SPATIAL STRUCTURE OF N^1H AND N^3H TAUTOMERS OF CARNOSINE IN ZWITTERION FORM

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Conformational profiles of N^1H and N^3H tautomers of carnosine in zwitterion form are investigated within framework of molecular mechanics. It is found that the stability of the spatial structure of this sequence is determined by the relative positions of its functional groups. Thus, the most stable conformations for both carnosine tautomers are characterized by close arrangement of α-amino group, C-terminal carboxyl group and imidazole ring of *L*-histidine in space. The salt bridges between nitrogen atom of α-amino group and oxygen atoms of deprotonated carboxyl group are revealed in these structures. The effects of intramolecular hydrogen bonding on geometry of molecule are observed in the investigated tautomers of carnosine.

Keywords: molecular mechanics; spatial structure; conformation; carnosine
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1. INTRODUCTION

Carnosine (β-alanyl-*L*-histidine, β-Ala-*L*-His) has antioxidant properties, therefore it is successful used at the treatment of various inflammatory processes that occur against the background of cell membrane damage; it has also ability to recognize dangerous molecules and neutralize them by chemical binding [1-3]. The zwitterion form of this dipeptide takes part in complex formation with ion metals and shows the important pharmacological activity. Many works are devoted to spectroscopic and structural characterization of carnosine [4-7]. However, in these studies the systematic conformational analysis was not carried out. To understand the mechanism of activity of the drug under investigation it is necessary to explore its conformational possibilities and determine bioactive conformation. The aim of this work is to investigate the conformational behavior of N^1H and N^3H tautomers of carnosine in zwitterion form by molecular mechanics to provide an improved description of the structure-functional interrelation to enable the designing of products for new medical applications. The geometry and energy parameters of the most stable conformations of both tautomers of carnosine are calculated.

2. COMPUTATIONAL METHODS

The conformational profiles of carnosine molecule in zwitterion form are investigated within framework of molecular mechanics as it is described in [8]. The conformational potential energy of this moleculee is given as the sum of the independent contributions of nonvalent (E_{nv}), electrostatic (E_{el}), torsional (E_{tor}) interactions and hydrogen bonds energy (E_{hb}). The energy of nonvalent interactions was described by the Lennard-Jones 6-12 potential with the parameters proposed by Scott and Sheraga [9]. The contribution of electrostatic interactions was taken into account in a monopole approximation corresponding to Coulomb's law with partial charges of atoms suggested by Scott and Sheraga [9]. The effective dielectric constant $\mathcal{E}$ was taken to be equal to ten described by Lipkind et al. [10]. A torsion energy was calculated using the value of internal rotation barriers given by Momany et al. [11]. Hydrogen bonding energy was calculated based on Morse potential and dissociation energy of the hydrogen bond was taken to be *1.5 kcal/mol*. A rigid valence scheme of the molecule was assumed, namely, the searches were made only on torsion angles. Conformational energy calculations were made with an IBM computer using a program in FORTRAN [12,13]. The program was developed from the matrix method principle of Hermans and Ferro [14]. The accepted nomenclature and conventions are recommended by IUPAC-IUB [15]. The computer modelling of the calculation results was carried out using the demonstration version of software package HyperChem (http://www.hyper.com).

3. RESULTS AND DISCUSSION

The conformational state of this molecule is characterized by dihedral angles of backbone and side chains *(τ1, τ2, τ3, ω, φ, χ1, χ2, ψ)* (Fig.1). The term "conformation" or "conformation state", used in the analysis of calculation results, will always imply exact quantitative characteristics of the geometry of this dipeptide. The calculated carnosine conformations were compiled on the basis of low-energy states of its amino-acid residues**.** β-alanyl is a non-standard amino-acid residue, because in it the C^β atom is bound to the carbon of the subsequent carbonyl group. For this reason, we designated its dihedral angles by τ1, τ2, τ3.

