-0.99894800
C	3.03991200	-1.05709500	0.76358900	C	2.76020400	1.03954700	0.68753500
H	1.15743400	-1.30338100	1.79223300	H	0.85499200	1.09398600	1.70644100
H	1.25858200	1.76900000	-1.22025700	H	1.31540400	-1.97852900	-1.27019200
H	3.64187200	1.22896800	-1.68949900	H	3.60579500	-1.17607700	-1.75790500
H	3.53692500	-1.84154200	1.33516500	H	3.16724100	1.88194700	1.24826900
H	4.78999400	-0.57672100	-0.41077700	H	4.54951300	0.75895500	-0.49598100
<b>5</b>				<b>6</b>			
C	2.82928000	-0.20394300	0.05698100	C	-2.84138700	-0.25776600	-0.04334200
O	3.57998200	-1.15724800	-0.09427300	O	-3.61046600	-1.18803300	0.10920900
O	3.24221800	1.05115300	-0.00950500	O	-3.25250700	1.00879100	0.01849000
H	2.39826000	1.64292800	0.00031300	H	-2.42564700	1.61132300	-0.00998200
C	1.34090600	-0.43324900	0.37462000	C	-1.34782800	-0.44710900	-0.36998200
H	1.22578600	-0.21531000	1.45272200	H	-1.25202500	-0.23282900	-1.45014800
C	0.40621600	0.51352400	-0.41916100	C	-0.42841800	0.53889100	0.40984000
H	0.62225100	0.37329000	-1.48560500	H	-0.64644700	0.41586900	1.47803200
O	1.00984500	-1.78268300	0.11637200	O	-1.01962800	-1.79732900	-0.10017400
H	1.85884000	-2.24820200	0.01932600	H	-0.10611500	-1.94525800	-0.38021200
N	0.80156900	1.90873900	-0.08516000	N	-0.82496700	1.92350300	0.05014000
H	0.45338700	2.55245900	-0.79230500	H	-0.47652100	2.58332100	0.74199600
H	0.39310300	2.20128700	0.80141100	H	-0.42528600	2.19912900	-0.84556300
C	-1.06735000	0.21588500	-0.18996400	C	1.04811000	0.23890900	0.19131400
C	-3.81481400	-0.28074100	0.19089300	C	3.79415500	-0.27576100	-0.17597400
C	-1.90185700	-0.06277700	-1.28104900	C	1.87671300	-0.04186200	1.28754400
C	-1.62689900	0.24154200	1.09816600	C	1.61370700	0.25428800	-1.09571600
C	-2.98961600	-0.00390600	1.28791000	C	2.97612900	-0.00034000	-1.27803800
C	-3.26694900	-0.30989400	-1.09510600	C	3.24090400	-0.29614100	1.10810200
H	-1.48196000	-0.08720100	-2.28764000	H	1.45220100	-0.05959400	2.29219800
H	-1.00367600	0.45040100	1.96896500	H	0.99689700	0.46710900	-1.97026500
H	-3.40822700	0.01889000	2.29451000	H	3.39926600	0.01568100	-2.28272500
H	-3.90093500	-0.52499400	-1.95583300	H	3.87025100	-0.51075000	1.97219100
H	-4.87766900	-0.47313400	0.33976300	H	4.85650400	-0.47460300	-0.31919800
<b>1w</b>				<b>29w</b>			
C	-1.81046500	0.94793500	-0.53046600	C	1.74634000	-1.20798600	0.08188800
O	-1.96158200	1.62862900	-1.53141800	O	1.85054400	-2.00198000	-0.83100600
O	-1.97084000	1.45077100	0.69228700	O	1.50476000	-1.60860700	1.33852500
H	-1.69301500	0.72834800	1.35996700	H	1.48225800	-0.80477400	1.89773200
C	-1.49767600	-0.56257400	-0.61497000	C	1.87178100	0.29805600	-0.10488500
H	-1.08761700	-0.75690400	-1.61384200	H	2.79673800	0.47527600	-0.67672700
C	-0.50433700	-1.07030100	0.45268400	C	0.67936400	0.89737500	-0.92504000
H	-0.45631000	-2.16058800	0.31482100	H	0.81285300	0.55361700	-1.96112600
O	-2.71591800	-1.29361700	-0.41470700	O	1.95714300	0.91072700	1.17472800
H	-3.30769500	-1.13143800	-1.16155600	H	1.61579000	1.81741900	1.03923000
N	-1.04526100	-0.72901100	1.78987200	N	0.81932300	2.35682700	-0.78260700
H	-0.33468300	-0.84365400	2.50872600	H	1.57975400	2.70051300	-1.36584200
H	-1.80879900	-1.36076300	2.02066900	H	-0.02731700	2.83048800	-1.08667700
C	0.89148900	-0.50745900	0.22789400	C	-0.68718500	0.43040000	-0.44771100
C	3.47816700	0.48624500	-0.29272300	C	-3.20631900	-0.50879100	0.40501400
C	1.74597600	-1.16520500	-0.67247200	C	-1.32496100	1.00213100	0.66598300

