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Effect of Solvation on Glycine Molecules: A Theoretical Study

Roman Boča,* Juraj Štofko, and Richard Imrich

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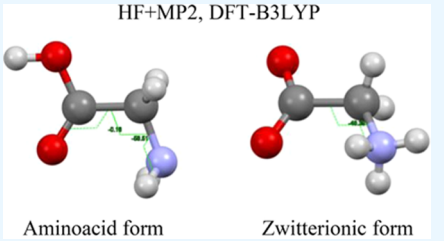
ABSTRACT: *Ab initio* calculations of HF+MP2 and DFT-B3LYP quality have been used in calculating the molecular geometries and properties of neutral and charged molecules of glycine in amino acid as well as zwitterionic forms. A traditional set of molecular descriptors has been enriched by the molecular chemical potential, expressed *via* the Mulliken electronegativity, and Pearson's chemical hardness. In the global energy minimum, the complete vibrational analysis allowed evaluating the standard Gibbs energy and related thermodynamic quantities.



INTRODUCTION

Glycine is a simple organic molecule containing only 10 atoms ($C_2NO_2H_5$ - 2-azaniumylacetate). It is the simplest (non-essential, proteinogenic) α-amino acid like alanine or tyrosine and other aliphatic and aromatic analogues.

The molecular structure of glycine shows great versatility since it can exist in the amino acid form possessing $-NH_2$ and $-COOH$ functional groups or in the form of a zwitterion characterized by $-NH_3^+$ and COO^- terminal groups (Figure 1). In neutral water solutions, the glycine molecule exists in the

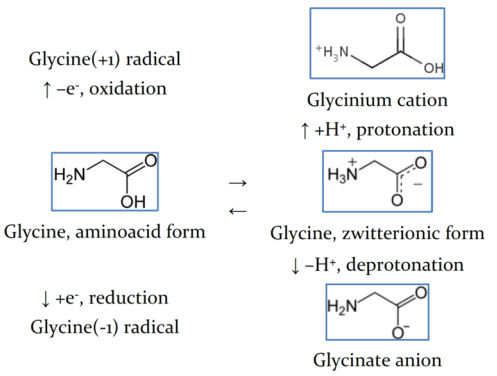


Figure 1. Sketch of the forms of the glycine molecule and its derivatives.

zwitterionic form. In acidic solutions, it is protonated, forming the glycinium cation, whereas in high pH, the deprotonated glycinate anion exists.

Glycine crystallizes in three polymorphs. The structures of the α- and γ-polymorphs have been determined at room temperature and low temperature.[1,2] The β-polymorph was structurally characterized previously[3] and later reinvestigated in the anhydrous form[4] (CCDC 189379, GLYCIN25 (Cambridge Crystallographic Data Centre)). Glycine crystallized as a dihydrate in the zwitterionic form and had a staggered conformation (Figure 2). There is an extensive system of hydrogen bonds and short contact in the solid state[5] (CCDC 1515323, BAHMAP).

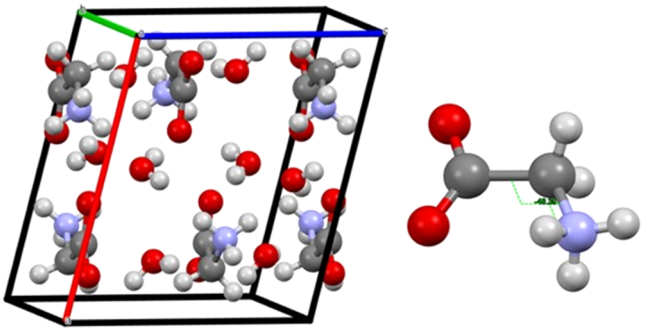


Figure 2. Left, crystal structure of glycine dihydrate (zwitterionic form): unit cell content. Right, individual molecule: the H−N−C−C−O linkage forms a staggered conformation, dihedral angle ϕ_2(C−C−N−H) = −48°. Color code: C, black; N, blue; O, red; H, white.

The molecule of glycine contains a single C−C rotatable bond; however, the bond C−N is also rotatable. Thus, the number of possible rotamers along with the positions of hydrogen atoms causes a structural versatility of glycine (like other α-amino acids). The PubChem database offers the amino acid form (PubChem CID 750) (Figure 3).

