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Molecular Mechanics Studies of Antihypertensive Val-Tyr Dipeptide

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The spatial structure of antihypertensive dipeptide, Valine-Tyrosine was investigated within molecular mechanics framework. It has been shown that the molecule has such a structural organization which does not exclude the realization of two types of conformation: folded and extended. The energy and geometrical parameters for the optimal conformations of dipeptide are obtained. The electronic characteristics for these structures were analyzed by quantum chemical calculations.

Key Words: Antihypertensive peptide, Conformational analysis, Molecular mechanics, Tyrosine, Valine.

INTRODUCTION

Modern diet and sedentary lifestyle have found to cause hypertension which causes death and disability. Therefore the influence of nutritive compounds on prevention and treatment of hypertension have been taken considerable interest in the recent years[1,2]. Val-Tyr dipeptide is known to be angiotensin converting enzyme (ACE) inhibitory peptide *in vitro*[1,2]. Absorption of Val-Tyr dipeptide with *in vitro* angiotensin I-converting enzyme inhibitory activity into the circulating blood system of mild hypertensive subjects has been shown[1]. Despite the interest in the biological role of H-Val-Tyr-OH dipeptide, only one work[3] was devoted to its spectroscopic and conformational characterization. Koleva *et al.*[3] published solid state IR spectrum of H-Val-Tyr-OH dipeptide and performed its *ab initio* quantum chemical calculations. In this study, however, systematic conformational analysis was not performed. To understand the mechanism of activity of the drug under investigation it is necessary to explore its conformational possibilities and determine physiologically active conformations. In this study conformational behaviour of antihypertensive dipeptide, H-Val-Tyr-OH has been investigated by molecular mechanics method.

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COMPUTATIONAL METHODS

The investigations were carried out using the theoretical conformational analysis as described by Godjayev *et al.*[4]. The conformational potential energy of the dipeptide is given as the sum of the independent contributions of non-valent (E_{nv}), electrostatic (E_{el}), torsional interactions (E_{tor}) and hydrogen bonds[5] (E_{hb}). The energy of non-valent interactions was described by the Lennard-Jones 6-12 potential with the parameters proposed by Scott and Sheraga[6]. The contribution of electrostatic interactions was taken into account in a monopole approximation, corresponding to Coulomb's law, with partial charges of atoms as suggested by Scott and Sheraga[6]. The effective dielectric constant ε was taken to be equal to 10, as described by Lipkind *et al.*[7]. The torsion energy was calculated using the value of internal rotation barriers given by Momany *et al.*[8]. The values of the internal barriers used are as follows: for the backbone chain U_0^{φ} = 0.6 kcal/mol, U_0^{ψ} = 0.2 kcal/mol, U_0^{ω} = 20.0 kcal/mol; for the side chains, Val: $U_0^{\chi 1}$ = 3.0 kcal/mol, $U_0^{\chi 2}$ = 3.0 kcal/mol, $U_0^{\chi 3}$ = 3.0 kcal/mol, Tyr: $U_0^{\chi 1}$ = 3.0 kcal/mol, $U_0^{\chi 2}$ = 0.2 kcal/mol, $U_0^{\chi 3}$ = 20 kcal/mol. The hydrogen bonding energy was calculated based on Morse potential and the 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.

The conformational state of each amino acid residue is characterized by backbone (φ, ψ) and side chain (χ1, χ2, χ3,…) dihedral angles. The term "conformational state" or "conformation", used in the following analysis, will always imply exact quantitative characteristics of the geometry of the residue or the fragment. For a stable conformation, the φ and ψ dihedral angles are located in the low energy regions R (φ,ψ = -180º-0º), B (φ = -180º-0º, ψ = 0^0-180º), L (φ,ψ = 0º-180º), P (φ = 0º-180º, ψ = -180º-0º) of the conformational map. The notion "form of a residue" was introduced to denote the above mentioned regions of its backbone dihedral angles. Therefore the conformational state of each amino acid residue is conveniently described by X_{ij} where X is the backbone of a residue (R, B, L, P) and ij = 11...., 12....,13....,21…. specify the positions of a side chain (χ1, χ2, χ3,…), the index '1' corresponds to the angle χ in the range from 0º to 120º, '2' corresponds to the angle range from 120º to -120º and '3' from -120º to 0º. The nomenclature and conventions adopted are those recommended by IUPAC-IUB[9]. The combination of the backbone forms of a residue in a given amino acid sequence will specify the backbone forms of a fragment. So, all backbone forms of a dipeptide can be classified into two types; folded (f shape) and extended (e shape). Forms, belonging to a particular type, have an analogous peptide chain contour and a similar mutual arrangement of backbones and side chains and thus, should exhibit similar medium-range interaction potentialities.