C	1.35299200	0.65294800	0.86745100	C	-1.33476800	-0.61104300	-1.13129400
C	2.63836100	1.14462900	0.60985500	C	-2.58223700	-1.08087800	-0.70857700
C	3.02685400	-0.67300000	-0.93478900	C	-2.57437800	0.53574000	1.08819200
H	1.40871700	-2.07633500	-1.16905600	H	-0.85388500	1.82218300	1.20518600
H	0.71734900	1.18377700	1.57398800	H	-0.85981700	-1.05758800	-2.00541600
H	2.98181100	2.04545000	1.11910800	H	-3.06970200	-1.88891000	-1.25495200
H	3.67621700	-1.19980400	-1.63459100	H	-3.05619200	0.99264200	1.95321200
H	4.47939800	0.86941600	-0.49141000	H	-4.18114200	-0.86979500	0.73423600
<b>4w</b>				<b>2w</b>			
C	-1.71857500	1.15708000	-0.18481200	C	1.85573300	-1.02712500	0.27626400
O	-0.83969400	1.99263900	-0.22836500	O	1.66033800	-1.53742300	1.36294300
O	-2.92631800	1.43826400	0.32948300	O	2.13659200	-1.71793600	-0.83790500
H	-3.47724300	0.63871000	0.18840400	H	2.13716500	-2.66764800	-0.62596500
C	-1.57746900	-0.27435000	-0.73206200	C	1.80519000	0.47458800	0.04237900
H	-1.30336500	-0.17432100	-1.79007500	H	2.74281200	0.77642800	-0.44647800
C	-0.50723200	-1.15852700	-0.01166800	C	0.64645800	0.88215600	-0.91300600
H	-0.46121800	-2.06270300	-0.63396200	H	0.86444400	0.40419100	-1.87758600
O	-2.83376900	-0.94398900	-0.64936100	O	1.72330700	1.14596000	1.28743100
H	-2.74741500	-1.50346200	0.15415800	H	1.42849300	0.49660400	1.94613900
N	-1.09797900	-1.58689400	1.26044100	N	0.75793300	2.33328800	-1.11372800
H	-0.64471900	-2.42577800	1.61080000	H	0.00486300	2.65421400	-1.71854000
H	-1.02986600	-0.87842800	1.98716800	H	0.64263600	2.81807200	-0.22571100
C	0.89708400	-0.56531500	0.01432600	C	-0.71609400	0.37504800	-0.44375400
C	3.51346700	0.48913100	-0.03191400	C	-3.21947900	-0.62125500	0.39803200
C	1.45619800	0.00959700	1.16282800	C	-1.41304300	0.98571000	0.61247200
C	1.67293700	-0.61610000	-1.15544400	C	-1.29757000	-0.73670100	-1.07374500
C	2.96754600	-0.09088300	-1.18314300	C	-2.53872800	-1.23309700	-0.65925600
C	2.75340500	0.53476900	1.14080800	C	-2.65190000	0.49077000	1.03151900
H	0.88941100	0.05456300	2.09226000	H	-0.99280900	1.85688500	1.11336700
