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Secondary Structure Effects on the Acidity of Histidine and Lysine-Based Peptides Model; A Theoretical Study

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In this study, the effect of the secondary structure of the protein on the acid strength of three structures of random (R), alpha helix (α) and beta sheet (β) were investigated theoretically. These structures are related to the cationic amino acids of histidine and lysine in the polypeptide chain of eight-glycine residue. Computational methods at the HF, B3LYP, X3LYP and M05-2X levels in the gas and solution phases were applied. Implicit CPCM solvation model and explicit 2-layer ONIOM methods for the computations in solution were used with the 6-31G (d) basis set. Comparison of pK_a values of histidine-based peptide shows that acid strength is accorded to: β > α > R, while in the case of lysine, acid strength is accordance to: α > β > R. Based on the obtained data, ONIOM method is unable to predict the pKa values in the explicit solvation model. NBO analysis showed that one of the main reasons for the increase in the acidity of the solution phase is the increase in delocalization energy difference ($\Delta E_{delocal}$) of the neutral acid and the corresponding cation. Topological analysis of quantum theory of atoms in molecules for the electron charge density at the bond critical points of the hydrogen bonds of the secondary structures in the presence of the solvent does not show a meaningful correlation with the interaction energy or acid strength. The absolute average ratio of 1.37 and 1.34 for the kinetic energy density to the local potential energy density of lysine and histidine-based peptides, respectively, reveals the non-covalent nature of the O···H bonds. Finally, based on the obtained results, pK_a of the proteins can be predicted as a function of hydrogen bond characters and their delocalization energy differences between the cationic and neutral forms.

Abbreviations in this paper

α	Alpha helix
β	Beta sheet
R	Random structure
NBO	Natural bond orbital
QTAIM	Quantum theory of atoms in molecules
CPCM	Conductor polarizable continuum model
BCP	Bond critical point
QM	Quantum mechanics
MM	Molecular mechanics
ONIOM	Our N-layered Integrated molecular Orbital + molecular Mechanics)

Keywords: Secondary structure, Alpha helix, Beta sheet, Histidine, Lysine, pK_a

INTRODUCTION

Life was made possible by the assembly of monomers such as nucleic acids, fatty acids and amino acids, which came together to form larger molecules, namely proteins, carbohydrates and lipids [1]. Amino acids are biologically important molecules made of amine (-NH_2) and carboxylic acid (-COOH) functional groups, along with a side-chain specific to each amino acid. This means that main difference between the various amino acids lies in the

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structure of the "R" group [2]. Twenty α-amino acids can be sub-classified according to how the properties of other functional groups in the "R" group influence the system; non-polar aliphatic side chain, relatively non-polar aromatic side chain, negatively charged side chain and positively charged side chain such as lysine and histidine [3].

Amino acids can be linked together by peptide bonds and form peptides and proteins. Many biological systems use proton-transfer reactions to perform communication between the extracellular and intracellular media. The rate of the proton-transfer reaction depend on many factors such as pK_a value [4,5].

Knowledge of the acid dissociation constants of the ionizable protons in molecules is important in many areas of chemistry and biochemistry as it allows the protonation states of acids to be determined at any particular pH value. Consequently, much effort has been devoted to the experimental determination of pK_a values and although in many cases, accurate experimental measurements can be easily made. There are other situations where accurate measurements are difficult. Hence, there is much interest in developing methodology for predicting pK_a values in a variety of chemical systems by various quantum chemical techniques. In addition, theoretical methods are able to elucidate some of the important factors in correlation between the molecular structure and pK_a values [6]. Generally, acid constants of protein residue play an important role in protein stability and function. Therefore, predicting protein pK_a shifts is very beneficial because obtaining pK_a values, experimentally, is not always feasible. Calculating these values, however, is a highly challenging task [7]. Chemical accuracy in pK_a calculations is difficult to achieve, because an error of 1.36 kcal mol^{-1} in the change of free energy for deprotonating in solvent results in an error of 1 pK_a unit [8,9].

In computational biology, protein pK_a calculations are used to estimate the pK_a values of amino acids as they exist within proteins. These calculations complement the pK_a values reported for amino acids in their free state and are used frequently within the fields of molecular modelling, structural bioinformatics and computational biology. As a part of our theoretical studies, we have investigated the aqueous pK_a for cationic amino acids of histidine and lysine in a peptide chain composed of eight-glycine residue.

