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Determination of acidic dissociation constants of glutamine and isoleucine in water using ab initio methods

[Ab initio yöntemler kullanılarak glutamin ve izolösinin sudaki asidik ayrışma sabitlerinin saptanması]

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ABSTRACT

Objective: In this study, pK_a values of glutamine and isoleucine were determined in aqueous solution by ab initio and DFT methods. To explain the obtained values of pK_a, the molecular conformations and solute-solvent interactions of the anions, cations, and neutrals molecules of glutamine and isoleucine were investigated. The experimental determination of these values, apart from been laborious, is a challenge because of the low water solubility of these compounds.

Methods: We have evaluated different models to determination of pK_a, using the density functional theory (DFT) method at the B3LYP level of the theory.

Results: this study shows the several ionization reactions and equilibriums in protic solvent, which possess a high hydrogen-band-donor capability. These reactions and equilibriums constitute the indispensable theoretical basis for calculation of glutamine and isoleucine acidity constants. Tomasi's method was used to analyze the formation of intermolecular hydrogen bonds between the existent species and water molecules. In this way, it is proposed that in alkaline aqueous solutions the cation, anion, and neutral species of glutamine and isoleucine are solvated with one, two, three, and four molecules of water, respectively. In this study, there is comparable agreement between the experimental and calculated pK_a values for the acid-base reactions proposed.

Conclusion: In this paper, The calculations performed at the B3LYP/6-31+G(d) levels of theory using Tomasi's method allowed us to prove that cations, neutral molecules, and anions form IHBs with some molecules of water. It is shown that, theoretically calculated pK_a values are in good agreement with the existing experimental pK_a values, which are determined from potentiometric titration and UV–visible spectrophotometric measurements.

Key Words: Ab initio method, DFT method, ionization constant, isoleucine, glutamine

Conflict of Interest: Authors have no conflict of interest.

ÖZET

Amaç: Çalışmada ab initio ve DFT yöntemleri kullanılarak glutamin ve izolösinin sulu çözeltideki pK_a değerleri saptanmıştır. Elde edilen pK_a değerlerini açıklamak amacıyla glutamin ve izolösinin anyon, katyon ve nötral moleküllerinin moleküler konformasyonları ve çözünen-çözücü etkileşimleri incelenmiştir. Bu değerlerin deneysel tayini zahmetli olmasının yanı sıra, bu moleküllerin suda çözünürlüğünün az olması nedeniyle oldukça güçtür.

Metod: pK_a tayini için, B3LYP düzeyinde yoğunluk işlevsel teorisi (density functional theory-DFT) kullanılarak farklı modeller değerlendirilmiştir.

Bulgular: Çalışma, yüksek hidrojen-bağı-verici kapasiteye sahip olan protik çözücü içerisinde çeşitli iyonizasyon tepkimelerini ve dengeyi göstermektedir. Bu tepkimeler ve denge glutamin ve izolösinin asitlik sabitlerinin hesaplanması için teorik temel oluşturmaktadır. Varolan türler ve su molekülleri arasındaki moleküller arası hidrojen bağlarının oluşumunu analiz etmek için Tomasi yöntemi kullanılmıştır. Bu yolla, alkali sulu çözeltide glutamin ve izolösinin katyon, anyon ve nötral türlerinin sırasıyla bir, iki, üç ve dört molekül su ile çözünür hale geldiği öne sürülmektedir. Çalışmada deneysel olarak bulunan ve hesaplanan pK_a değerlerinde kıyaslanabilir bir uyum bulunmaktadır.

Sonuç: Tomasi yöntemi kullanılarak B3LYP/6-31+G(d) teori düzeyinde gerçekleştirilen hesaplamalar, katyon, anyon ve nötral moleküllerin bazı su molekülleri ile IHB (moleküller arası hidrojen bağı) oluşturduğunu kanıtlamaya izin vermektedir. Teorik olarak hesaplanan pK_a değerlerinin, potensiyometrik titrasyon ve UV-görünür spektrofotometrik ölçüm yöntemleri kullanılarak elde edilen deneysel pK_a değerleri ile oldukça uyumlu olduğu görülmektedir.

Anahtar Kelimeler: Ab initio yöntemi, DFT yöntemi, iyonizasyon sabiti, izolösin, glutamin

Çıkar Çatışması: Yazarların çıkar çatışması yoktur.

Introduction

Glutamine is the most abundant amino acid in the body [1]. The consumption of glutamine increases under such stresses as exercise and disease. Glutamine has received considerable attention, because decreased plasma glutamine concentration is associated with both immunosuppression after intense exercise and the over-training syndrome [2,3]. Therefore glutamine supplementation is recommended for athletes [4]. Recently, the role of glutamine in immunosuppressive condition is a hot topic. Supplementation of glutamine was reported to reduce the infectious incidents after marathon [5], but failed to improve the post exercise decreases of lymphocyte functional [6] whereas meta-analysis proved a beneficial effect of glutamine on the incidents of infectious complications after surgery and trauma [7].

The level of glutamine in body of many people with cancer is low. Due to this reason, some researchers think that glutamine may be useful when added to conventional cancer treatment for some people. Supplemental glutamine is often given to malnourished cancer patients undergoing chemotherapy or radiation treatments and sometimes used in patients undergoing bone marrow transplants.

Isoleucine (Ile) a side-chain and hence it is analogous to alanine, valine and leucine. However isoleucine is the only one of the four amino acids with and aliphatic side-chain that has a stereocenter at the β-carbon. This carbon has an R-absolute configuration. Isoleucine is an isomer of the leucine and higher homologue of valine. This also implies that the isoleucine side-chain can reach further out than that of valine. For this reason, isoleucine in a protein may have not only a structural but also a functional role to play. Recent studies have shown that Ile may be useful in the treatment of metabolic syndrome, diabetes, adiposity, and hepatic encephalopathy [8-10]. Furthermore, Ile derivatives have been targeted for the development of drugs, such as (2S,3R,4S)-4-hydroxyisoleucine [11], neuropeptide glutamic acid-isoleucine [12], and N-methyl-4-isoleucine cyclosporine [13]. Traditionally, Ile has been extracted from animal tissues and produced through chemical synthesis.