H	1.26368300	-1.07677300	-2.05642500	H	-0.77720700	-1.21727900	-1.90372500
H	3.55394600	-0.14328300	-2.10113400	H	-2.97545600	-2.09374600	-1.16717800
H	3.17113000	0.97759800	2.04553800	H	-3.17772900	0.97690400	1.85414600
H	4.52560400	0.89441000	-0.04737200	H	-4.18804000	-1.00302500	0.72243500
<b>10w</b>				<b>3w</b>			
C	2.85984600	-0.13569800	0.06478300	C	-2.87036500	-0.18066800	-0.10225800
O	3.58915100	-1.10817300	-0.22344500	O	-3.18178400	1.05818500	0.06887900
O	3.20626900	1.08799600	0.15301100	O	-3.65695300	-1.13600200	-0.07801700
H	1.84935000	1.86400800	0.07939400	C	-1.36374200	-0.43334200	-0.41068800
C	1.36770000	-0.46922300	0.35947900	H	-1.21085800	-0.12111600	-1.45882100
H	1.21771600	-0.33872200	1.44552500	C	-0.42339000	0.40457200	0.50414100
C	0.40185400	0.46792300	-0.40231000	H	-0.63992100	0.13267300	1.54325400
H	0.62132900	0.38461200	-1.47199900	O	-1.07262900	-1.81174600	-0.25836900
O	1.09674400	-1.80776800	-0.00595800	H	-0.18186000	-1.97695800	-0.59591900
H	1.98351400	-2.15977100	-0.22610000	N	-0.82210600	1.85161300	0.36712100
C	-1.07109800	0.19551700	-0.17481400	H	-1.92934600	1.77787900	0.25586200
C	-3.81850300	-0.28192000	0.19100000	H	-0.54002900	2.40182700	1.17859700
C	-1.92391500	0.05893200	-1.27897500	C	1.05231700	0.19095500	0.23063800
C	-1.60838300	0.08842000	1.11830200	C	3.79315300	-0.22347000	-0.24697100
C	-2.97412200	-0.14627000	1.29926400	C	1.61235300	0.49826700	-1.02081800
C	-3.29031600	-0.18053700	-1.09958500	C	1.87988100	-0.32924400	1.23593500
H	-1.51727000	0.13779600	-2.28787500	C	3.24273700	-0.53791700	0.99926000
H	-0.96852700	0.17575100	1.99704700	C	2.97468900	0.29612300	-1.25671800
H	-3.37894200	-0.22900200	2.30805400	H	0.99234500	0.89699000	-1.82511400
H	-3.94016600	-0.28758000	-1.96824700	H	1.45691200	-0.57130900	2.21144200
H	-4.88290300	-0.46916300	0.33454400	H	3.87354800	-0.94335700	1.79044200
N	0.77100400	1.88972900	-0.02586500	H	3.39676900	0.54193100	-2.23120100
H	0.47656200	2.55798900	-0.73943200	H	4.85546700	-0.38282900	-0.43279200
H	0.34662300	2.17666900	0.85841900	H	-0.41313800	2.28783300	-0.46066500
<b>1z</b>				<b>2z</b>			