In order to determine the possible values of the dihedral angles that correspond to the low-energy states of β-alanyl the conformational maps of the potential surfaces over the τ1-τ2, τ2-τ3, τ1-τ3 angles were constructed. Thus, the dihedral angles around N - C^α, C^α - C^β, C^β –C' bonds of the peptide chain of this residue were varied and their optimal values were

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determined. The conformational maps given in the Fig.2-4 were constructed by step of 30^0 and by step of 5^0 in the low-energy regions. The values of the dihedral angles corresponding to the optimal energy are marked by crosses, and the relative energy on equipotential lines is given in kcal/mol.

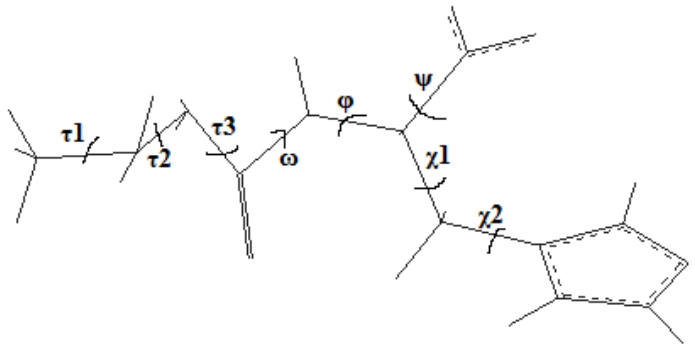


Fig.1 Calculated model of carnosine molecule.

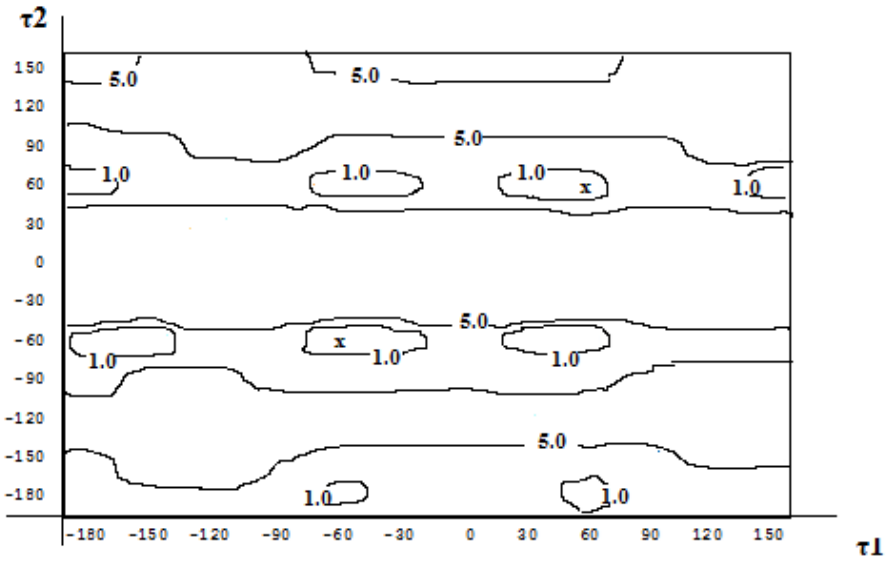


Fig.2. Conformational energy map over τ1-τ2 angles of β-alanyl amino-acid residue.

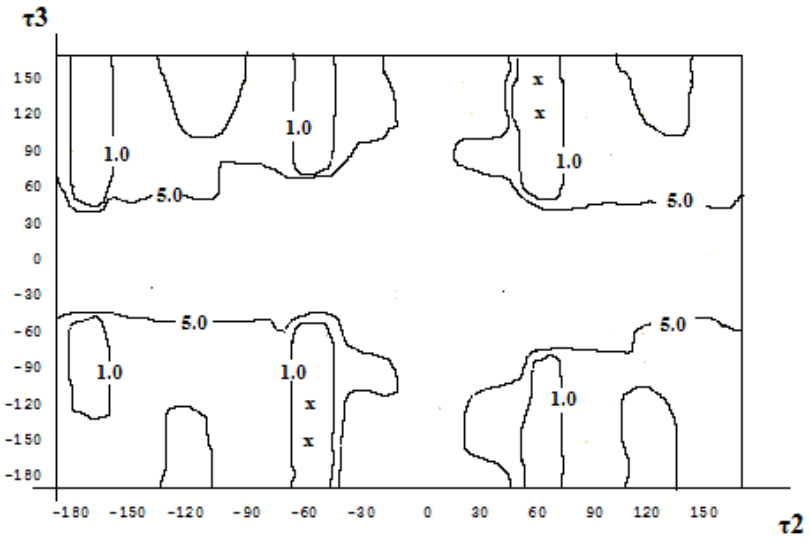


Fig.3. Conformational energy map over τ2-τ3 angles of β-alanyl amino-acid residue.