Histidine is an essential amino acid in humans and animals. It was initially thought that it was only essential for infants, but longer-term studies established that it is also essential for adult humans [10]. The imidazole ring of histidine is aromatic at all pH values [11]. It can form π stacking interactions [12], but is complicated by the positive charge [13]. It is not absorbed at 280 nm in either states, but is in the lower UV range more than some amino acids [14]. Lysine is an α-amino acid with the chemical formula $HO_2CCH(NH_2)(CH_2)_4NH_2$. It is an essential amino acid which means that the human body cannot synthesize it. In plants and bacteria, it is synthesized from aspartic acid (aspartate) [15].

The obvious extension of this work is to consider the effect of the protein secondary structure from a theoretical point of view which according to the best of our knowledge, no such study has been done. Knowledge of the structural effects on the molecular properties of individual components of the acid-base reaction is important for the understanding the structure-activity relationship which is operative.

We believe that the real system is very complex. There are many parameters affecting the pK_a of these structures. For example pK_a is fluctuated by both amino acid chain sequence and Van der Waals interactions in the tertiary structure. At this stage of our studies, the simplest model has been investigated. It is clear that for better analysis of more real behaviors, designing different peptides with different sequences of amino acids and considering all possible interactions related to the tertiary structures of peptides are necessary. Our final goal is to obtain a meaningful correlation between pK_a and all studied quantum chemistry parameters.

pK_a CALCULATION METHODS AND THEORETICAL PROCEDURE

Corresponding pK_a values were evaluated using the Gaussian 09 computational software at the HF, B3LYP, X3LYP and M05-2X levels of the calculations for the gas and solution phases [16-19]. Avogadro 2.0.7 open source software has been employed for the structure modelling. The explicit and implicit solvated models of ONIOM and CPCM calculations for the solution phase were applied

with the QM method/UFF and 6-31G (d) basis set for the QM section, respectively. In a two-layer ONIOM QM/MM calculation, the real system contains all the atoms (including both QM and MM regions) and is calculated at the MM level ($E^{real,MM}$). The model system is the QM region treated at the QM level ($E^{model,QM}$). To obtain the total ONIOM energy, the model system also needs to be treated at MM level ($E^{model,MM)}$ and be subtracted from the real system MM energy [20]. In the explicit model two hundreds water molecules were selected for simulation through the 2-layer ONIOM method. Peptide and water molecules were located in the high and low layer of calculations, respectively.

In this study, two different thermodynamic cycles, namely the direct method and the proton exchange method have been used as shown in schemes 1 and 2, respectively.

Cycle1

In this thermodynamic cycle (Scheme 1), pK_a value is obtained by Eq. (1).

$$pKa = \Delta Gaq/2.303RT \quad (1)$$

Gibbs free energy change for the dissociation reaction can be computed using the gas phase free energies and solvation energies, in which ΔG_{aq} is declared by Eq. (2).

$$\Delta G_{aq} = \Delta G_{gas} + \Delta\Delta G_{solv} \quad (2)$$

where ΔG_{gas} and $\Delta\Delta G_{solv}$ are the gas-phase Gibbs free energy and the aqueous solvation Gibbs free energy produced by Eqs. (3) and (4), respectively [21]. In this thermodynamic cycle, $\Delta G_{aq}(H^+)$ is -269 kcal mol^{-1} [8].

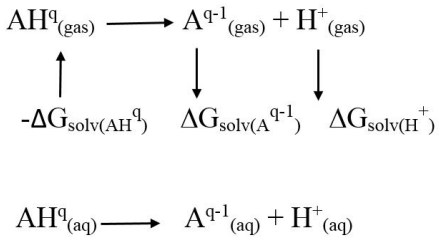
$$\Delta G_{gas} = G_{gas}(H^+) + G_{gas}(A^{q-1}) - G_{gas}(AH^q) \quad (3)$$

$$\Delta\Delta G_{solv} = \Delta G_{solv}(H^+) + \Delta G_{solv}(A^{q-1}) - \Delta G_{solv}(AH^q) \quad (4)$$