C	-1.88956400	0.95203100	-0.46161400	C	-1.90059200	0.94133100	-0.46798200
O	-1.08805000	1.84702500	-0.33792900	O	-2.19636200	1.60335700	-1.43921500
O	-3.06648636	1.16181424	-0.56575217	O	-1.98111779	1.37250173	0.65971805
C	-1.51677400	-0.54493200	-0.53015500	H	-1.77734149	-0.22563812	1.73481135
H	-1.15273200	-0.73926100	-1.54815600	C	-1.49016600	-0.54163900	-0.62306500
C	-0.44402900	-0.97812300	0.50002900	H	-1.08674500	-0.65042400	-1.63909000
H	-0.39732700	-2.07058500	0.38127700	C	-0.45907000	-1.08428100	0.38681200
O	-2.69191600	-1.34165900	-0.34786300	H	-0.39141200	-2.16242800	0.17111600
H	-2.75914000	-1.46993700	0.61611300	O	-2.66152500	-1.35776600	-0.45523500
N	-1.02637100	-0.74338600	1.82778300	H	-3.33286500	-1.06786300	-1.08656400
H	-0.51304500	-1.24526800	2.54702500	N	-0.97179000	-0.85087900	1.75848900
H	-1.00114000	0.24396400	2.07404300	H	-0.21105814	-0.62071037	2.39255997
C	0.96242700	-0.45156700	0.22380400	H	-1.42089798	-1.69734757	2.10116312
C	3.58119300	0.41753400	-0.35419900	C	0.92503900	-0.48790400	0.18433000
C	1.52739300	0.62365100	0.91935700	C	3.49959500	0.55921700	-0.28147900
C	1.73301300	-1.09045000	-0.76027700	C	1.85181800	-1.18362400	-0.60776200
C	3.02908800	-0.65967000	-1.05378500	C	1.30823500	0.74105900	0.74376300
C	2.82599200	1.05496900	0.63425700	C	2.58720500	1.25796400	0.51355100
H	0.95394700	1.14894900	1.68126300	C	3.12732700	-0.66544700	-0.84400900
H	1.31789500	-1.94232800	-1.30341100	H	1.57358400	-2.14545000	-1.04209200
H	3.61043100	-1.17080900	-1.82193500	H	0.60999400	1.30780300	1.35664200
H	3.24661400	1.89771500	1.18353200	H	2.86776900	2.21479000	0.95442700
H	4.59384600	0.75569500	-0.57562800	H	3.83263100	-1.22192600	-1.46192200
H	-1.95049346	-1.14835148	1.87361566	H	4.49546200	0.96529500	-0.46064400
<b>3z</b>				<b>4z</b>			
C	-1.70389800	1.05817800	-0.12257600	C	1.83493600	-1.13867800	0.07994100
O	-1.94583700	1.30445400	1.04112100	O	1.99459000	-1.85834700	-0.87826000
O	-1.55939747	1.92299388	-0.95643036	O	1.66037048	-1.56907511	1.19725260
C	-1.57872000	-0.35034600	-0.72130500	C	1.83760700	0.38424000	-0.03838100
H	-1.26127500	-0.25353100	-1.76541200	H	2.77546100	0.65398600	-0.55416600
C	-0.55609200	-1.22200000	0.05749200	C	0.65259300	0.90453900	-0.90795600
H	-0.50811300	-2.16156600	-0.51208400	H	0.82913000	0.52378100	-1.92521300
O	-2.85301100	-0.96722600	-0.71588900	H	0.41377414	2.68792841	0.07582008
H	-2.93068000	-1.38421900	0.16155400	N	0.72673100	2.37590700	-0.82123100
N	-1.15671100	-1.55635400	1.35210700	H	1.68403528	2.69516268	-0.95301070
H	-0.52997245	-2.12321461	1.91491672	H	0.16000108	2.80912168	-1.54556213
H	-1.23276000	-0.74054800	1.95460100	C	-0.70783400	0.40158200	-0.44977200
C	0.84369500	-0.61169600	0.05533300	C	-3.20532900	-0.60602000	0.37885900
C	3.42794900	0.51400200	-0.05095300	C	-1.43937900	1.04538000	0.56103000
C	1.70947800	-0.89363500	-1.01344900	C	-1.24805600	-0.75092600	-1.04174800
C	1.29551200	0.24116500	1.07300800	C	-2.48471600	-1.25331600	-0.62928100
C	2.57666100	0.79967900	1.02040000	C	-2.67930300	0.54566400	0.97089800
C	2.98965400	-0.33685600	-1.07048100	H	-1.04527000	1.94510300	1.03094900
H	1.38039700	-1.56457800	-1.80956200	H	-0.68980300	-1.26584600	-1.82377400
H	0.64780300	0.47810600	1.91614100	H	-2.88663100	-2.15112300	-1.09957400
H	2.91102700	1.45940500	1.82180400	H	-3.23505100	1.05864300	1.75658500
H	3.64790900	-0.57363200	-1.90713300	H	-4.17208300	-0.99542300	0.69935800
H	4.42806200	0.94671500	-0.08860500	O	1.81513868	0.89220048	1.11272364
H	-1.94843486	-1.97592995	1.81818569	H	1.57156165	1.81862925	1.04947837
<b>5z</b>				<b>6z</b>			