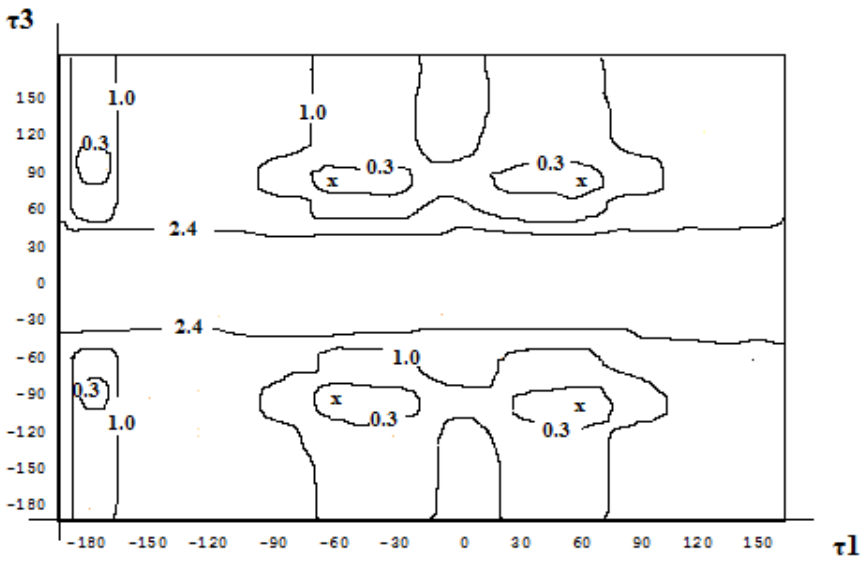


Fig.4. Conformational energy map over τ1- τ3 angles of β-alanyl amino-acid residue

For calculation of carnosine molecule, the values of dihedral angles defining 8 forms of the backbone of β-alanyl residue marked by symbols A1-A8 are selected from the conformational maps and are represented in Table 1. Note that conformations A1, A2, A3, A4 are the same as A7, A8, A5, A6, respectively, since they differ only on angle τ1, which determines the isoenergetic position of three hydrogen atoms relative to the rest part of the molecule. This fact was taken into account in the subsequent analysis of the characteristic conformations of carnosine.

Table 1.

The dihedral angles (in degree) of the low-energy states A1-A8 of β-alanyl amino-acid residue

Angles	A1	A2	A3	A4	A5	A6	A7	A8
τ1	-60	-60	-60	-60	60	60	60	60
τ2	-60	-60	60	60	60	60	-60	-60
τ3	90	-90	90	-90	90	-90	90	-90

For stable conformations of L-histidine the φ and ψ dihedral angles of backbone chain are located in the low energy regions R (φ,ψ=-180⁰-0⁰), B (φ= -180⁰-0⁰, ψ=0⁰-180⁰), L (φ,ψ=0⁰-180⁰) of the Ramachandran's map. Therefore the conformational state of this residue is conveniently described by X_{ij}, where X is the backbone form of a residue (R, B, L), and ij= 11, 13, 21, 23, 31, 33 specify the positions of a side chain (χ1, χ2), the index '1' corresponds to the angle χ in the range from 0⁰ to 120⁰, '2' corresponds to the angle range from 120⁰ to –120⁰ and '3' from -120⁰ to 0⁰.

The possible stable conformational states of the histidine side chain corresponding to torsion minima: to three values 60⁰, 180⁰, -60⁰ of the dihedral angle χ_1 and two values 90⁰ and -90⁰ of the dihedral angle χ_2, orienting the aromatic ring, were considered. The initial values of dihedral angles of low-energy conformations of L-histidine using for calculation of carnosine molecule are given in Table 2. Based on the foregoing, 288 conformations were calculated for two tautomers of this dipeptide.