There are numerous reports on quantum-chemical calculations of glycine. For instance, 8 glycine conformers and 15 saddle points between them were investigated using density

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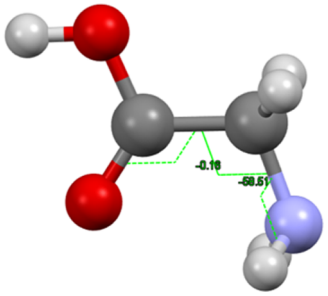

Figure 3. Reported amino acid form of glycine (PubChem CID 750). Dihedral angles ϕ_1(O−C−C−N) = −0.2° and ϕ_2(C−C−N−H) = −58.5°.

functional theory (DFT) with the B3LYP hybrid functional; calculations were conducted *in vacuo* (no solvent) but only for the amino acid forms.[6] These calculations follow up an increasing number of theoretical investigations of glycine *in vacuo* and in water as a solvent.[7−14]

Glycine is very soluble in water: solubility s = 25.0 g in 100 cm^3 H_2O at 25 °C. The acidity constants are pK_{a1} = 2.34 (carboxyl) and pK_{a2} = 9.60 (amino), and the octanol/water partition coefficient log P is −3.21. It is generally assumed that the solvent effect plays a crucial role in properties of glycine in aqueous solutions and in blood. Notice that the solvent effect is dominated by electric permittivity, which, however, depends on the temperature and concentration of salts.[15] In blood, it is different for men and women.[16] The glycine molecule docked to a receptor no longer is in the polar surroundings so its molecular properties are also relevant to study *in vacuo*.

Glycine is not an innocent agent with respect to redox processes.[17] It reduces Fe(II) salts under mild conditions, forming a suspension of Fe(0) under anaerobic conditions.[18] Some aspects of these redox processes have already been studied.[19,20]

Glycine acts as an inhibitory neurotransmitter in the mammalian brain. Amino acid is an important biosynthetic intermediate and serves as a precursor to proteins in virtually all living organisms. Collagen, the most abundant human protein, contains more than 30% glycine. Amino acid is essential for the formation of α-helices in the secondary structure of proteins. Due to its small size and lack of side chain, glycine is a stabilizing component of the triple-helix structure, giving collagen its strength and flexibility. In osteoarthritis, collagen synthesis is not sufficient to compensate for the excessive degradation, resulting in progressive cartilage damage.[21] In fact, the capacity of its synthesis is much lower than its actual need. It has been shown that a high glycine concentration increases collagen synthesis by articular chondrocytes *in vitro*.[22] Insufficient supply of glycine may result in decreased collagen synthesis and/or deficient structure of the protein, which may play a role in the pathophysiology of osteoarthritis. Furthermore, the plasma glycine level is low in patients with obesity or type 2 diabetes and the improvement of insulin resistance increases the plasma glycine concentration.[23] Hence, defective glycine-deficient collagen is likely predisposed to degradation and secondary calcification, which may be instrumental in explaining the development of atherosclerosis in type 2 diabetes. Better understanding of the physical and chemical properties of glycine in aqueous solutions under different conditions can help understand a fundamental role in several common human pathologies.

Hereafter, we are reporting about the molecular properties of glycine using *ab initio* calculations for amino acid as well as zwitterionic forms. The calculations were done *in vacuo* as well as in water as a solvent. The redox ability of these species was also studied.

METHODS

Theoretical investigation of glycine was conducted using the *ab initio* methods based on the Hartree−Fock (MO-LCAO-SCF) approximation with the following improvements: (i) the correlation energy (and density) was partly included by the second-order many-body perturbation theory with the Moller−Plesset partitioning (abbr. MP2); (ii) the solvent effect was involved in the conductor-like polarizable continuum model (CPCM) for water with the electric permittivity ε_r = 80.4;[24] (iii) full geometry optimization was applied followed by complete vibrational analysis with the assurance that no imaginary vibrational frequencies occur; (iv) basis sets with better quality were selected: def2-TZVP (185) and def2-TZVPD (236), where numbers in parentheses refer to the number of basis-set functions (the diffuse functions in def2-TZVPD are essential for a reliable description of molecular anions); (v) three sets of molecular species were considered: the molecular cation L^+, the neutral molecule L^0, and the molecular anion L^- with an unrestricted Hartree−Fock (UHF) variant for open shell systems; and (vi) the geometry optimization started from the amino acid as well as zwitterionic forms. Also, the DFT-B3LYP method was applied.