Table 4SI. The total energies (E, hartree), the total energies corrected for zero-point energies ( $E_0$ , hartree), the Gibbs free energies in 298.15 K (G, hartree), relative total energies ( $\Delta E$ , kcal/mol), and corresponding relative energies referred to the most stable conformer (kcal/mol) for the B3LYP/aug-cc-pVDZ optimized 51 stable structures of phenylisoserine (PhIS) in water (Fig 2SI).

Conformer number	E	$\Delta E$	$E_0$	$\Delta E_0$	G	$\Delta G$
<b>1w</b>	-630.1274942	0.00	-629.934426	0.00	-629.97271	0.00
<b>29w</b>	-630.1234995	2.51	-629.930403	2.52	-629.968907	2.39
<b>4w</b>	-630.1218852	3.52	-629.928629	3.64	-629.967247	3.43
<b>2w</b>	-630.1203843	4.46	-629.927059	4.62	-629.965973	4.23
<b>10w</b>	-630.1183024	5.77	-629.924701	6.10	-629.963721	5.64
<b>3w</b>	-630.1175119	6.26	-629.924941	5.95	-629.964382	5.23
<b>5w</b>	-630.1173267	6.38	-629.924702	6.10	-629.964185	5.35
<b>25w</b>	-630.1173143	6.39	-629.92424	6.39	-629.963485	5.79
<b>7w</b>	-630.1172018	6.46	-629.924042	6.52	-629.963612	5.71
<b>8w</b>	-630.1169491	6.62	-629.924451	6.26	-629.964041	5.44
<b>13w</b>	-630.1167367	6.75	-629.923494	6.86	-629.963208	5.96
<b>38w</b>	-630.1166688	6.79	-629.923859	6.63	-629.963409	5.84
<b>6w</b>	-630.1165664	6.86	-629.92391	6.60	-629.963089	6.04
<b>14w</b>	-630.1165433	6.87	-629.923898	6.61	-629.963478	5.79
<b>16w</b>	-630.1164254	6.95	-629.92293	7.21	-629.961753	6.88
<b>17w</b>	-630.1159534	7.24	-629.923289	6.99	-629.963198	5.97
<b>22w</b>	-630.1158667	7.30	-629.922271	7.63	-629.960988	7.36
<b>18w</b>	-630.1157736	7.35	-629.92334	6.96	-629.962924	6.14
<b>11w</b>	-630.1157306	7.38	-629.92319	7.05	-629.962988	6.10
<b>9w</b>	-630.1155498	7.50	-629.922859	7.26	-629.961416	7.09
<b>15w</b>	-630.1153072	7.65	-629.922513	7.48	-629.961915	6.77
<b>12w</b>	-630.1151704	7.73	-629.922382	7.56	-629.96175	6.88
<b>26w</b>	-630.115061	7.80	-629.922506	7.48	-629.962176	6.61
<b>30w</b>	-630.1149096	7.90	-629.922353	7.58	-629.962367	6.49
<b>21w</b>	-630.1147499	8.00	-629.921978	7.81	-629.961325	7.14
<b>48w, 49w</b>	-630.1146891	8.04	-629.921896	7.86	-629.961961	6.75
<b>32w</b>	-630.1146769	8.04	-629.92224	7.65	-629.962404	6.47
<b>40w</b>	-630.1146158	8.08	-629.922089	7.74	-629.962325	6.52
<b>47w</b>	-630.114573	8.11	-629.921651	8.02	-629.961284	7.17
<b>34w</b>	-630.1145137	8.15	-629.92187	7.88	-629.961819	6.83
<b>31w</b>	-630.1143004	8.28	-629.921898	7.86	-629.961914	6.77
<b>27w</b>	-630.113985	8.48	-629.921435	8.15	-629.96095	7.38
<b>28w</b>	-630.113875	8.55	-629.92152	8.10	-629.961862	6.81
<b>45w, 46w</b>	-630.1136956	8.66	-629.920722	8.60	-629.960064	7.94
<b>24w</b>	-630.1136391	8.69	-629.921192	8.30	-629.961444	7.07
<b>20w</b>	-630.1136189	8.71	-629.921137	8.34	-629.961279	7.17
<b>23w</b>	-630.1135816	8.73	-629.921139	8.34	-629.958718	8.78
<b>19w</b>	-630.1134553	8.81	-629.921082	8.37	-629.961592	6.98
<b>39w</b>	-630.1133042	8.90	-629.920847	8.52	-629.960469	7.68
<b>36w</b>	-630.1131221	9.02	-629.920745	8.58	-629.961135	7.26
<b>42w</b>	-630.1128456	9.19	-629.920196	8.93	-629.959754	8.13
<b>54w</b>	-630.1127004	9.28	-629.919565	9.33	-629.958669	8.81
<b>50w</b>	-630.1126834	9.29	-629.919983	9.06	-629.959231	8.46

<b>35w, 37w</b>	-630.1124753	9.42	-629.91973	9.22	-629.959527	8.27
<b>43w</b>	-630.1124013	9.47	-629.919967	9.07	-629.960237	7.83
<b>41w</b>	-630.1121916	9.60	-629.920058	9.02	-629.959034	8.58
<b>51w</b>	-630.1121247	9.64	-629.919375	9.44	-629.959504	8.29
<b>52w</b>	-630.1116789	9.92	-629.919316	9.48	-629.958839	8.70
<b>53w</b>	-630.1110108	10.34	-629.918646	9.90	-629.958735	8.77
<b>44w</b>	-630.1108167	10.47	-629.918337	10.10	-629.958305	9.04
<b>33w</b>	-630.1105046	10.66	-629.917664	10.52	-629.955643	10.71

Table 5SI. The selected dihedral angles (deg) for the B3LYP/aug-cc-pVDZ optimized 51 stable structures of phenylisoserine (PhIS) in water (Fig 2SI). Atom numbering as in Scheme 1SI.