Table 2.

The initial values of dihedral angles (in degree) corresponding to the low-energy states of L-histidine amino-acid residue

Backbone form	φ	ψ	χ1	χ2
R	-100	-40	60	90, -90
	-120	-60	180	90, -90
	-120	-60	-60	90, -90
B	-120	160	60	90, -90
	-120	140	180	90, -90
	-140	140	-60	90, -90
L	60	80	60	90, -90
	60	100	180	90, -90
	60	60	-60	90, -90

The massiveness of the side chain of histidine amino-acid residue and also existence of the N-and C-terminal opposite charged groups of atoms are important factors, which form the stabilizing forces: dispersion contacts of L-histidine amino-acid residue and electrostatic interactions of the protonated α-amino group and the partially protonated imidazole side chain with deprotonated C-terminal carboxyl group of this molecule. Therefore, the energy of dipeptide is very sensitive to the positions of the mentioned parts of this molecule. The observed differentiation of the calculated conformations on energy is determined both nonvalent and electrostatic interactions. The energy parameters of the favorable conformations for tautomers of this dipeptide are given in Tables 3 and 4. The calculation results reveal that 10% of the examined conformations of this dipeptide have the relative energy up to 3 kcal/mol. It is shown that β-alanyl fragment is more mobile than other segment of this molecule, therefore it may bend α-amino group (H_3N^+) towards C-terminal carboxyl group (COO^-) or L-histidine imidazole ring. The spatial structure of both tautomers of carnosine molecule may be characterized by three types of conformations (I, II, III), which are determined by different arrangement of mentioned functional groups. In the conformations of I type group H_3N^+, group COO^- and imidazole ring of L-histidine are closely spaced; in the conformations of II type groups H_3N^+ and COO^- are closely spaced, but imidazole ring of L-histidine is turned away; in the conformations of III type group H_3N^+ and imidazole ring of L-histidine are closely spaced, but group COO^- is turned away. For both tautomers the conformations of I, II, III types are characterized by R, L, B forms of His backbone respectively. As it is seen from the represented results in the conformations of I type the dispersion, electrostatic and torsion interactions are the best balanced, so they are most stable for both tautomers. The conformations of II type are inferior in energy to torsion interactions on 1 - 1.6 kcal/mol. The best representatives of II type are inferior in total energy on 1.3 kcal/mol. Only the conformations of III type proved to have high energy; the best representatives of these conformational type for both carnosine tautomers are inferior in energy on 4 – 5 kcal/mol to global conformation.

Table 3.

Energy parameters (in kcal/mol) of the favorable conformations for N^1H tautomer of carnosine