The prediction of pK_a values of solvated molecules has attracted much attention in the computational chemistry community over many years. The acid dissociation (ionization) constant pK_a is one of the fundamental properties of organic molecules determining degree of dissociation at a given pH. Acidic dissociation constants have many usages in chemical, biological, environmental, and pharmaceutical research because the important physicochemical properties, like lipophilicity, solubility, and permeability, are all dependent on pK_a. Acid dissociation constants also provide an insight into interactions of drugs containing ionizable groups with a receptor [14]. In addition, the determination of dosage forms and the regimes of drugs are also related to their pK_a values [15].

With the high speed development of computer technology and the wide applications of G98 program package [16,17], more and more quantum chemical computations on transition metal complexes, in particular, the computations applying density functional theory (DFT), which account better for electron correlation energies and reduces greatly the computation expenses, have been reported [18]. Recently, more and more quantum chemical density functional theory (DFT) [19-21] investigations, which are based upon a strategy of modeling electron correlation via general functional of electron density, have been reported [22-28]. DFT method can better consider the electron correlations and needs less computational expense. Although the computations of the energies and spectral properties in an absolute meaning still have errors to a certain extent for transition metal complexes with relatively large size, some interesting trends in the electronic structures and related properties of the complexes can be obtained, and such trends can be used for references in the synthesis and the mechanistic analysis of the complexes [29]. Therefore, it is of particular interest to perform theoretical studies on these systems, especially using density functional theory (DFT) methods which have been developed recently and which produce very encouraging results. Density functional theory methods offer an alternative use of inexpensive computational method and are capable of handling fairly large chemical systems. If the DFT method scan accurately describes a potential energy surface, they will become a method of choice for studying various biological systems [30].

In this paper, the effective factors such as the self-consistent reaction filed (SCRF) and selecting thermodynamic equation used for atomic and cavity formation in solution (water) are checked and geometry optimization in water, including electron correlation on the power play sets and compensation-free solution and pK_a values of glutamine and isoleucine in aqueous solutions are calculated using the ab initio and DFT methods at 25°C. As pK_a is equal to $\Delta G/2.303RT$, where ΔG is a free energy change of the dissociation reaction either in a gas or solution, activity of compound can be determined by the ΔG values.

Calculated total energy (using the Tomasi's method at the B3LYP/6-31+G(d) level of theory) for cationic, neutral, and anionic species of glutamine and isoleucine at T=298.15 K are shown in Table 1.

Methods

Figure 1 shows the structure of glutamine and isoleucine the practical numbering system adopted for performed the calculations. The initial geometries of the molecules of glutamine and isoleucine also, their anions and cations were modeled by the semiempirical PM3 method included in the program HyperChem version 7.0. These geometries were optimized with the Gaussian 98 [31] program packages, using the B3LYP/6-31+G(d) method and

Table 1. Calculated total energy using the Tomasi's method at the B3LYP/6-31+G(d) level of theory for cationic, neutral, and anionic species of glutamine and isoleucine at *T*=298.15 K

No	Solvated Species (Glutamine)	G^0sol (Hartree) (Kj.mol-1)	G^0sol/molecule (Kj.mol-1)	Solvated Specie (Isoleucine)	G^0sol (Hartree) (Kj.mol-1)	G^0sol/molecu (Kj.mol-1)
0	HL:UZ	-531.822473	-1396299.769	HL:UZ	-441.710 855	-1159711.744
1	$HL(H_2O)$:UZ	-608.250287	-798480.4876	$HL(H_2O)$:UZ	-518.147339	-680197.854
2	$HL(H_2O)_2$:UZ	-684.687498	-599215.6099	$HL(H_2O)_2$:UZ	-594.59694	-520356.2789
3	$HL(H_2O)_3$:UZ	-761.12074	499586.4851	$HL(H_2O)_3$:UZ	- 671.023751	-44043.1723
4	$HL(H_2O)_4$:UZ	-837.583201	-439814.8966	$HL(H_2O)_4$:UZ	-747.460136	-392491.2797
0	HL:Z	-531.827551	-136313.101	HL:Z	-441.71159	-1159713.679
1	$HL(H_2O)$:Z	- 608.264148	-798498.6836	$HL(H_2O)$:Z	-518.147197	-680197.6676
2	$HL(H_2O)_2$:Z	- 648.669581	-567693.9405	$HL(H_2O)_2$:Z	-594.604718	-529378.179
3	$HL(H_2O)_3$:Z	-761.140492	-499593.5425	$HL(H_2O)_3$:Z	- 671.033887	-440449.8253
4	$HL(H_2O)_4$:Z	-837.582931	-439814.7549	$HL(H_2O)_4$:z	-747.484402	-392504.0218
0	$H2L^+$	-532.270967	-1397477.29	$H2L^+$	-442.16023	-1160891.593
1	$H_2L^+(H_2O)$	-608.711725	-799086.2403	$H_2L^+(H_2O)$	-518.599669	-680791.6501
2	$H_2L^+(H_2O)_2$	-685. 152161	-599622.2753	$H_2L^+(H_2O)_2$	-595.04373	-520762.3877
3	$H_2L^+(H_2O)_3$	-671.587662	-440813.3093	$H_2L^+(H_2O)_3$	-671.480996	-440743.2964
4	$H_2L^+(H_2O)_4$	-838.023354	-440046.0209	$H_2L^+(H_2O)_4$	-747.925723	-392735.7595
0	L^-	-531.361 348	-1395089.085	L^-	- 441.925723	-158530.949
1	$L^-(H_2O)$	-607.800692	-797890.2818	$L^-(H_2O)$	-517.681973	-679868.9448
2	$L^-(H_2O)_2$	-648.245245	-567322.578	$L^-(H_2O)_2$	-594.138491	-519970.1528
3	$L^-(H_2O)_3$	-670.429536	-440053.144	$L^-(H_2O)_3$	-670.579576	-440151.627
4	$L^-(H_2O)_4$	-837.11112	-439567.0069	$L^-(H_2O)_4$	-775.93491	-407443.3821
Water						
0	H_3O^+	-76.862	-201801.1616			
0	H_2O	-76.434	-200677.4477			
0	OH^-	-75.952	-199411.9569			
2	$(H_2O)_2$	-152.868	-133786.7155			
3	$(H_2O)_3$	-229.302	-602032.3432			
1	$OH^-(H_2O)$	-152.4	-200063.0808			

[a] *N*: total number of solvation water molecules; G^0_{sol}, total free energy in solution; G^0_{sol}/molecule, total energy of solvated species per water molecule; H_2L^+, cation species; HL, neutral; L-, anion species.

the default convergence criteria. To analyze the solvent effects on all the species involved in the proposed ionization reactions, the polarized continuum model (PCM) of Tomasi's et al. is used [32].