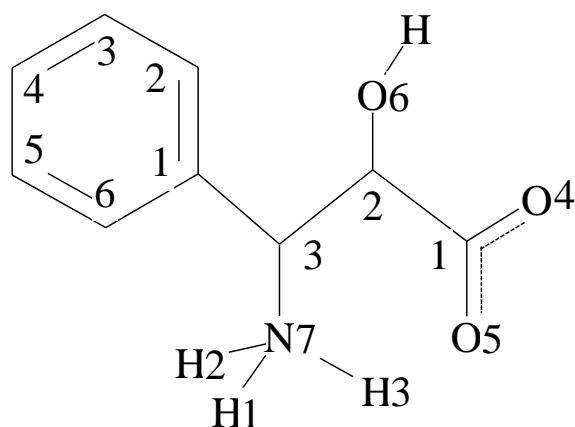
	d(H1N7C3C2)	d(H2N7C3C2)	d(N7C3C2C1)= =(Ph1C3C2C1)	d(O4C1C2C3)	d(HO5C1C2)	d(HO6C2C1)	d(Ph2Ph1C3C2)
	f1	f2	f3	f4	f5	f6	f7
<b>1w</b>	160.8	-81.3	-58.4	-137.6	-10.5	13.7	57.7
<b>29w</b>	161.5	-80.3	-60.0	-139.0	-9.7	175.8	58.9
<b>4w</b>	75.3	-166.7	56.4	142.3	9.3	67.0	94.2
<b>2w</b>	-166.2	75.3	169.3	68.3	-1.5	-154.0	-99.0
<b>10w</b>	-81.4	157.8	76.9	64.0	-2.9	-100.5	-76.5
<b>3w</b>	-61.9	-178.7	-176.8	-115.4	-178.9	-18.3	-103.3
<b>5w</b>	57.9	175.3	-70.2	66.9	-2.2	-159.0	74.0
<b>25w</b>	-165.7	76.3	172.9	-113.5	-178.6	-161.3	-100.3
<b>7w</b>	-77.8	161.5	74.5	-77.2	-177.5	-88.8	-83.2
<b>8w</b>	-52.3	63.9	-178.8	-112.8	-178.3	-20.6	-98.8
<b>13w</b>	-79.2	159.9	79.2	105.2	179.5	-93.8	-82.2
<b>38w</b>	-54.1	62.6	-174.1	62.2	-1.6	106.5	-98.0
<b>6w</b>	58.3	174.0	51.4	-114.1	179.7	-3.2	-73.0
<b>14w</b>	49.4	-67.7	-65.4	69.2	-3.2	-156.6	61.3
<b>16w</b>	-59.4	-177.2	-159.4	46.8	1.4	-90.3	-89.2
<b>17w</b>	172.9	-70.7	-51.2	-76.7	-179.0	-49.9	64.5
<b>22w</b>	-50.9	66.0	-161.6	49.1	0.3	-92.6	-85.0
<b>18w</b>	-179.0	65.1	-172.8	-114.3	-178.8	-20.0	-99.6
<b>11w</b>	66.8	-175.9	-67.3	-103.5	-178.1	-20.5	68.7
<b>9w</b>	56.9	172.9	52.8	-125.6	-8.8	6.5	-71.6
<b>15w</b>	56.0	-61.8	59.9	-103.5	-178.2	-16.5	-69.2
<b>12w</b>	-59.0	-176.3	-168.1	65.5	178.8	-54.5	-96.6
<b>26w</b>	53.1	-65.2	-65.5	-107.3	-178.2	-14.5	59.8
<b>30w</b>	171.8	-71.7	-49.5	114.0	-178.2	-65.5	63.8
<b>21w</b>	-50.5	65.7	-170.2	66.9	177.9	-55.8	-93.7
<b>48w,49w</b>	56.1	-62.4	60.2	69.8	-3.4	99.5	-67.3
<b>32w</b>	171.8	-71.4	-56.2	-68.2	-178.3	179.2	66.2
<b>40w</b>	170.4	-73.3	-51.4	-69.5	-178.9	74.8	62.4
<b>47w</b>	177.8	-65.9	-49.9	91.0	-7.7	83.2	64.7
<b>34w</b>	171.0	-72.5	-49.2	117.2	-179.2	74.7	63.5
<b>31w</b>	172.4	-70.7	-53.4	115.2	-179.9	176.5	66.4
<b>27w</b>	-178.8	64.9	-164.6	67.4	178.6	-66.2	-96.0
<b>28w</b>	-175.4	67.7	-58.2	93.8	178.5	-60.0	68.5
<b>45w,46w</b>	-79.5	159.5	71.5	-96.7	-2.2	-85.5	-69.8
<b>24w</b>	62.0	179.4	-63.6	84.9	177.5	-177.5	73.8
<b>20w</b>	76.6	-166.8	-58.3	-16.3	175.6	74.3	67.2
<b>23w</b>	54.1	-63.4	59.6	-121.0	-5.0	1.0	-63.4
<b>19w</b>	75.4	-168.1	-61.9	-10.6	178.6	175.0	72.5
<b>39w</b>	-61.3	-178.4	-176.3	-109.8	4.6	-21.4	-101.8
<b>35w,36w</b>	54.8	-63.5	-57.0	87.5	177.6	-58.9	62.7
<b>42w</b>	-52.4	67.5	71.0	96.9	179.4	-56.6	-74.2
<b>54w</b>	-165.8	76.0	172.6	-107.0	5.0	160.6	-99.1
<b>50w</b>	-51.5	64.8	-179.2	-108.9	5.3	-21.3	-97.0
<b>37w</b>	57.5	-58.4	71.1	99.8	178.7	69.7	-73.7
<b>43w</b>	-61.7	56.8	-60.6	-8.5	176.5	68.6	61.7
<b>41w</b>	159.3	-84.4	33.0	63.4	178.9	-60.0	-122.3