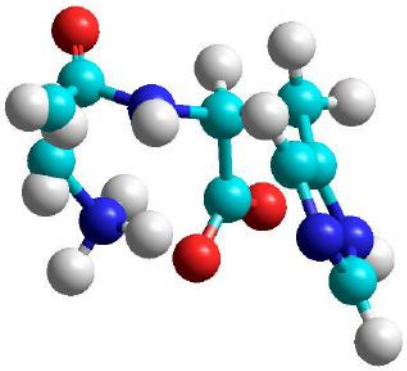
Type	Conformation of molecule	Energy interaction of β-Ala and L-His	$E_{nonval.}$	$E_{elst.}$	$E_{tors.}$	$E_{tot.}$
I	A4-R_{11}	-14.61	-6.87	-4.96	2.14	-9.69
	A4-R_{21}	-14.29	-6.01	-5.13	2.42	-8.72
	A4-R_{31}	-14.60	-6.09	-4.97	1.95	-9.11
	A6-R_{11}	-14.99	-6.78	-5.14	2.57	-9.35
	A6-R_{21}	-14.41	-6.09	-5.10	2.73	-8.46
	A6-R_{31}	-10.16	-4.93	-3.37	1.08	-7.23
	A8-R_{11}	-14.86	-6.30	-5.15	2.28	-9.17
	A2-R_{13}	-15.57	-6.46	-5.37	2.79	-9.04
	A4-R_{13}	-14.46	-6.71	-4.84	2.11	-9.43
	A4-R_{33}	-14.43	-6.03	-5.11	2.22	-8.91
	A6-R_{13}	-15.53	-6.82	-5.21	2.73	-9.30
	A6-R_{23}	-14.19	-6.24	-5.09	2.73	-8.60
	A6-R_{33}	-14.92	-6.22	-5.21	2.65	-8.78
II	A1-L_{21}	-13.53	-6.12	-4.86	3.72	-7.26
	A1-L_{31}	-14.34	-6.81	-4.98	3.66	-8.13
	A3-L_{21}	-13.73	-6.09	-5.12	3.68	-7.53
	A3-L_{31}	-14.18	-6.60	-4.98	3.18	-8.40
	A5-L_{21}	-13.42	-5.60	-5.05	3.29	-7.36
	A5-L_{31}	-14.20	-6.51	-5.03	3.35	-8.19
	A7-L_{21}	-13.76	-6.44	-5.02	3.98	-7.48
	A7-L_{31}	-14.52	-7.12	-5.05	3.75	-8.41
	A1-L_{33}	-14.21	-6.61	-4.99	3.65	-7.96
	A3-L_{23}	-13.76	-6.01	-5.20	3.58	-7.63
	A3-L_{33}	-14.14	-6.42	-5.05	3.21	-8.26
	A5-L_{23}	-13.47	-5.82	-5.05	3.49	-7.39
	A5-L_{33}	-18.08	-6.50	-5.20	3.62	-8.08
	A7-L_{23}	-13.67	-6.36	-5.01	3.79	-7.59
	A7-L_{33}	-14.43	-6.90	-5.06	3.73	-8.24
III	A3-B_{33}	-7.19	-5.78	-0.96	0.97	-5.78
	A7-B_{11}	-6.06	-5.07	-.52	.84	-4.75

Table 4.

Energy parameters (in kcal/mol) of the favorable conformations for N^3H tautomer of carnosine

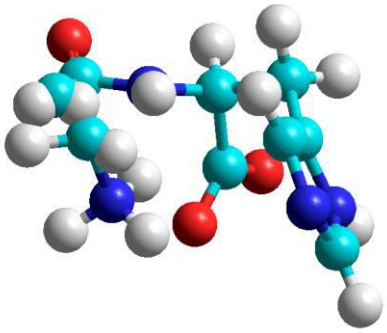
Type	Conformation of molecule	Energy interaction of β-Ala and L-His	$E_{nonval.}$	$E_{elst.}$	$E_{tors.}$	$E_{tot.}$
I	A2-R_{11}	-15.15	-5.92	-5.09	2.60	-8.41
	A4-R_{11}	-14.60	-6.48	-4.77	2.27	-8.99
	A4-R_{21}	-14.05	-5.74	-5.05	2.34	-8.46
	A4-R_{31}	-14.87	-5.74	-5.22	2.23	-8.74
	A6-R_{11}	-15.04	-6.30	-5.05	2.77	-8.58
	A6-R_{31}	-14.91	-5.89	-5.19	2.58	-8.50
	A8-R_{11}	-14.94	-6.09	-4.85	2.35	-8.59
	A2-R_{13}	-15.07	-5.95	-5.30	2.49	-8.76
	A4-R_{13}	-14.70	-6.45	-5.12	2.26	-9.32
	A4-R_{23}	-14.61	-5.61	-5.01	2.15	-8.47
	A6-R_{13}	-15.28	-6.44	-5.29	2.61	-9.13
	A6-R_{23}	-14.60	-5.73	-5.05	2.69	-8.09
	A6-R_{33}	-14.94	-6.06	-5.16	2.67	-8.54
	A8-R_{13}	-15.00	-6.00	-5.31	2.52	-8.80
II	A1-L_{31}	-14.22	-6.29	-4.88	3.60	-7.57
	A3-L_{21}	-13.79	-5.88	-5.16	3.70	-7.33
	A3-L_{31}	-14.15	-6.10	-4.96	3.19	-7.88
	A5-L_{31}	-14.35	-6.22	-5.09	3.63	-7.68
	A7-L_{21}	-13.88	-6.08	-5.13	3.84	-7.38
	A7-L_{31}	-14.44	-6.52	-5.05	3.70	-7.87
	A1-L_{33}	-14.22	-6.40	-4.94	3.64	-7.71
	A3-L_{23}	-13.81	-5.83	-5.13	3.70	-7.26
	A3-L_{33}	-14.05	-6.19	-4.93	3.12	-8.00
	A5-L_{23}	-13.77	-5.48	-5.19	3.56	-7.11
	A5-L_{33}	-14.56	-6.27	-5.26	3.71	-7.82
	A7-L_{23}	-13.88	-6.13	-5.05	3.97	-7.21
	A7-L_{33}	-14.42	-6.67	-5.02	3.69	-7.99
III	A3-B_{31}	-7.13	-5.65	-0.65	0.98	-5.32
	A1-B_{13}	-6.83	-4.80	-.86	.72	-4.93