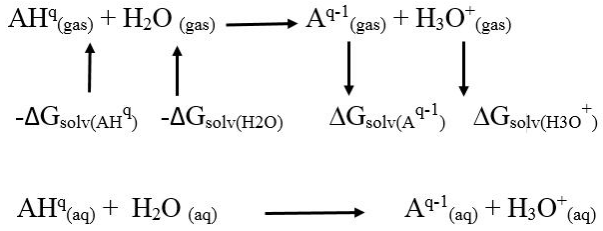
Cycle 2

In the second thermodynamic cycle, proton is substituted by the hydronium cation. In this thermodynamic cycle, Scheme 2, Eq. (5) is used to obtain pK_a.

$$pKa = \Delta Gaq/2.303RT - \log[H_2O] \quad (5)$$



Scheme 1. Thermodynamic cycle 1 which considers the dissociation of the acid species in the conjugate bases and protons.



Scheme 2. Thermodynamic cycle 2 which considers an acid -base reaction between acidic species and water.

Water is added to the reactants side to balance the chemical equation. ΔG_{gas} and $\Delta\Delta G_{solv}$ are obtained by Eqs. (6) and (7), respectively.

$$\Delta G_{gas} = G_{gas}(H_3O^+) + G_{gas}(A^{q-1}) - G_{gas}(AH^q) - G_{gas}(H_2O) \quad (6)$$

$$\Delta\Delta G_{solv} = \Delta G_{solv}(H_3O^+) + \Delta G_{solv}(A^{q-1}) - \Delta G_{solv}(AH^q) - \Delta G_{solv}(H_2O) \quad (7)$$

In these equations, the values of gas phase and solvation Gibbs free energies of H_2O are -76.43107 Hartree and -28.6 kJ mol^{-1}, respectively. These values for H_3O^+ are -76.69160 Hartree and -461.9 kJ mol^{-1}, respectively [22]. ΔG_{solv} has been determined by using the polarizable continuum model (PCM) [23,24].

For exploring the distribution of electrons, natural bond orbital analysis which suggested by Reed *et al.* was applied [25]. Through NBO method, donor-acceptor interactions for the reactants and products, a key factor in determining the reaction proceeding, has been analyzed.

For investigation of the topological properties, QTAIM

[26] has been used by AIM 2000 package [27]. In this method, wave functions generated by the B3LYP/6-311++G(d,p) level, were applied to determine the electron density, local kinetic and potential electronic energy density at the bond critical points.

Sources of Error in pK_a Calculation

One of the main sources of error in pK_a calculations is the value used for the free energy of solvation for H^+, which is explicitly needed in certain thermodynamic cycles. A proton contains no electrons and its free energy cannot be calculated quantum mechanically. The calculation of this energy is possible using the standard equations of thermodynamics. The largest source of error in pK_a calculations is the change in free energy of solvation calculation for the reaction which is based on the type of solvation model used and the specific level of theory [8,9,28,29].

The basic problem is that experimental free energies of solvation for ions have error bars of roughly 2-5 kcal mol^{-1} and so models that have been developed to reproduce experimental values, have the same inherent uncertainty. It is not possible to improve a particular solvation model by simply increasing the basis set in ab initio calculations in the gas phase.

Gas-phase free energy calculation is the lowest source of error in pK_a calculations. High levels of theory, such as CBS-QB3 and CBS-APNO, produce reliable ΔG_{gas} values with root-mean-square deviations of 1.1-1.6 kcal mol^{-1} from the free energy of gas-phase deprotonating reactions compiled in the NIST online database [30,31]. The other error appears when we use different models of solvation to calculate the Gibbs free energy of solvation of species. Several versions of PCM model have been frequently used for these calculations. This part of uncertainty is usually larger than that in gas phase energies.

RESULTS AND DISCUSSION

pK_a Analysis

In this study, it has been chosen eight amino acids of glycine in the peptide structure in which one molecule of histidine or lysine have been introduced. Our aim is investigation of the secondary structure effects of proteins on the thermodynamics of cationic amino acids and also analyzing the role of internal hydrogen bonding on pK_a values.