In addition, to shed light on the experimental pK_a values of glutamine and isoleucine in water, the some conformers were examined by the program. Eventually, we selected the solvation of the specimen by means of intermolecular hydrogen bonds (IHB) that involves one molecule of the mentioned specimen and some molecules of water.

Results and Discussion

Amino acids are chemical subunits of proteins. They make up proteins and therefore are called the building blocks of

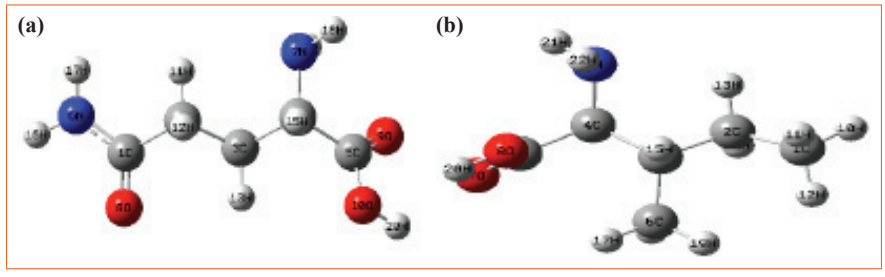

Figure 1. Optimized struccure of glutamine **(a)** and isoleucine **(b)** for carrying out the calculations.

Table 2. Values of pK_a for protonation of glutamine and isoleusine obtained using the Tomasi's method at the B3LYP/6-31+G(d) level of theory at T=298.15 K[a]

Species	Selected Equation	pK_a (calculated)	pK_a (experimental)	Ref
Glutamine	$H_2L^+(H_2O)_3$+ $2H_2O \rightleftharpoons HL(H_2O)_4$:Z+$H_3O^+$	2.259357912	2.17 (I=0)	33
	$HL(H_2O)_4$:Z+$H_2O \rightleftharpoons L^-(H_2O)_4+H_3O^+$	9.30465144	9.28 (I=0)	33
Isoleucine	$H_2L^+(H_2O)_2+H_2O \rightleftharpoons HL(H_2O)_2$:Z+$H_3O^+$	2.388293887	2.35 (I=0)	33
	$HL(H_2O)_3$:Z+$H_2O \rightleftharpoons L^-(H_2O)_3+H_3O^+$	9.433723942	9.68 (I=0)	33

proteins. Thus, amino acids studied in recent years have become a major issue. Also studied the biological activity is not limited only to amino acids. In both aqueous solution and the crystalline state amino acids exist as zwittern ions, in which both the amino and carboxylic groups ionized (NH^{3+} – CH(R) – COO^-). In matrices of noble gas they can be obtained in their non–ionizied form. The loss of the hydrogen atom, the proton, the acid dissociation constant of the acid pK_a is determined. Glutamine and isoleucine are two acidic groups include the ammonium and carboxyl. Loss of protein from the ammonium group of the carboxyl group is therefore more likely, so this is equal to the ionization for k_1:

$$k_1 = \frac{[H^+][NH_3^+RCHCOO^-]}{[NH_3^+RCHCOOH]} \quad (1)$$

And k_2 Included the ammonium proton is:

$$k_2 = \frac{[H^+][NH_2RCHCOOH]}{[NH_3^+RCHCOOH]} \quad (2)$$

Where R is $H_2NCOCH_2CH_2$ and $CH_3CHCH_2CH_3$ for glutamine and isoleucine, respectively. It can be shown that for a dibasic acid the first ionization constant K_1 is the sum k_1+k_2 and the second ionization constant K_2 is $(k_{12}\cdot k_{21})/(k_{12}+k_{21})$, where the subscript 12 denotes loss of proton 2 following loss of proton 1 and subscript 21 denotes loss of proton 1 following loss of proton 2 [34].

Solvent–solute interactions

It is known that all aqueous solutions contain hydrogen (H^+) and hydroxyl (OH^-) ions. In pure water, these ions are completely derived from the ionization of the water molecules:

$$H_2O \rightleftharpoons H^+ + OH^- \quad (3)$$

The K_w constant is the ionic product of water. Taking into account that the H^+ ion is hydrated, appearing predominantly as H_3O^+ the autoprotolysis of water is better represented by the following reaction:

$$2H_2O \rightleftharpoons H_3O^+ + OH^- \quad (4)$$

Taking into account that water is only slightly dissociated and to simplify the discussion, we shall make the approximations of replacing the activities in acidity constants by the numerical values of the molar concentrations. Consequently [35]:

$$K_w=[H_3O^+][OH^-]=1.008\times10^{-14} \quad (5)$$

First ionization constant of glutamine and isoleucine

It can be selected that in alkaline solutions glutamine suffers a reaction of partial neutralization as follows:

$$H_2L^+(H_2O)_3+OH\text{-}(H_2O) \rightleftharpoons HL(H_2O)_4\text{:}Z+H_2O \quad K_{C1} \quad (6)$$

In this reaction, $H_2L^+(H_2O)_3$ is the glutamine cation solvated with three water molecule and $HL(H_2O)_4$:Z represents glutamine natural solvated with four molecules of water. The previous reaction is characterized by an equilibrium constant, K_{C1}, which was theoretically determined. Besides, water auto pyrolysis also takes place:

$$3H_2O \rightleftharpoons OH^-(H_2O)+H_3O^+ \quad (7)$$

The selected reaction considers that both H^+ and OH^- ions are hydrated with one water molecule. Further, indicating with K_N the equilibrium constant of the reaction of equation 7 and taking into account equations 4 and 5, it is inferred that K_W=K_N [H_2O]. Thus, it can be found that:

$$K_N = \frac{K_W}{[H_2O]} = 1.831\times10^{-16} \quad (8)$$

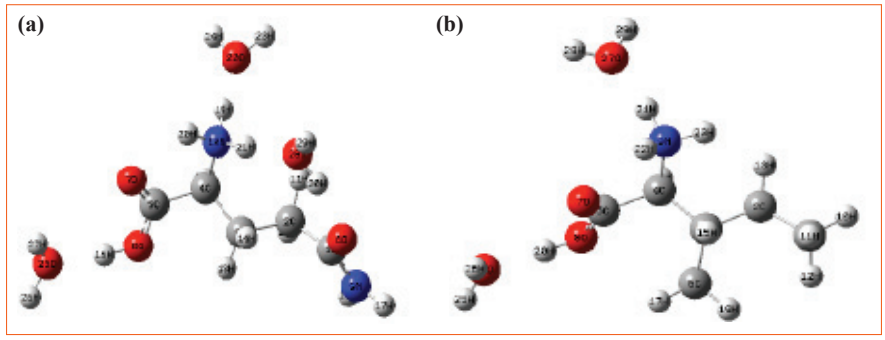

Figure 2. (a) Optimized structure of the glutamine cation with three water molecules **(b)** and isoleucine cation solvated with two water molecule.