Each conformational type for both tautomers of carnosine includes two characteristic conformations which are defined by the same arrangement of the functional groups in space, but differ from each other only by the geometry of β-alanyl fragment (Fig.5 and 6). The dihedral angles of these conformations for N^1H and N^3H tautomers of carnosine are represented in the Tables 5 and 6, respectively.

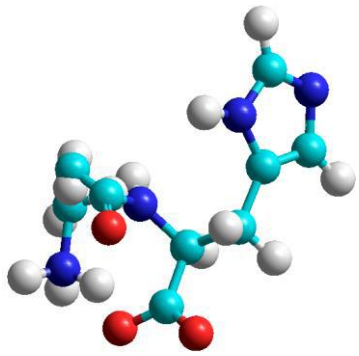


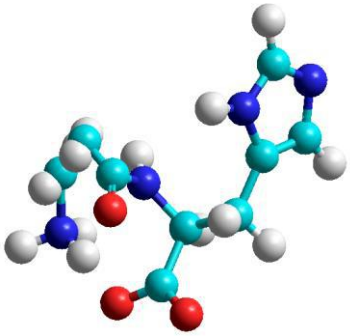
Conformation A4-R_{11}

(a)



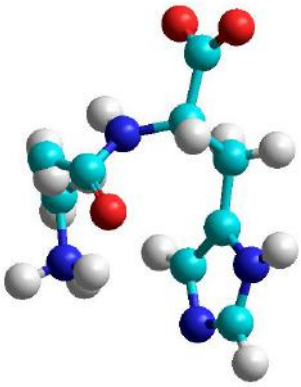
Conformation A8-R_{11}

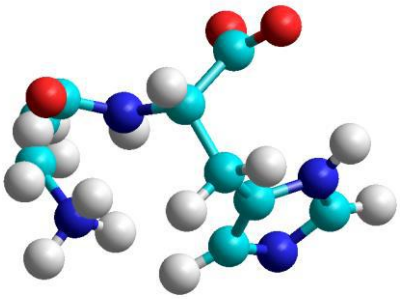




(b)

Conformation A3-L_{31} Conformation A7-L_{31}

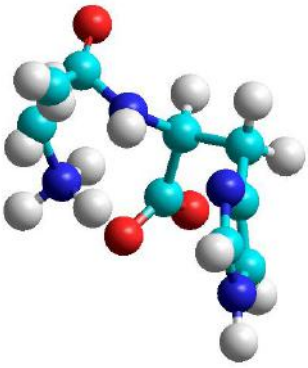


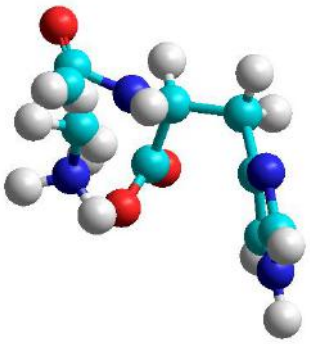


(c)

Conformation A3-B_{33} Conformation A7-B_{11}

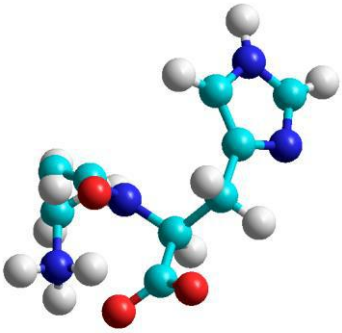
Fig.5. The characteristic conformations of I type (a), II type (b) and III type (c) for N^1H tautomer of carnosine.