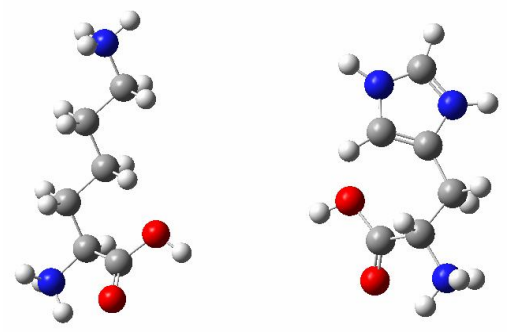


Fig. 1. Optimizes structures of the cationic forms of lysine and histidine.

Histidine is an α-amino acid with an imidazole functional group. Experimental value for side chain pK_a of histidine is 6.04, while in the case of lysine is 10.53 [32]. These molecules are further categorized as cationic as shown in Fig. 1.

Figures 2 and 3 show three types of optimized structures for the positivly charged of histidine and lysine in a peptid chain of eight-glycines residue.

Gas phase, aqueous and solvation Gibbs free energies in addition to pK_a values of these structures, by using two thermodynamic cycles 1 and 2, have been reported in Table 1. As shown in Table 1, the acidic character of beta sheet is more than that of alpha helix and random structures in histidine-based protein (β > α > R). For lysine-based protein, acidic character is accordance to: α > β > R.

What is concluded from the calculated pK_as is that HF method is not a good method for pK_a evaluation in comparison with B3LYP and X3LYP methods. Comparison between the theoretical data and experimental pK_a values of amino acids shows that X3LYP method, because of dispersion forces inclusion, is somewhat a better method for pK_a estimation than B3LYP. Finally, outputs of cycle 2 are more reasonable than those of cycle 1.

According to calculated pK_as, minimum acid strength of these peptides is related to the random structures while