By combining equations 6 and 7, we obtain the reaction of equation 9 which defines the first ionization constant of glutamine and glutamine solvation and neutral review:

$$H_2L^+(H_2O)_3+2H_2O \rightleftharpoons HL(H_2O)_4{:}Z+H_3O^+ \qquad K_{a1} \qquad (9)$$

It is evident that:

$$K_{a1}=K_{C1}\times K_N \qquad (10)$$

The above equation is used for the first ionization constant. In Table 2, a summary of the optimized properties of the molecular cation $H_2L^+(H_2O)_3$ (Figure 2) and $HL(H_2O)_4$:Z molecules neutralized (Figure 3) states that the level of theory B3LYP/6-31+G(d) with Tomasi's method in water and at 298 K has been obtained.

It must be noted that the structure of solvated natural glutamine ($HL(H_2O)_4$:Z) is practically different to its cation ($H_2L^+(H_2O)_3$) (Table 3 and Figure 3). As seen in Table 3, O_8 atomic charge in the neutral glutamine is more negative than one in its cation.

The first ionization constant for isoleucine, It is selected that in alkaline solutions isoleucine suffers a reaction of partial neutralization as follows:

$$H_2L^+(H_2O)_2+OH^-(H_2O) \rightleftharpoons HL(H_2O)_2{:}Z+(H_2O)_2 \qquad K_{d1} \qquad (11)$$

The first ionization constant for isoleucine is obtained from combining equations (7) and (11) and is shown in equation (12). Table 2 summarizes the values of pK_a for protonation of $H_2L^+(H_2O)_2$ (Figure 2) and $HL(H_2O)_2$:Z (Figure 4). According to Table 4, O_8 atomic charge in $HL(H_2O)$:Z is more negative than once in $H_2L^+(H_2O)$.

$$H_2L^+(H_2O)_2+H_2O \rightleftharpoons HL(H_2O)_2{:}Z+H_3O^+ \qquad K_{b1} \qquad (12)$$

It is evident that:

$$K_{b1}=K_{d1}\times K_N \qquad (13)$$

Second ionization constant of glutamine and isoleucine

Here, it is selected that the neutral $HL(H_2O)_4$:Z and anion L-$(H_2O)_4$ (for glutamine) suffer total neutralization as follows:

$$HL(H_2O)_4{:}Z+OH^- \rightleftharpoons L\text{-}(H_2O)_4+H_2O \qquad K_{C2} \qquad (14)$$

In the above reaction, $L^-(H_2O)_4$ (Figure 5) represents the anion solvated with four water molecules. The reaction described in equation 14 is characterized by another equilibrium constant, K_{C2}, which was also theoretically determined. Combining equations 4 and 14, the second ioniza-

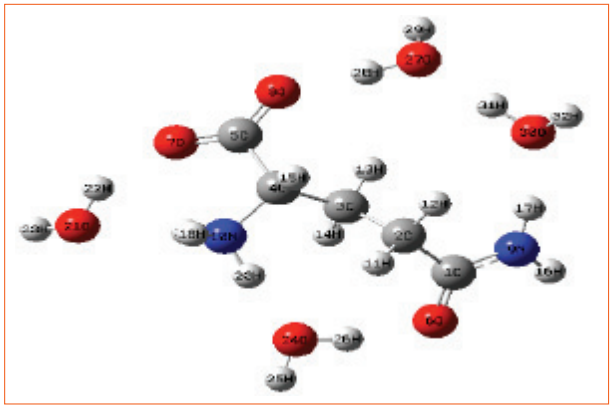

Figure 3. Calculated structure for neutral glutamine solvated with four water molecules at the B3LYP/6-31+G (d) level theory and using the Tomasi's method in water at T=298.15 K.

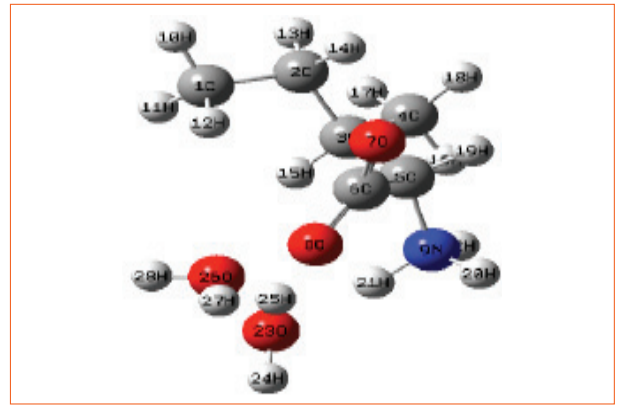

Figure 4. Calculated structure for neutral isoleucine solvated with two water molecules at the B3LYP/6-31+G(d) level theory and using the Tomasi's method in water at T=298.15 K.

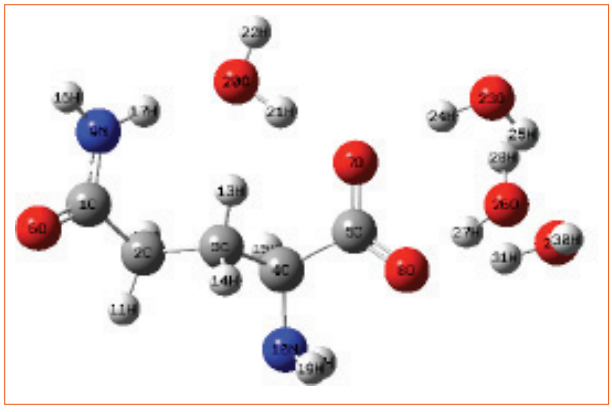

Figure 5. Calculated structure for anion glutamine solvated with four water molecules at the B3LYP/6-31+G (d) level theory and using the Tomasi's method in water at T=298.15 K.