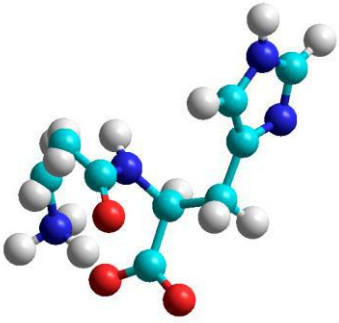




(a)

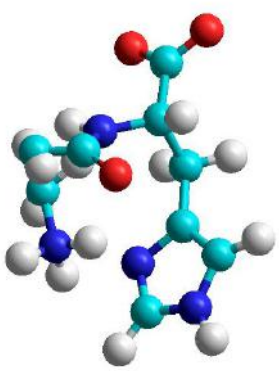
Conformation A4-R_{13} Conformation A8-R_{13}

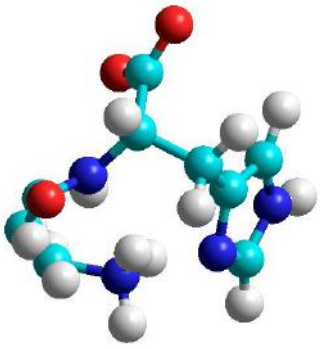




(b)

Conformation A3-L_{33} Conformation A7-L_{33}





(c)

Conformation A3-B_{31} Conformation A1-B_{13}

Fig.6. The characteristic conformations of I type (a), II type (b) and III type (c) for N^3H tautomer of carnosine.

Table 5.

The geometry parameters (in degrees) of the characteristic conformations for N^1H tautomer of carnosine

Amino-acid residue	Dihedral angles	Conformations					
		I type		II type		III type	
		A4-R_{11}	A8-R_{11}	A3-L_{31}	A7-L_{31}	A3-B_{33}	A7-B_{11}
β-Ala	τ1	-64.9	64.3	61.9	-61.7	-56.7	62.7
	τ2	56.6	-45.8	-50.1	44.7	61.4	-57.7
	τ3	-83.0	-50.6	92.4	60.0	93.1	92.1
	ω	167.0	169.6	-161.0	-164.0	179.8	-176.9
L-His	φ	-88.2	-75.9	50.5	48.4	-136.1	-118.6
	χ1	62.6	61.9	-51.7	-54.9	-58.0	64.0
	χ2	84.8	81.0	88.6	85.2	-86.6	85.4
	ψ	-27.8	-25.4	51.3	47.4	141.9	165.2

Table 6.

The geometry parameters (in degrees) of the characteristic conformations for N^3H tautomer of carnosine

Amino-acid residue	Dihedral angles	Conformations					
		I type		II type		III type	
		A4-R_{13}	A8-R_{13}	A3-L_{33}	A7-L_{33}	A3-B_{31}	A1-B_{13}
β-Ala	τ1	-64.1	64.8	-61.7	62.0	-55.9	-46.7
	τ2	56.6	-45.6	45.1	-49.0	61.3	-60.8
	τ3	-82.3	-51.1	59.9	92.1	93.6	88.7
	ω	166.1	168.1	-164.3	-161.3	-177.9	-177.7
L-His	φ	-91.0	-78.1	48.6	49.8	-135.3	-130.0
	χ1	63.3	65.2	-55.3	-52.4	-58.0	60.4
	χ2	-96.2	-101.6	-95.0	-91.5	92.4	-92.8
	ψ	-26.4	-25.3	46.9	51.0	142.2	166.0