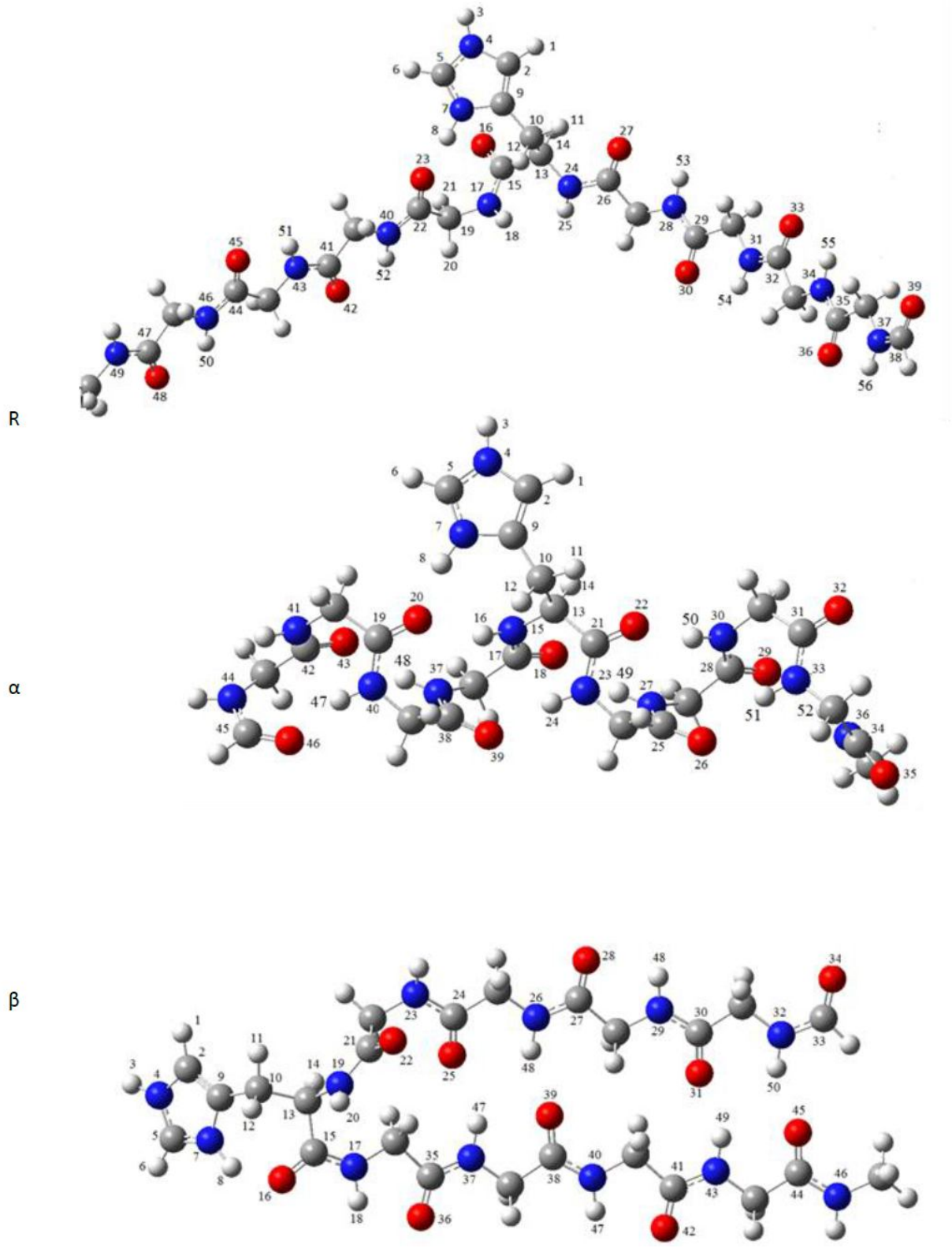


Fig. 2. Optimized cationic structures of histidine-based peptides in a chain of glycine, using the B3LYP/6-31G (d) method.