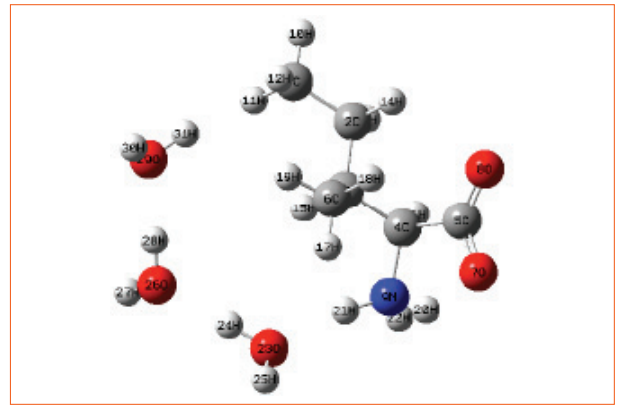

Figure 6. Calculated structure for neutral isoleucine solvated with three water molecules at the B3LYP/6-31+G (d) level theory and using the Tomasi's method in water at T=298.15 K.

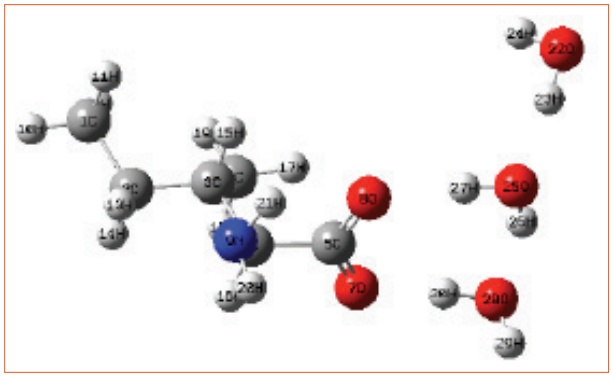

Figure 7. Calculated structure for anion isoleucine solvated with three water molecules at the B3LYP/6-31+G (d) level theory and using the Tomasi's method in water at T=298.15 K.

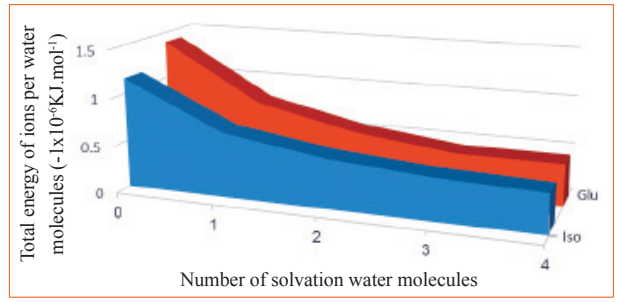

Figure 8. Plot of the total energy (kj.mol^{-1}) of solvated glutamine and isoleucine anions per water molecule against the total number of solvation water molecules.

tion reaction of glutamine was obtained:

$$HL(H_2O)_4{:}Z+H_2O \rightleftharpoons L^-(H_2O)_4+H_3O^+ \qquad K_{a2} \qquad (15)$$

The equilibrium constant K_{a2} that characterizes the above reaction is linked with constants K_{C2} and K_N by:

$$K_{a2}=K_{C2}\times K_w \qquad (16)$$

It is clear that the formation of the neutral glutamine implies that the electronic density of the N_{10} atom decrease notably (in absolute value) with respect to the N_{10} atom of the glutamine anion.

The second ionization constant is obtained for isoleucine molecule:

$$HL(H_2O)_3{:}Z+OH^-(H_2O) \rightleftharpoons L^-(H_2O)_3+2H_2O \qquad K_{d2} \qquad (17)$$

In the above reaction, $HL(H_2O)_3{:}Z$ (Figure 6) represents the neutral isoleucine with three water molecule and $L^-(H_2O)_3$ (Figure 7) represents the anion isoleucine solvated with three water molecules. The reaction described in equation 17 is characterized by another equilibrium constant, K_{C2}, which was also theoretically determined. Combining equations 7 and 17, the second ionization reaction of isoleucine was obtained:

$$HL(H_2O)_3{:}Z+H_2O \rightleftharpoons L^-(H_2O)_3+H_3O^+ \qquad K_{b2} \qquad (18)$$

Also for isoleucine observe that N_9 of neutral electronic density decrease respect to N_9 atom of isoleucine anion (becomes more positive).

The equilibrium constant K_{a2} that characterizes the above reaction is linked with constants K_{C2} and K_N by:

$$K_{b2}=K_{d2}\times K_N \qquad (19)$$

The pK_a values of glutamine and isoleucine theoretically calculated are relatively comparable with the experimentally determined pK_a (see Table 2).

The molecule of water originated from the acid-base reaction, together with the hydration water molecules of the glutamine and isoleucine, and these are the molecules of water that interact with the glutamine and isoleucine molecules by means of IHBs. The distances and angles that characterize these IHBs (Tables 3 and 4) indicate that they belong to the class of weak closely to moderate and moderate IHB. According to references [36] and [34], the properties of the moderate hydrogen bonds have the following characterization: bond lengths of H···B is between (1.5 and 2.2) Å, and the bond angle is 130° to 180°. For weak hydrogen bonds, the bond length and angle are (2.2 to 3.2) Å and 90° to 150°, respectively, and for strong hydrogen bonds are (1.2 to 1.5) Å and 175° to 180°, respectively. The IHB of the all species of two drugs belongs to the weak closely to moderate and moderate.

As shown in the Figures 8, the total free energy increase when number of solvation water molecules increase. Therefore, we can result that solvation of species is endothermic phenomena.

Conclusions

In this paper, we show the feasibility of a theoretical method that uses pH values to determine the acidic dissociation constants of glutamine and isoleucine. Also, we have shown that these constants can be calculated with an acceptable degree of accuracy. With this purpose, we selected various acid-base reactions that take into account the solvation of the hydrogen, hydroxyl ions, and other cations or anions in protic solvents such as water, which possess a high hydrogen-bond-donor capability. We also observed that the nucleophilic attack on the hydrogen atoms of the COOH and $NH3^+$ groups but for glutamine drug molecule, the three nucleophilic attacks on the hydrogen atoms of $NH3^+$ and two OH^- groups. The calculations performed at the B3LYP/6-31+G(d) levels of theory using Tomasi's method allowed us to prove that cations, neutral molecules, and anions form IHBs with some molecules of water. It was shown that, theoretically calculated pK_a values are in good agreement with the existing experimental pK_a values, which are determined from potentiometric titration and UV–visible spectrophotometric measurements.