The effects of intramolecular hydrogen bonding on geometry of molecule were observed in the investigated carnosine tautomers. In dependence on the arrangement of the functional groups the following hydrogen bonds appear in the stable conformations of the molecule. Since the conformations of I type for both carnosine tautomers are characterized by close positions of COO^- group, H_3N^+ group and imidazole ring of L-His in space, therefore two types of the hydrogen bond form in the most stable conformations A4-R_{11} for N^1H tautomer and A4-R_{13} for N^3H tautomer: 1) between the nearest oxygen and hydrogen atoms of the N- and C-terminal charged groups, 2) between the hydrogen atom of amid group of backbone of L-His and oxygen atoms of COO^- group. In other characteristic conformations of I type only first type of hydrogen bond forms for both tautomers. In the conformations of II type groups COO^- and H_3N^+ are closely spaced, but the imidazole ring of L-His is turned away for both carnosine tautomers. Therefore the most stable conformation A3-L_{31} of II type for N^1H tautomer is characterized by formation of two types of the hydrogen bond: 1) between the nearest oxygen and hydrogen atoms of N- and C-terminal charged groups, 2) between the oxygen atom of the carbonyl group of β-Ala backbone and H atom, attached to N^1 atom of the imidazole ring of L-His. But in the characteristic conformation A7-L_{31} of II type for N^1H tautomer and in the characteristic conformations A3-L_{33} and A7-L_{33} of II type for N^3H

tautomer only first type of the hydrogen bond forms. Since in the conformations of III type H_3N^+ group and imidazole ring of L-His are closely spaced, but COO^- group is turned away for both carnosine tautomers, therefore the characteristic conformations A3-B_{33} for N^1H tautomer and A3-B_{31} for N^3H tautomer of mentioned type are characterized by formation only one type hydrogen bond between the hydrogen atom of H_3N^+ group and oxygen atom of the carbonyl group of β-Ala backbone. There are no hydrogen bonds in other characteristic conformations of III type for both tautomers. The energy and geometry parameters of the hydrogen bonds in the characteristic conformations for N^1H and N^3H tautomers of carnosine are given in Tables 7 and 8, respectively.

Table 7.

The length (in Å) and energy (shown in brackets, in kcal/mol) of the hydrogen bonds in the characteristic conformations for N^1H tautomer of carnosine

H-bond	I type		II type		III type	
	A4-R_{11}	A8-R_{11}	A3-L_{31}	A7-L_{31}	A3-B_{33}	A7-B_{11}
NH_3^+...$^-$OOC	1.95 (-1.30)	1.89 (-1.41)	1.90 (-1.41)	1.92 (-1.36)		
L-His NH… $^-$OOC	2.90 (-0.11)					
β-Ala CO…HN^1 L-His			2.90 (-0.11)			
NH_3^+...OC β-Ala					2.58 (-0.28)	

Table 8.

The length (in Å) and energy (shown in brackets, in kcal/mol) of the hydrogen bonds in the characteristic conformations for N^3H tautomer of carnosine

H-bond	I type		II type		III type	
	A4-R_{13}	A8-R_{13}	A3-L_{33}	A7-L_{33}	A3-B_{31}	A1-B_{13}
NH_3^+...$^-$OOC	1.92 (-1.36)	1.86 (-1.46)	1.93 (-1.34)	1.89 (-1.41)		
L-His NH… $^-$OOC	2.86 (-0.12)					
NH_3^+...OC β-Ala					2.56 (-0.29)	

The interatomic distances between the nitrogen atom of α-amino group and oxygen atoms of deprotonated carboxyl group is 2.9Å in the most stable conformations of I and II type for both carnosine tautomers, that confirms the formation of the salt bridge in them. In the characteristic conformations of III type the value of this distance varies in the interval 6.4 –7.2Å.

The obtained results allow us to better describe the structure-functional interrelation of carnosine.

4. CONCLUSION

The energy and geometry parameters characterizing the stabile states for N^1H and N^3H tautomers of carnosine in zwitterion form are obtained by method of molecular mechanics. The effects of intramolecular hydrogen bond on geometry of carnosine molecule are observed in the investigated carnosine tautomers. As seen from the obtained results the angles involved in β-alanyl fragment are more mobile than in the other segment of the molecule, therefore it may bend α-amino group toward deprotonated carboxyl group or imidazole ring of L-histidine. It was shown that the most stable conformations for both tautomers of carnosine are characterized by close positions of the functional groups of molecule in space.

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