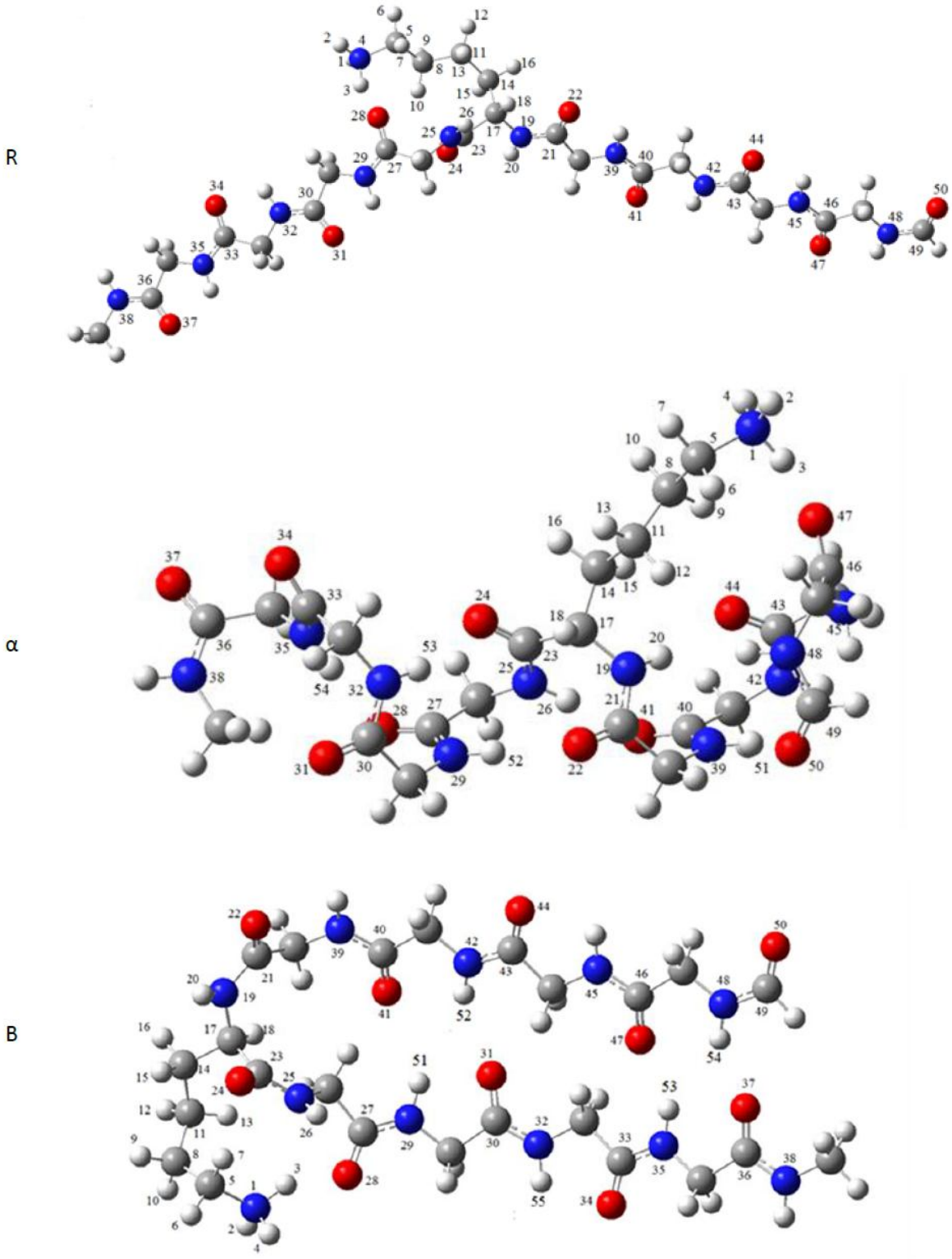


Fig. 3. Optimized cationic structures of lysine-based peptides in a chain of glycine, using the B3LYP/6-31G (d) method.

Table 1. Calculated Thermodynamic Parameters and pK_a Values for Lysine and Histidine-Baased Peptides Using 6-31G(d)

		G_{gas}(Hartree)		ΔG_{solv} (Hartree)		ΔG_{aq} (Hartree)		pK_a	
		Cation	Neutral	Cation	Neutral	Cation	Neutral	Cycle1	Cycle2
	B3LYP								
	R	2345.485967	2345.093633	0.111217	0.059600	2345.597184	2345.153233	7.04	8.01
Histidine	α	2345.476159	2345.096790	0.125177	0.061401	2345.601336	2345.158191	6.67	6.37
	β	2331.765658	2331.390729	0.122420	0.057449	2331.888078	2331.448178	5.53	5.23
	R	2293.689966	2293.307773	0.119265	0.052493	2293.809231	2293.360266	13.85	13.40
Lysine	α	2293.644567	2293.274527	0.142977	0.059728	2293.787544	2293.334255	11.07	11.07
	β	2293.671043	2293.280099	0.105830	0.042740	2293.776873	2293.322839	11.69	11.40
	HF								
	R	2331.795359	2331.403055	0.125559	0.071823	2331.920918	2331.474878	8.01	7.71
Histidine	α	2331.784152	2331.405104	0.137591	0.071839	2331.921743	2331.476943	7.43	7.13
	β	2345.480943	2345.102022	0.108348	0.046596	2345.589291	2345.148618	5.17	4.87
	R	2280.194012	2279.813691	0.132523	0.062899	2280.326535	2279.876590	9.81	9.51
Lysine	α	2280.144979	2279.778516	0.157128	0.074867	2280.302107	2279.853383	9.24	8.90
	β	2280.161449	2279.775308	0.118771	0.055345	2280.280220	2279.830653	9.64	9.34
	X3LYP								
	R	2344.507227	2344.115628	0.111249	0.059600	2344.618476	2344.175228	5.80	6.72
Histidine	α	2344.500672	2344.121942	0.125846	0.061863	2344.626518	2344.183805	5.56	6.47
	β	2344.499854	2344.127221	0.115810	0.046501	2344.615664	2344.173722	5.01	6.12
	R	2292.719299	2292.337475	0.127931	0.052966	2292.847230	2292.390441	12.05	12.97
Lysine	α	2292.677180	2292.306858	0.143025	0.060267	2292.820205	2292.367125	11.25	10.34
	β	2292.734545	2292.341541	0.104907	0.043075	2292.839452	2292.384616	12.06	11.15

maximum value is fluctuated between β and α secondary structures. Comparison between the theoretical and experimental values reveals that there is a small discrepancy between theory and experiment [32]. Considering the histidine or lysine as a single molecule and comparing its thermodynamic parameters with a nearly long chain of added glycine residue, induces the idea that the intermolecular interaction contribution on these parameters is not negligible and it is the source of some degrees of discrepancies between the theoretical data and experiments. Considering this phenomenon and acid strength fluctuation between alpha helix and beta sheet structures needs to focus on the interaction energy and hydrogen bonds (See Figures S1 and S2) which are important in the formation of the secondary structures of the proteins. To study this behavior, the structural, NBO and QTAIM analyses at the B3LYP/6-311++G(d,p) level have been applied.