<b>51w</b>	68.8	-53.6	54.2	47.7	0.8	-92.3	-66.0
<b>52w</b>	-178.6	65.0	-172.9	-11.3	3.6	-20.0	-100.5
<b>53w</b>	61.1	-62.8	-58.4	-97.7	4.8	-24.5	61.0
<b>44w</b>	-78.5	163.3	45.6	44.0	-177.0	44.4	-66.6
<b>33w</b>	58.9	-59.5	-62.1	-13.1	178.1	176	66.4



Table 6SI. The total energies (E, hartree), the total energies corrected for zero-point energies ( $E_0$ , hartree), the Gibbs free energies in 298.15 K (G, hartree), relative total energies ( $\Delta E$ , kcal/mol), and corresponding relative energies referred to the most stable conformer (kcal/mol) for the B3LYP/aug-cc-pVDZ optimized 6 stable zwitterions structures of phenylisoserine (PhIS) in water (Fig 3).

Conformer number	E	$\Delta E$	$E_0$	$\Delta E_0$	G	$\Delta G$
<b>1z</b>	-630.126535	0.00	-629.932640	0.00	-629.971425	0.00
<b>2z</b>	-630.119178	4.62	-629.926594	3.80	-629.965478	3.75
<b>3z</b>	-630.118980	4.75	-629.924472	5.13	-629.963330	5.09
<b>4z</b>	-630.118855	4.83	-629.925236	4.65	-629.964083	4.62
<b>5z</b>	-630.117319	5.79	-629.923112	5.98	-629.962063	5.89
<b>6z</b>	-630.116805	6.11	-629.921792	6.81	-629.960686	6.75



Scheme 2SI

Table 7SI. The selected dihedral angles (deg) and N-H bond length (Å) for the B3LYP/aug-cc-pVDZ optimized 6 stable zwitterions structures of phenylisoserine (PhIS) in water (Fig 3). Atom numbering as in Scheme 2SI.

	d(H1N7C3C2)	d(H2N7C3C2)	d(H3N7C3C2)	d(N7C3C2C1)= =(Ph1C3C2C1)	d(O4C1C2C3)	d(HO6C2C1)	d(Ph2Ph1C3C2)	H3-N
	f1	f2	f8	f3	f4	f6	f7	
<b>1z</b>	156.2	-83	35.4	-55.8	-132.1	7.5	51.2	1.084
<b>2z</b>	156.6	-82.2	35.7	-54.7	-138.3	170.5	61.3	1.115
<b>3z</b>	74.1	-164.8	-43.3	23.3	-154.7	23.6	55.8	1.062
<b>4z</b>	77.6	-160.9	-38.5	51.7	148.2	56.7	75.4	1.095
<b>5z</b>	83.8	-155.3	-33.4	58.1	123.1	-23.4	78.9	1.074
<b>6z</b>	-50.2	68.4	-170.7	174.5	-120	-4.1	-115.3	1.023