Acknowledgment

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Conflict of Interest

There are no conflicts of interest among the authors.

Table 3. Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G (d) level of theory for the cation, neutral molecule, and anion of glutamine at T=298.15 K_a

Glutamine	$H_2I^+(H_2O)_3$	$HI(H_2O)_4$	$L^-(H_2O)_4$
K_{C1}	$3.00576\times10^{+13}$	–	–
K_{C2}	49191.26919	–	–
K_{a1}	0.005503539	0.005503539	–
K_{a2}	–	49191.26919	4.95848×10^{-10}
α_0	4.96	4.74	5.04
D-$C_4C_3C_2C_1$	153.969991	157.905336	–157.611635
D-$C_5C_4C_3C_2$	167.481478	151.161049	154.936007
D-$O_6C_1C_2C_3$	–62.344023	–83.039764	–112.103097
D-$O_7C_5C_4C_3$	122.517181	115.9805550	–66.498435
D-$O_8C_5C_4C_3$	–58.276144	–64.077101	113.6398435
D-$N_9C_1C_6C_2$	–179.850548	–178.158053	179.067047
D-$N_{10}C_4C_3C_2$	–72.692505	–86.701988	–76.845715
D-$H_{11}C_2C_1O_6$	58.053477	37.748619	11.297138
D-$H_{12}C_2C_1O_6$	174.028970	155.412480	127.856793
D-$H_{13}C_3C_2C_1$	–85.649750	–81.702207	–36.328199
D-$H_{14}C_3C_2C_1$	31.773929	35.489731	80.244680
D-$H_{15}C_4C_3C_2$	47.178246	30.523911	40.193698
D-$H_{16}O_8C_5C_4$	–177.885201	–	–
D-$H_{16}N_9C_1O_6$	–	3.055472	7.898867
D-$H_{17}N_9C_1O_6$	–1.297895	–175.352537	171.529834
D-$H_{18}N_9C_1O_6$	–179.232737	–	–
D-$H_{18}N_{10}C_4C_3$	–	151.657708	171.621278
D-$H_{19}N_{10}C_4C_3$	116.955876	–94.005318	–76.520448
D-$H_{20}N_{10}C_4C_3$	–124.450336	27.470638	–
D-$O_{20}O_7C_5C_4$	–	–	6.699877
D-$H_{21}N_{10}C_4C_3$	–124.450336	–	–
D-$O_{21}O_7C_5C_4$	–	7.75365	–
D-$H_{21}O_{20}O_7C_5$	–	–	–72.802446
D-$O_{22}N_{10}C_4C_3$	155.464364	–	–
D-$H_{22}O_{20}O_7C_5$	–	–	–177.738795
D-$H_{22}O_{21}O_7C_5$	–	167.260620	–
D-$H_{23}O_{22}N_{10}C_4$	–128.699570	–	–
D-$H_{23}O_{21}O_7C_5$	–	–162.653768	–
D-$O_{23}O_7C_5C_4$	–	–	–174.302099
D-$H_{24}O_{23}O_7C_5$	–	–	–173.804454
D-$H_{24}O_{22}N_{10}C_4$	77.959239	–	–
D-$O_{24}O_6C_1N_9$	–	–171.243142	–
D-$H_{25}O_{24}O_6C_1$	–	–161.783312	–
D-$H_{25}O_{23}O_7C_5$	–	–	42.150155
D-$O_{25}O_8C_5C_4$	–176.048612	–	–
D-$H_{26}O_{25}O_8O_5$	–152.185916	–	–
D-$H_{26}O_{24}O_6C_1$	–	–164.282704	–
D-$O_{26}O_{23}O_7C_5$	–	–	–37.820812
D-$H_{27}O_{26}O_{23}O_7$	–	–	17.920120
D-$H_{27}O_{25}O_8C_5$	–12.378379	–	–
D-$O_{27}O_8C_5C_4$	–	24.703746	–
D-$H_{28}O_{27}O_8C_5$	–	–68.353396	–
D-$H_{28}O_{26}O_{23}O_7$	–	–	–119.590421
D-$O_{28}O_6C_1N_9$	168.690742	–	–
D- $H_{29}O_{28}O_6C_1$	–176.476610	–	–

Table 3. (continued) Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G (d) level of theory for the cation, neutral molecule, and anion of glutamine at T=298.15 K_a

Glutamine	$H_2I+(H_2O)_3$	$HI(H_2O)_4$	$L-(H_2O)_4$
$D-H_{29}O_{27}O_8C_5$	–	137.154014	–
$D-O_{29}O_8C_5C_4$	–	–	142.052888
$D-H_{30}O_{29}O_8C_5$	–	–	122.682907
$D-H_{30}O_{28}O_6C_1$	–170.030318	–	–
$D-O_{30}O_{27}O_8C_5$	–	–0.963888	–
$D-H_{31}O_{30}O_{27}O_8$	–	110.308825	–
$D-H_{31}O_{29}O_8C_5$	–	–	–22.947827
$D-H_{32}O_{30}O_{27}O_8$	–	–137.330436	–
qC_1	0.666813	0.552990	0.508924
qC_2	–0.594546	–0.504114	–0.472919
qC_3	–0.481591	–0.417340	–0.163347
qC_4	0.485768	–0.038070	–.276198
qC_5	0.153343	0.543618	0.489192
qO_6	–0.469532	–0.649470	0.621142
qO_7	–0.516420	–0.730505	–0.806282
qO_8	–0.636284	–0.714284	–0.892370
qN_9	–0.825193	–0.872381	–0.847548
qN_{10}	–1.326282	–1.121619	–0.866434
qH_{11}	0.258205	0.249741	0.234081
qH_{12}	0.252816	0.252636	0.239370
qH_{13}	0.271178	0.251242	0.219685
qH_{14}	0.270523	0.269865	0.232140
qH_{15}	0.337456	0.315383	0.266577
qH_{16}	0.614382	0.465977	0.450374
qH_{17}	0.472328	0.511226	0.490470
qH_{18}	0.459219	0.546187	0.437518
qH_{19}	0.594864	0.522228	0.396399
qH_{20}	0.529747	0.578543	–
qO_{20}	–	–	–1.122809
qH_{21}	0.606630	–	0.596103
qO_{21}	–	–1.085970	–
qH_{22}	–	0.560217	0.530724
qO_{22}	–1.063739	–	–
qH_{23}	0.537477	0.546665	–
qO_{23}	–	–	–1.199544
qH_{24}	0.541161	–	0.610264
qO_{24}	–	–1.138422	–
qH_{25}	–	0.555857	0.567397
qO_{25}	–1.045860	–	–
qH_{26}	0.533467	0.566232	–
qO_{26}	–	–	–1.139666
qH_{27}	0.533928	–	0.577307
qO_{27}	–	–1.122879	–
qH_{28}	–	0.592660	0.574359
qO_{28}	–1.130024	–	–
qH_{29}	0.557583	0.527965	–
qO_{29}	–	–	–1.121749
qH_{30}	0.572585	–	0.547742
qO_{30}	–	–1.123718	–
qH_{31}	–	0.585075	0.588418