In order to construct a more real thermodynamic modelling of the medium-peptide interactions, two hundred water molecules were added to the modeled peptide and optimized through the ONIOM method. Calculated pK_a values by this procedure have been reported in Table 2. The obtained pK_as confirme that ONIOM method is not a reasonable procedure for pK_a evaluation.

Table 2. Calculated pKa Values for Lysine and Histidine-Based Peptides Using the Explicit Solvation Model within ONIOM Method (Method: 6-31G(d)/UFF)

B3LYP		Cycle 1	Cycle 2
	R	5.84	4.93
	α	-19.73	-20.64
	β	-22.93	-22.93
X3LYP			
	R	-19.86	-20.77
	α	-21.33	-22.24
	β	-19.48	-20.39
M05-2X			
	R	2.96	2.04
	α	-23.68	-24.60
	β	-25.34	-26.25

Table 3. Average Hydrogen Bond Length and its Number at the B3LYP/6-31G(d) Level of the Theory

Parameter	Histidine			Lysine		
	R	α	β	R	α	β
Number of H bond	7	9	10	6	8	7
Average length of H bond (Å)	2.04	2.02	2.07	2.07	2.15	2.19
η of Cations (a.u.)	0.320	0.202	0.201	0.399	0.375	0.387

STRUCTURAL ANALYSIS

After optimization of all studied structures, total number of hydrogen bonds and their lengths have been computed and reported in Table 3. According to Table 3, it is expected a linear correlation between the number of hydrogen bonds and acid strength. This means that the increase in the hydrogen bond number decreases the corresponding pK_a. If the average bond length of the hydrogen bonds (Figs. S1 and S2) is considered, a meaningful correlation is not presented.

Chemical hardness, η, is one of the important concepts in describing the reactivity order. The natural way to approximate η in DFT calculations is evaluating the Koopmans and Kohn-Sham theorems, using HOMO-LUMO energy differences [33,34]. The magnitudes of η have been also reported in Table 3.

Chemical hardness of the cationic forms of the studied peptides reveals that η has an adverse effect on acid strength of lysine and histidine-based peptides. This means that the increase in cationic η increases pK_a of the corresponding peptides. In other words, the chemical hardness controls the acid-base reaction by affecting the hydronium release.

Selected HOMO and LUMO orbitals of the structures with the highest acidity for histidine and lysine-based peptides are depicted in Figs. 4 and 5, respectively. Corresponding figures for other structures have been prepared as Figs. S3 and S4 in supplementary materials. Among the highest occupied MOs of histidine-based peptides structures, the largest numbers constitute lone pair

Table 4. Natural Charges on the N and H Atoms at the Acid Center of Cations

	Structure	-10^5Q_{N+}	$10^5Q_{\text{Acidic H}}$	Charge transfer (ΔQ)
Histidine	R	51565	48489	1.001
	α	50737	49057	1.003
	β	60238	45989	1.062
Lysine	R	80216	48715	1.289
	α	89370	49558	1.389
	β	81399	47971	1.294

Table 5. Calculated NBO and QTAIM Data at the B3LYP/6-311++G(d,p) Level

	$\Delta E_{(delocal)}$ (kcal mol^{-1})	Σρ for O…H bonds (a.u.)	-G/U
Histidine			
R	31.24	0.188	1.39
α	32.12	0.183	1.35
β	40.70	0.207	1.37
Lysine			
R	11.20	0.177	1.36
α	34.84	0.133	1.31
β	29.96	0.137	1.34

of N4 (LP_{N4}) and Π orbitals of histidine ring with a contribution of the N and O atoms from the residual chain. Corresponding lowest unoccupied MOs can be represented as a combination of Π^*_{ring}, $\Pi^*_{C=O}$, σ^*_{C-N}, with the predominant involvement of the former corporate. In the highest occupied MOs of lysine-based peptide structures, the most important contributions are related to lone pair of N1 (LP_{N1}) and $\Pi_{C=O}$ orbitals of lysine with a little contributions from the non-bonding orbitals of N and O atoms of glycine in the central neighborhood. Corresponding lowest unoccupied MOs can be considered as a combination of $\Pi^*_{C=O}$, σ*C−N, and σ*C−N molecular orbitals.