Table 8SI. The B3LYP/aug-cc-pVTZ and MP2/aug-cc-pVDZ optimized for 6 most stable structures of phenylisoserine (PhIS) in water as neutral and zwitterion forms. G stands for Gibbs free energies (hartree),  $\Delta G$  stands for G referred to the most stable conformer (kcal/mol). The populations X(G) were calculated based on  $\Delta G$  values (DFT) and  $\Delta E$  values (MP2) separately for the 6 structures of each type.

Conformer	B3LYP/aug-cc-pVTZ			MP2/aug-cc-pVDZ		
	G	$\Delta G$	X(G)	G	$\Delta G$	X(G)
<b>1w</b>	-630.126755	0.00	86.36	-628.389609	0.000	54.98
<b>29w</b>	-630.122806	2.48	1.32	-628.3864887	1.958	2.02
<b>4w</b>	-630.120885	3.68	0.17	-628.3869802	1.650	3.40
<b>2w</b>	-630.120060	4.20	0.07	-628.38684	1.738	2.93
<b>10w</b>	-630.118358	5.27	0.01	-628.3826218	4.385	0.03
<b>3w</b>	-630.118500	5.18	0.01	-628.3839233	3.568	0.13
<b>1z</b>	-630.124891	1.17	11.99	-628.38921	0.250	36.03
<b>2z</b>	-630.118717	5.04	0.02	-628.3822281	4.632	0.02
<b>3z</b>	-630.116861	6.21	0.00	-628.3824612	4.485	0.03
<b>4z</b>	-630.117684	5.69	0.01	-628.3842131	3.386	0.18
<b>5z</b>	-630.115630	6.98	0.00	-628.3842179	3.383	0.18
<b>6z</b>	-630.114389	7.76	0.00	-628.3836654	3.730	0.10

Table 9SI. The Laplacian in the H-bond BCP and H-bond distance in 18 selected phenylisoserine conformers calculated for vacuum, water and zwitterions in water at the B3LYP/aug-cc-pVDZ level.

H-bond type	Laplacian in H-Bond BCP (au)	H-bond distance (Å)
1v-OHc-NH2	-0.0314	1.741
1v-OHa-O=C	-0.0237	2.014
2v-OHa-NH2	-0.0176	2.162
2v-OHc-OHa	-0.0261	1.940
3v-OHa-O=C	-0.0242	2.088
3v-CH-OHa	-0.0074	2.745
4v-OHa-NH2	-0.0315	1.743
4v-PhCH-OHa	-0.0069	2.489
5v-NH-O=C	-0.0132	2.184
5v-OHc-OHa	-0.0297	1.886
6v-OHa-O=C	-0.0239	2.036
1w-OHc-NH2	-0.0301	1.621
1w-OHa-O=C	-0.0227	2.041
2w-OHa-NH2	-0.0202	2.060
2w-OHc-OHa	-0.0270	1.921
7w-OHa-NH2	-0.0313	1.652
10w-OHc..OHa	-0.0270	1.903
10w-OHa-NH2	-0.0231	1.988
29w-OHc-NH2	-0.0270	1.632
1z-NH3+-OCO-	-0.0315	1.565
1z-OHa-OCO-	-0.0412	1.919
19z-NH3+-OCO-	-0.0265	1.457
14z-NH3+-OCO-	-0.0340	1.454
5z-NH3+-OCO-	-0.0336	1.456
10z-NH3+-OCO-	-0.0340	1.661
10z-OHa-OCO-	-0.0393	2.014
10z-CH-OCO-	-0.0226	2.479
4z-NH3+-OCO-	-0.0077	1.522
4z-CH-OCO-	-0.0400	2.553
10z-CH-HNH2+	-0.0073	2.595

The H-bond type is denoted as follows nk-AH...B where n is the conformer label, k=v, w, z, and v - stands for vacuum, w- stands for water, z stands for zwitterion in water, indices a and c denote alcoholic and carboxylic, respectively.