Table 3. (continued) Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G (d) level of theory for the cation, neutral molecule, and anion of glutamine at T=298.15 K_a

Glutamine	$H_2I+(H_2O)_3$	$HI(H_2O)_4$	$L-(H_2O)_4$
qH_{32}	–	0.524448	–
$d-H_{16}O_{25}$	1.65137	–	–
$d-H_{17}O_{20}$	–	–	1.98654
$d-H_{17}O_{30}$	–	1.87520	–
$d-H_{19}O_{21}$	–	2.03442	–
$d-H_{19}O_{22}$	1.81119	–	–
$d-H_{20}O_{24}$	–	1.78190	–
$d-H_{21}O_7$	–	–	1.71388
$d-H_{21}O_{28}$	1.70245	–	–
$d-H_{22}O_7$	–	1.80434	–
$d-H_{24}O_7$	–	–	1.82497
$d-H_{26}O_6$	–	1.73044	–
$d-H_{27}O_8$	–	–	2.03522
$d-H_{30}O_6$	1.74146	–	–
$d-H_{31}O_8$	–	–	1.94551
$A-O_6H_{26}O_{24}$	–	166.82063	–
$A-O_6H_{30}O_{28}$	164.43814	–	–
$A-O_7H_{24}O_{23}$	–	–	171.61015
$A-O_8H_{16}O_{25}$	175.30348	–	–
$A-O_8H_{27}O_{26}$	–	–	156.30942
$A-O_8H_{28}O_{27}$	–	173.36767	–
$A-N_9H_{17}O_{20}$	–	–	174.02793
$A-N_{10}H_{19}O_{21}$	–	139.10457	–
$A-N_{10}H_{19}O_{22}$	174.89186	–	–
$A-N_{10}H_{21}O_{28}$	174.05360	–	–
$A-O_{20}H_{21}O_7$	–	–	177.33520
$A-O_{21}H_{22}O_7$	–	148.58269	–
$A-O_{24}H_{20}N_{10}$	–	171.63456	–
$A-O_{29}H_{31}O_8$	–	–	158.21763
$A-O_{30}H_{17}N_9$	–	169.40309	–

K_c and K_{c2}, equilibrium constants of equations; K_{a1} and K_{a2}, first and second acidic dissociation constant between the indicated atoms (A°); D, dihedral angle between the indicated atoms (°); a_0, bohr radius (A°); q, total atomic charges (Muliken) (au); d, distance of the IHB between the indicated atoms (A°); A, H-bond angle(°).

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Table 4. Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G (d) level of theory for the cation, neutral molecule, and anion of isoleucine at T=298.15 K[a]

Isoleucine	$H_2L^+(H_2O)_2$	$HL(H_2O)_2$:Z	$HL(H_2O)_3$:Z	$L^-(H_2O)_3$
K_{C1}	$2.23336\times10^{+13}$	–	–	–
K_{C2}	2011813.48	–	–	–
K_{a1}	0.004089838	0.004089838	–	–
K_{a2}	–	–	3.38363×10^{-10}	3.68363×10^{-10}
α_0	4.65	4.64	4.86	5.10
D-$C_4C_3C_2C_1$	167.329782	148.337911	169.906558	163.809853
D-$C_5C_3C_2C_1$	–	–88.621360	–	–
D-$C_5C_4C_3C_2$	175.146594	–	78.731672	173.627656
D-$C_6C_3C_2C_1$	–68.454357	–	–64.841065	–70.698710
D-$C_6C_5C_3C_2$	–	43.931954	–	–
D-$O_7C_5C_4C_3$	92.135227		117.830101	101.044677–
D-$O_7C_6C_5C_3$	–	–90.067776	–	–
D-$O_8C_5C_4C_3$	–88.119934	–	–61.778.801	78.78538
D-$O_8C_6C_5C_3$	–	90.348912	–	–
D-$N_9C_4C_3C_2$	–68.823834	–	163.754305	–62.699902
D-$N_9C_5C_3C_2$	–	166.444435	–	–
D-$H_{10}C_1C_2C_3$	–176.354611	–178.531242	–177.246886	–178.635220
D-$H_{11}C_1C_2C_3$	–56.868537	–59.287715	–58.690336	–59.205084
D-$H_{12}C_1C_2C_3$	64.266619	61.821011	63.700942	61.072539
D-$H_{13}C_2C_1C_3$	123.439069	120.118084	121.139042	121.205245
D-$H_{14}C_2C_1C_3$	–122.269759	–123.696454	–123.105322	–122.278651
D-$H_{15}C_3C_2C_1$	50.4942201	30.474444	54.201407	48.064943
D-$H_{16}C_4C_3C_2$	50.212300	179.5444490	–44.005256	55.045208
D-$H_{17}C_4C_3C_2$	–	–61.463384	–	–
D-$H_{17}C_6C_3C_2$	173.531954	–	–178.217778	175.165918
D-$H_{18}C_4C_3C_2$	–	57.922507	–	–
D-$H_{18}C_6C_3C_2$	–65.282097	–	57.829130–	–65.397271
D-$H_{19}C_5C_3C_2$		–78.873420	–	–
D-$H_{19}C_6C_3C_2$	54.320762	–	62.435016	54.727314
D-$H_{20}N_9C_4C_3$	–	–	–119.290658	166.639716
D-$H_{20}N_9C_5C_3$	–	170.135759	–	–
D-$H_{20}O_8C_5C_4$	178.998929	–	–	–
D-$H_{21}N_9C_4C_3$	155.100207	–	0.561037	–81.538312
D-$H_{21}N_9C_5C_3$	–	–72.171642	–	–
D-$H_{22}N_9C_4C_3$	–87.573794	–	125.968453	–
D-$H_{22}N_9C_5C_3$	–	49.346309	–	–
D-$O_{22}O_8C_5C_4$	–	–	–	–141.551080
D-$H_{23}N_9C_4C_3$	32.585332	–	–	–
D-$H_{23}O_{22}O_8C_5$	–	–	–	–83.925134
D-$O_{23}O_8C_6C_5$	–	–8.993103	–	–
D-$O_{23}N_9C_4C_3$	–	–	4.704999	–
D-$O_{24}O_8C_5C_4$	–179.331234	–	–	
D-$O_{24}O_{23}N_9C_4$	–	–	17.074803	
D-$H_{24}O_{22}O_8C_5$	–	–	–	67.352869
D-$H_{24}O_{23}O_8C_6$	–	147.722509	–	–
D-$H_{25}O_{23}N_9C_4$	–	–	–125.503628	–
D-$H_{25}O_{23}O_8C_6$	–	–142.660798	–	–
D-$H_{25}O_{24}O_8C_5$	–156.830690	–	–	–
D-$O_{25}O_{22}O_8C_5$	–	–	–	–80.416090
D-$H_{26}O_{25}O_{22}O_8$	–	–	–	110.131296