All calculations were done by the ORCA 5.0.3 computational package.[25−27] At the SCF level of calculation, the energies of HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) were evaluated. The ionization energy $E_i(L^0 \rightarrow L^+ + e^-)$ and the electron affinity $E_{eg}(L^0 + e^- \rightarrow L^-)$ were calculated in the vertical variants (the energies of the molecular cation and anion were calculated in the frozen geometry of L^0) at the SCF and also MP2 levels. They were used in evaluating the chemical potential expressed *via* the Mulliken electronegativity

$$-\mu = (\partial E/\partial N) \sim \chi_M = (E_i - E_{eg})/2) \quad (1)$$

and the chemical hardness according to Pearson's correlation[28−30]

$$\eta_p = (\partial^2 E/\partial N^2)/2 \sim (E_i + E_{eg})/2 \quad (2)$$

The above-defined chemical potential can be viewed as a gradient with respect to the number of electrons (electron cloud), and the hardness is an electronic force constant. When the geometry optimizations for L^+ and L^- were completed, the ionization energy, electron affinity, electronegativity, and the hardness of L^0 were evaluated also in the adiabatic variants (e.g., between the respective minima of energies).

The complete vibrational analysis performed in the global minimum (vanishing coordinate gradient) allows the construction of the thermodynamic partition function Z, which is then utilized in evaluating the thermodynamic functions at standard conditions: inner energy U°, enthalpy H°, entropy S°, and Gibbs energy G° (individual electronic, vibrational, rotational, and translational contributions are also tabulated).

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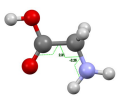
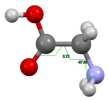
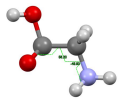
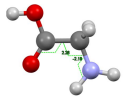
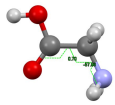
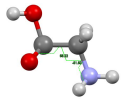
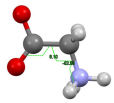
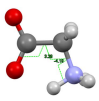
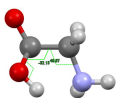
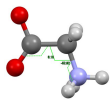
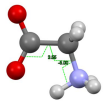
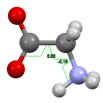
Table 1. Results of Geometry Optimization for Glycine Forms using MP2 in Water[a]

	Def2-TZVP, 185 functions			Def2-TZVPD, 236 functions		
	L^+	L^o	L^-	L^+	L^o	L^-
Optimized geometry for aminoacid						
ϕ_1 = O-C-C-N	2.3	0.7	56.2	2.2	0.7	56.2
ϕ_2 = C-C-N-H	-2.3	-57.6	-48.8	-2.2	-58.0	-51.5
$\Delta_r E = E^q - E^o$	149.1	← o →	-19.7	150.7	← o →	-24.9
Optimized geometry for zwitterion						
ϕ_1 = O-C-C-N	6.1	3.3	49.9	6.1	3.6	6.8
ϕ_2 = C-C-N-H	-52.9	-4.2	H-O-C-C -32.1	-52.8	-5.0	0.6
$\Delta_r E = E^q - E^o$	160.1	← o →	-16.5	162.7	← o →	-14.1

[a]All energies are relative to the neutral species in kcal mol^{-1}, 1 kcal mol^{-1} = 4.184 kJ mol^{-1}; angles in degree.

Table 2. Calculated Molecular Properties of Glycine in the Amino Acid Form[a]

def2-TZVP, 185 basis functions		*in vacuo*		in solvent (water)	
item, vertical ionization/affinity processes		ΔSCF	+MP2 corr.	ΔSCF	+MP2 corr.
1	energy of HOMO	−257		−257	
2	energy of LUMO	82		90	
3	energy of molecular cation E^+ (fs)	−177,356	−178,001	−177,434 [−78]	−178,077 [−76]
4	energy in optimized geometry E^0	−177,558	−178,234	−177,568 [−10]	−178,244 [−10]
5	energy of molecular anion E^- (fs)	−177,477	−178,164	−177,547 [−70]	−178,231 [−67]
6	ionization energy $E_i = E^+ - E^0$ (v)	202	233[b]	134	167
7	electron affinity $E_{eg} = E^- - E^0$ (v)	81	70	21	13
8	Mulliken electronegativity χ_M (v)	60	81	56	77
9	Pearson hardness η_P (v)	141	151	77	90
10	dipole moment p/debye	1.277	1.189	1.826	1.721
11	quadrupole moment Q/ea_0^2	−22.22	−22.36	−22.30	−22.42
12	dipole polarizability α/a_0^3	34.70	37.18	43.40	47.13
13	solvated surface S/a_0^2			397	
14	solvated volume V/a_0^3			616	
15	E_{vib}(ZPE)—zero-point energy	53.79		53.51	
16	overall $E_{vib}(T^o)$ contribution	55.38		55.09	
17	$E_{rot} = E_{trs}$ contribution	0.89		0.89	
18	inner energy U^o	−177,500.4		−177,511.1 [−10.7]	
19	enthalpy H^o	−177,499.8		−177,510.5 [−10.7]	
20	$S_{vib}{\cdot}T^o$ contribution	2.65		2.61	
21	$S_{rot}{\cdot}T^o$ contribution	7.56		7.56	
22	$S_{trs}{\cdot}T^o$ contribution	11.59		11.59	
23	total entropic term $S{\cdot}T^o$	21.80		21.76	
24	Gibbs energy G^o	−17,7521.6		−177,532.3 [−10.7]	