NATURAL BOND ORBITAL ANALYSIS

NBO calculations provide information on a large variety of interactions that may occur between the orbitals individually [35]. The general object of NBO methods is to translate accurate calculations into chemical insights. Such insights are formulated in terms of commonly understood bonding concepts such as atomic charge, Lewis structure, bond type, hybridization, bond order, charge transfer, resonance weights, steric, energy decomposition analysis and spectroscopic properties [36,37].

Natural charges on the N and H atoms of histidine and lysine-based peptides at the acid center of cationic structures have been reported in Table 4. Negative charge of N atom and positive character for H atom confirm the charge transfer process due to deprotonation process. According to Table 4, calculated atomic charge transfer (ΔQ) between N and H atoms in the cationic forms of studied peptides are correlated with the acid strength and it is possible to differentiate between pK_a values according to charge transfer. Increase in ΔQ for three structures of histidine and lysine-based peptides elevates the acid strength.

Based on the previous studies [38,39] which claimed that delocalization energy and its fluctuation during the reaction is an important factor in chemical reactivity, this type of the energy changes between donors and acceptors or reactant and product is calculated and reported in Tables 5, S1 and S2. Comparison between the calculated $\Delta E_{(delocal)}$ and pK_a predicts a good correlation which can be considered as a quantum chemistry variable in describing the acid strength of peptides. Correlation coefficient for the linear correlation of pK_a as a function of $\Delta E_{(delocal)}$ for histidine and lysine-based peptides (Figs. S5 and S6) are 0.977 and 0.997, respectively. The changes of delocalization energies between the reactants and products in the deprotonating process is a scale for estimation of the acidic character of the corresponding H^+. This means that the increase in delocalization energy, especially for H-O bond of the modeled systems, increases the ability of the H release and consequently reduces the PKa.

QTAIM ANALYSIS

Atom is defined as a proper open system, a system that can share energy and electron density, which is localized in the 3-D space from QTAIM point of view. The mathematical study of these features is usually referred in the literature as charge density topology [40]. By topological analysis of the electronic charge density during the reaction, it can be computed the value of charge density ρ(r), Laplacian L(r), kinetic (G) and potential (U) electronic energy density and their behavior as a function of the critical reaction coordinate, O···H bonds.

Theoretical QTAIM properties for O···H bonds in the cationic forms of peptides (Σρ) are calculated and summarized in Table 5. Considering these average data, there is not a linear correlation between the average total electron density of O…H bonds and pK_a. Local kinetic and the potential energy densities [$V_{(rBCP)}$ and $G_{(rBCP)}$] on O···H bonds have been calculated. Average value of -1.37 and -1.34 for G/U quantity of lysine and histidine-based peptides, respectively, reveals the non-covalent nature of O···H bonds.

CONCLUSIONS

In this study, the aqueous pK_a for the cationic amino acids of histidine and lysine in a peptide chain of eight-glycine residue have been calculated by employing the quantum chemistry calculations. Two different thermodynamic cycles, namely the direct method and the proton exchange method have been used for calculation of pK_a. The results show that the proton exchange method is more accurate than those derived from pK_a of the direct method.

Comparison of the theoretical and experimental results shows that HF method is not useful for calculation of pKa values, while data from the X3LYP and B3LYP methods are in good agreement with experimental ones. Explicit solvent model (ONIOM method) with water molecules has been employed for recalculation of the pKa, but the obtained data, using this method, are not in agreement with the experimental pKa values.

Calculated acid strength of histidine is accordance to: β > α > R and α > β > R for lysine-base peptides. Structural analysis showed that these trends are due to the formation of hydrogen bonds in the structures of alpha helix and beta sheet.

NBO analysis showed that one of the main reasons for the increase of the solution phase acidity is the promotion of the delocalization energy ($\Delta E_{delocal}$) for the neutral acid relative to the positively charged ones.

Finally, calculated quantum reactivity indices confirm that the increase in the chemical hardness increases in pKa, while the increase in delocalization energy of O···H bond reduces pKa values. QTAIM analysis confirmed the non-covalent nature of O…H hydrogen bonding in the secondary structures of the studied peptides.

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