Table 4. (continued) Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G (d) level of theory for the cation, neutral molecule, and anion of isoleucine at T=298.15 K[a]

Isoleucine	$H_2L^+(H_2O)_2$	$HL(H_2O)_2$:Z	$HL(H_2O)_3$:Z	$L^-(H_2O)_3$
D-$O_{26}O_{23}O_8C_6$	–	–39.808349	–	–
D-$O_{26}O_{23}N_9C_4$	–	–	16.723383	–
D-$H_{26}O_{24}O_8C_5$	–16.072843	–	–	–
D-$H_{27}O_{26}O_{23}O_8$	–	–	105.656484	–
D-$H_{27}O_{25}O_{22}O_8$	–	–	–	–5.163877
D-$H_{27}O_{26}O_{23}C_6$		–118.803513		
D-$O_{27}N_9C_4C_3$	156.547731	–	–	–
D-$H_{28}O_{27}N_9C_4$	88.827936	–	–	–
D-$H_{28}O_{26}O_{23}O_8$	–	–103.864740	–	–
D-$H_{28}O_{26}O_{23}N_9$	–	–	–30.278884	–
D-$H_{28}O_7C_5C_4$	–	–		–178.885150
D-$O_{29}O_{26}O_{23}N_9$	–	–	–29.817636	
D-$H_{29}O_{28}O_7C_5$	–	–	–	104.013648
D-$H_{29}O_{27}N_9C_4$	–101.335274	–	–	–
D-$H_{30}O_{29}O_{26}O_{23}$	–	–	–102.308514	–
D-$H_{30}O_{28}O_7C_5$	–	–	–	–94.469239
D-$H_{31}O_{29}O_{26}O_{23}$	–	–	26.732077	–
qC_1	–0.905839	0.672947–	–.0803929	–0.878632
qC_2	–0.107809	0.329052–	–0.281524	–0.172187
qC_3	–0.072594	0.043996	0.008587	0.166854
qC_4	0.181004	–0.861312	–0.180581	–0.425902
qC_5	0.226120	–0.025527	0.517403	0.663772
qC_6	–0.681242	0.478141	–0.671447	–0.755249
qO_7	–0.495468	–0.637487	–0.685806	–0.746360
qO_8	–0.605837	–0.706602	–0.640821	–0.786525
qN_9	–1.179135	–1.161485	–1.134396	–0.882969
qH_{10}	0.212886	0.206975	0.218805	0.203605
qH_{11}	0.214300	0.210701	0.195432	0.197808
qH_{12}	0.208146	0.211923	0.207289	0.202268
qH_{13}	0.197115	0.208081	0.204566	0.225765
qH_{14}	0.222855	0.220277	0.229141	0.197237
qH_{15}	0.231715	0.242228	0.220773	0.157124
qH_{16}	0.331405	0.193858	0.293846	0.203570
qH_{17}	0.222781	0.232669	0.226734	0.214803
qH_{18}	0.233039	0.233845	0.231639	0.217165
qH_{19}	0.218568	0.284986	0.211113	0.206171
qH_{20}	0.609576	0.552159	0.528723	0.437399
qH_{21}	0.599996	0.578200	0.567763	0.413105
qH_{22}	0.539011	0.508966	0.508271	–
qO_{22}	–	–	–	–1.063565
qO_{23}	–	–1.147417	–1.104539	–
qH_{23}	0.536621	–	–	0.575902
qO_{24}	–1.049176	–	–	–
qH_{24}	–	0.556263	0.587322	0.487786
qO_{25}	–	–	–	–1.183513
qH_{25}	0.552979	0.572468	0.530489	–
qH_{26}	0.536169	–	–	0.573849
qO_{26}	–	–1.082616	–1.102621	–
qH_{27}	–	0.566578	0.528206	0.592559
qO_{27}	–1.063122	–	–	–

Table 4. (continued) Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G (d) level of theory for the cation, neutral molecule, and anion of isoleucine at T=298.15 K[a]

Isoleucine	$H_2L^+(H_2O)_2$	$HL(H_2O)_2$:Z	$HL(H_2O)_3$:Z	$L^-(H_2O)_3$
qH_{28}	0.535956	0.524112	0.581787	–
qO_{28}	–	–	–	–1.174760
qH_{29}	0.549998	–	–	0.534388
qO_{29}	–	–	–1.034689	–
qH_{30}	–	–	0.549383	0.598577
qH_{31}	–	–	0.493080	–
$d\text{-}O_8H_{25}$	–	1.57991	–	–
$d\text{-}H_{21}O_{23}$	–	1.79341	–	–
$d\text{-}O_{24}H_{20}$	1.65258	–	–	–
$d\text{-}H_{27}O_8$	–	–	–	1.79624
$d\text{-}O_{27}H_{21}$	1.76069	–	–	–
$d\text{-}H_{30}O_7$	–	–	–	1.69007
$A\text{-}O_8H_{20}O_{24}$	177.26008	–	–	–
$A\text{-}N_9H_{21}H_{23}$	–	166.90970	163.22272	–
$A\text{-}N_9H_{21}O_{27}$	175.11466	–	–	–
$A\text{-}O_{23}H_{25}O_8$	–	160.37625	–	–
$A\text{-}O_{25}H_{27}O_8$	–	–	–	157.77260
$A\text{-}O_{28}H_{30}O_7$	–	–	–	175.36889

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