[a]Values in brackets are relative to the unsolvated species. All energy quantities are in units of kcal mol^{-1}, 1 kcal mol^{-1} = 4.184 kJ mol^{-1}; debye, D = 3.336×10^{-30} Ams; *angstrom*, Å = 10^{-10} m; *bohr*, a_0 = 5.292×10^{-11} m; special units for polarizability $\alpha_{ij} = dp_i/dE_j$: $\alpha(Å^3) = 10^{-24} \times \alpha(cm^3) = 0.1482 \times 10^{-24} \times \alpha(a_0^3)$. Standard temperature T^o = 298.15 K. Data for p and Q (isotropic value) in MP2 calculations refer to the relaxed electron density. Abbr.: (fs), frozen structure; (v), vertical process. [b]The experimental vertical ionization energy of glycine *in vacuo* is 10.0 eV = 231 kJ mol^{-1}.[31]

RESULTS AND DISCUSSION

True energy minimum is confirmed when no imaginary vibrational frequencies are found. The suggested amino acid form is rather rigid upon oxidation and reduction and also to the solvent effect. The optimized structure of the glycine molecule *in vacuo* as well as in water refers to the most stable conformer No1, in agreement with the B3LYP and CCSD(T)-F12 calculations:[6,7] ϕ_1(O−C−C−N) = 0.8°, ϕ_2(C−C−N−H) = −57.7° (Figure 3). Results of geometry optimization by the MP2 method in water are shown in Table 1.

The zwitterionic form, however, is more flexible. The staggered form as found in the solid state for L^0(s) with the dihedral angle ϕ_2 = C−C−N−H = −48° is retained only in the molecular cation L^+(aq), ϕ_1 = −53°. For L^0(aq), the eclipsed form is obtained with $\phi_2 \sim -5°$, where the linkage O−C−C−N−H forms a five-membered ring.

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Table 3. Molecular Properties of Glycine in the Amino Acid Form by MP2 Calculations in Water[a]

optimized geometry and vibrational analysis		Def2-TZVP, 185 functions			Def2-TZVPD, 236 functions		
item, adiabatic ionization/affinity		L^+	L^0	L^-	L^+	L^0	L^-
6, 7	electronic energy $\Delta_r E = E^q - E^0$	149.1	← 0 →	−19.7	150.7	← 0 →	−24.9
15	zero-point energy E_{vib}	49.12	50.17	48.04	49.02	50.01	47.88
23	total entropic term $S{\cdot}T^o$	22.30	22.03	22.86	22.30	22.02	22.86
25	Gibbs energy $\Delta_r G^o = G^q - G^0$	ox: 147.84	← 0 →	red: −22.43	ox: 149.34	← 0 →	red: −27.73
26	redox potential $E_{abs}{}^o(L^0/L^q)$/V	ox: −6.41		red: +0.97	ox: −6.48		red: +1.20

[a]Footnote as in Table 2. The absolute redox potential $E_{abs}{}^o(L^0/L^q)$ [V] = $-\Delta_r G^o$[J mol^{-1}]/zF, for F = 96485 C·mol^{-1} and z = 1.

Table 4. Molecular Properties of Glycine in the Zwitterionic Form by MP2 Calculations in Water

optimized geometry and vibrational analysis		Def2-TZVP, 185 functions			Def2-TZVPD, 236 functions		
item, adiabatic ionization/affinity		L^+	L^0	L^-	L^+	L^0	L^-
6, 7	electronic energy $\Delta_r E = E^q - E^0$	160.1	← 0 →	−16.5	162.7	← 0 →	−14.1
15	zero-point energy E_{vib}	51.21	51.25	48.54	51.12	51.15	46.09
23	total entropic term $S{\cdot}T^o$	22.53	21.78	22.26	22.58	21.82	22.63
25	Gibbs energy $\Delta_r G^o = G^q - G^0$	ox: 159.46	← 0 →	red: −19.61	ox: 162.05	← 0 →	red: −19.80
26	redox potential $E_{abs}{}^o(L^0/L^q)$/V	ox: −6.91	ox ← → red	red: +0.85	ox: −7.02	ox ← → red	red: +0.86

Table 5. Review of Molecular Descriptors for Glycine in Water[a]

details	Ion. energy	El. affinity	Electroneg.	Hardness	Dip. mom.	Polarizabil.	Reduct. pot.
			Amino Acid Form				
ΔSCF (v) BS1	134	21	56	77	1.826	43.4	
+MP2 corr. (v) BS1	167	13	77	90	1.721	47.1	
MP2 (a) BS1	149	−19.7	84	64	1.736	48.4	0.97
MP2 (a) BS2	151	−25.0	88	63	1.780	55.4	1.02
DFT (a) BS2	147	−25.1	86	61	1.754	56.8	1.21
			Zwitterionic Form				
MP2 (a) BS1	150	−16.5	83	67	13.51	49.7	0.85
MP2 (a) BS2	163	−14.1	88	74	14.53	58.1	0.86
DFT (a) BS2	150	−18.9	84	66	13.88	58.8	1.05

[a]Basis sets BS1 = def2-TZVP, BS2 = def2-TZVPD; units as in Table 2; (v), vertical ionization process; (a), adiabatic process.

A comparison of the total energies at the optimized structures by the MP2 method confirms that the zwitterionic (Z) form is more stable than the amino acid (A) form under the same conditions: the same basis set and solvent (Z: −178249.2; A: −178245.4 kcal mol^{-1}); the energy differences are 3.8 and 4.6 kcal mol^{-1} for def2-TZVP and def2-TZVPD, respectively.

The calculated molecular properties for the amino acid form of glycine are listed in Table 2. They confirm that the MP2 correction (in the frozen geometry) increases the vertical ionization energy and lowers the electron affinity [items 6, 7]. Solvation has a minor effect on electronegativity but a strong effect on hardness [items 8, 9]. Expectantly, the solvent effect increases the dipole moment and the dipole polarizability, whereas the quadrupole moment remains unaffected [items 10−12]. Nonelectronic contributions to thermodynamic functions such as vibration, rotation, and translation increments are almost unaffected by the solvation [items 15−17, 20−23]. The solvent effect on the final thermodynamic functions U^o, H^o, and G^o has an electronic origin [items 18, 19, 24].

The results of the calculations at the MP2 level or the amino acid form of glycine are listed in Table 3. The full geometry optimization of the neutral and ionized species allows evaluation of the adiabatic ionization energy, electron affinity, electronegativity, and hardness (see later). This table contains the same set of molecular parameters, however, calculated for an enlarged basis set def2-TZVPD. For an enlarged basis set, the LUMO (89 *vs* 38) and electron affinity (−20 *vs* −25) are lowered [items 2 and 7 in Tables S1 and S2]; all energies are in kcal mol^{-1}.

Not only the total energy E (or inner energy U^o) is more negative for the molecular anion but also the reaction Gibbs energy $\Delta_r G^o$(red) for reduction is negative. This causes the absolute reduction potential to become positive.

Table 4 contains the calculated molecular properties for the zwitterionic form of glycine. The other molecular properties are influenced insignificantly. Since the geometry optimization and vibrational analysis were performed for the neutral and ionized species, the evaluations of the adiabatic ionization energy, electron affinity, electronegativity, and hardness are facilitated.

Also, Table 4 allows comparing the impact of the enlargement of the basis set by diffuse functions on passing from def2-TZVP to def2-TZVPD. For the neutral species L^0, the energy of the LUMO is reduced by half: from 81 to 39 kcal mol^{-1}. However, the adiabatic electron affinity is not altered substantially: it changes from −16 to −14 kcal mol^{-1} [item 7 in Tables S3 and S4].

The adiabatic electronegativity (and hardness) is raised a bit: 83 (88) and 67 (74) kcal mol^{-1} [items 8, 9]. The dipole moment, solvated surface area, and volume are not affected visibly by diffuse functions.

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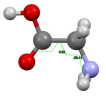
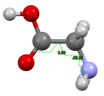
Table 6. Molecular Properties of Glycine by DFT-B3LYP Calculations in Water[a]

Optimized geometry & vibrational analysis		Def2-TZVP, 185 functions		Def2-TZVPD, 236 functions	
	Item	Aminoacid A	Zwitterion Z	Aminoacid A	Zwitterion Z
					
	Angle ϕ_1(O-C-C-N)	0.7	3.3	0.6	2.2
	Angle ϕ_2(C-C-N-H)	-58.4	-4.2	-58.9	-2.4
1	HOMO	-162	-157	-163	-159
2	LUMO	0.16	14.2	-3.4	-0.03
3	Energy difference E^o(Z) – E^o(A)	origin	-3.23	origin	-3.86
15	Zero-point energy E_{ZPE}	49.62	50.79	49.57	50.74
23	Total entropic term $S{\cdot}T^o$	22.08	21.75	22.08	21.84
24	Gibbs energy difference G^o(Z) – G^o(A)	origin	-1.92	origin	-2.60
	Lowest vibrational frequency /cm^{-1}	73.60	86.14	75.78	70.54

[a]Energies in kcal mol^{-1}.

The same holds true for nonelectronic (vibrational, rotational, translational) contributions to thermodynamic functions. The electronic contribution, however, is lowered and consequently also U^o, H^o, and G^o [items 18, 19, 24]. The reaction Gibbs energies on oxidation and reduction allow evaluating the absolute values of the redox potentials; these are affected only slightly on oxidation and more visibly on reduction where the molecular anion is considered [items 25, 26].

Table 5 shows a review of the molecular descriptors of glycine in water depending upon the calculation method and the extent of the basis set. The most reliable data in water refers to the adiabatic processes calculated at the MP2 level using the extended basis set def2-TZVPD.

The adiabatic ionization energies of glycine in its A and Z forms are rather high, 151 and 163 kcal mol^{-1}, respectively; the electron affinity is negative (−25 and −14 kcal mol^{-1}) because the molecular anion is more stable in water. The molecular electronegativity (the chemical potential) is the same, but the Z-form possesses higher hardness—a resistivity against electron transfer (63 *vs* 73 kcal mol^{-1}). High dipole moment for the zwitterionic form is a consequence of a large spatial separation of centers of positive/negative charges. The polarizability is higher for the Z-form (55 *vs* 58 a_0^3); the absolute redox potential for reduction is lower (1.02 *vs* 0.86 V).

The molecular properties of glycine were also calculated by the DFT-B3LYP method using two basis sets (Tables 6, S5, and S6). In both cases, the Z-form is more stable (in water, in optimized geometry) by ca. 3 kcal mol^{-1}. As expected, the involvement of the diffuse functions in def2-TZVPD causes an energy-lowering for LUMO, whereas the impact on HOMO is negligible. The molecular properties are not very different from those calculated by the MP2(BS2) method (except for the absolute reduction potential) as confirmed by Table 5.

CONCLUSIONS

Ab initio calculations confirm that the zwitterionic (Z) form of the glycine molecule in water as a solvent is more stable relative to the amino acid (A) form by 3.4 (MP2) and 2.6 (DFT) kcal mol^{-1}, respectively. The solvent effect has a dramatic impact on the electron affinity (which switches from positive to negative values) and consequently on the chemical hardness, which is lowered. The stabilization of the molecular anion in water relative to the electroneutral molecule (measured by the standard Gibbs energy) causes the absolute reduction potential to become positive for A and Z forms, respectively: $E_{abs}{}^o(L^0/L^-)$ = 1.02 and 0.86 V using the MP2 method and 1.21 and 1.05 V by the DFT method.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02972.

Detailed tables of calculated molecular properties (Tables S1−S6) along with comments about explicit solvation accompanied by Table S7 and Figures S1 and S2 (PDF)

AUTHOR INFORMATION

Corresponding Author

Roman Boča − *University of SS Cyril and Methodius, Faculty of Health Science, 917 01 Trnava, Slovakia;* orcid.org/0000-0003-0222-9434; Email: roman.boca@ucm.sk

Authors

Juraj Štofko − *University of SS Cyril and Methodius, Faculty of Health Science, 917 01 Trnava, Slovakia*

Richard Imrich − *University of SS Cyril and Methodius, Faculty of Health Science, 917 01 Trnava, Slovakia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c02972

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

CCDC, Cambridge Crystallographic Data Centre; DFT, density functional theory; MP2, Moller−Plesset partitioning in the second-order many-body perturbation theory; SCF, self-consistent field in the molecular-orbital linear combination of atomic orbitals method

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