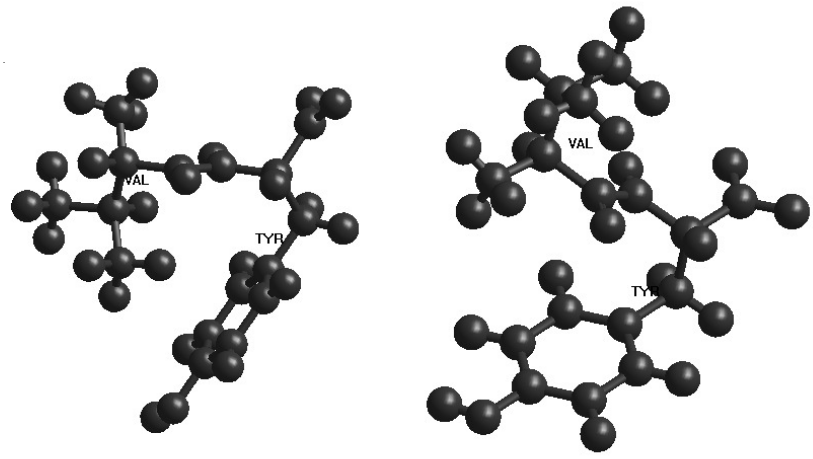
RESULTS AND DISCUSSION

The backbone chains of amino acid residues that construct dipeptide Val-Tyr can be in R, B and L forms. Since the dihedral angle ψ characterizes the spatial arrangement of two C-terminal oxygen atoms of the molecule, the forms B and R of Tyr, which differ in angle ψ, can be assumed to be identical. For the above reasons, the extended shape e was represented by the BB, LB and RL forms of the main chain and the folded shape f, by the RR, BL and LL forms. For the dihedral angle χ_1 of the side chains of both Val and Tyr, all three values of torsion minima 60, 180, -60º were considered. The value 180º for χ_2 and χ_3 of Val and the values 900 and 180º, respectively, for χ_2 and χ_3 of Tyr, which correspond to stable states of side chains of these residues, were taken. Thus, 54 conformations, belonging to the folded and extended shapes of backbone were calculated.

The energy parameters of the favourable conformations of both shapes of the investigated dipeptide are given in Table-1. The dimension of the side chains of the constituent amino acid residues is an important factor, which form the stabilizating forces: dispersion interactions of side chains of Val and Tyr. Therefore the energy of dipeptide is very sensitive to the conformations of the side chains of the amino acid residues. The observed differentiation in energy of the calculated conformations is mainly determined by the nonvalent interactions. There are also insignificant stabilizing effects because of electrostatic interactions of the charged atom groups on the N-and C-terminals of the molecule. Calculation results reveal that 20 % of the examined conformations have the relative energy up to 2 kcal/mol and both shapes have equi-probable energy for this dipeptide. Only the conformations of the e shape have the RL form and the conformations of the f shape that have the LL form of the backbone proved to have high energy. The best representatives of these forms have a relative energies of 3.8 and 4.3 kcal/mol. In the folded conformations, the dispersion, electrostatic and torsion interactions are the best balanced, whereas in all the conformations of the e shape, the torsion interactions make destabilizing contribution, up to 1.5 kcal/mol. Though the extended shape of this dipeptide is the best from the point of view of monopeptide energy. In the folded backbone conformations, the side chains are more close to each other and form effective dispersion contacts. In addition, the folded structures are also favourable as regards dispersion contacts of the backbone elements, which result in the density packing of monopeptide links. It is noted that in the low-energy conformations of the dipeptide, the side chains of the valine and tyrosine amino acid residues are coplanar and thus interact more efficiently. Such a spatial arrangement of the side chains makes the molecule compact and also ensures the proximity between the atoms of the side chains and the atoms of the amino- or carboxyl- group at the terminals of the molecule. The optimal conformations of folded ($E_{rel.}$ = 0.0 kcal/mol) and extended ($E_{rel.}$ = 0.5 kcal/mol) backbone shapes are illustrated in Fig. 1. Table-2 presents the main- and side- chain dihedral angles in these structures. It was established that the distances from atom CG1 of side chain of Val to atom O of side chain of Tyr are 4.1 and 7.7 Å.

TABLE-1
ENERGIES (kcal/mol) OF FAVOURABLE
CONFORMATIONS OF VAL-TYR DIPEPTIDE

Shape	Conformation	E_{rel}	Energy contributions (kcal/mol)		
			E_{nb}	E_{el}	E_{tors}
f	$R_{222}R_{312}$	0.0	-5.4	-0.5	0.5
	$R_{222}R_{112}$	0.6	-4.8	-0.6	0.6
	$R_{222}R_{212}$	1.9	-3.3	-0.5	0.5
	$B_{122}L_{312}$	2.1	-4.1	-0.5	1.4
e	$B_{122}B_{312}$	0.5	-5.3	-0.4	0.9
	$L_{122}B_{312}$	0.5	-5.4	-0.4	1.0
	$L_{122}B_{112}$	1.0	-5.1	-0.3	1.2
	$B_{222}B_{312}$	1.1	-4.9	-0.3	1.0
	$B_{122}B_{112}$	1.5	-4.3	-0.3	0.7
	$L_{222}B_{312}$	1.5	-4.6	-0.2	0.9
	$B_{222}B_{112}$	1.8	-4.3	-0.2	1.0
	$L_{222}B_{112}$	2.0	-4.2	-0.1	1.1
	$L_{122}B_{212}$	2.1	-3.8	-0.3	0.9
	$B_{122}B_{212}$	2.2	-3.6	-0.3	0.7
	$B_{222}B_{212}$	2.7	-3.2	-0.2	0.8
	$B_{322}B_{312}$	2.7	-3.7	-0.4	1.4



(a) (b)

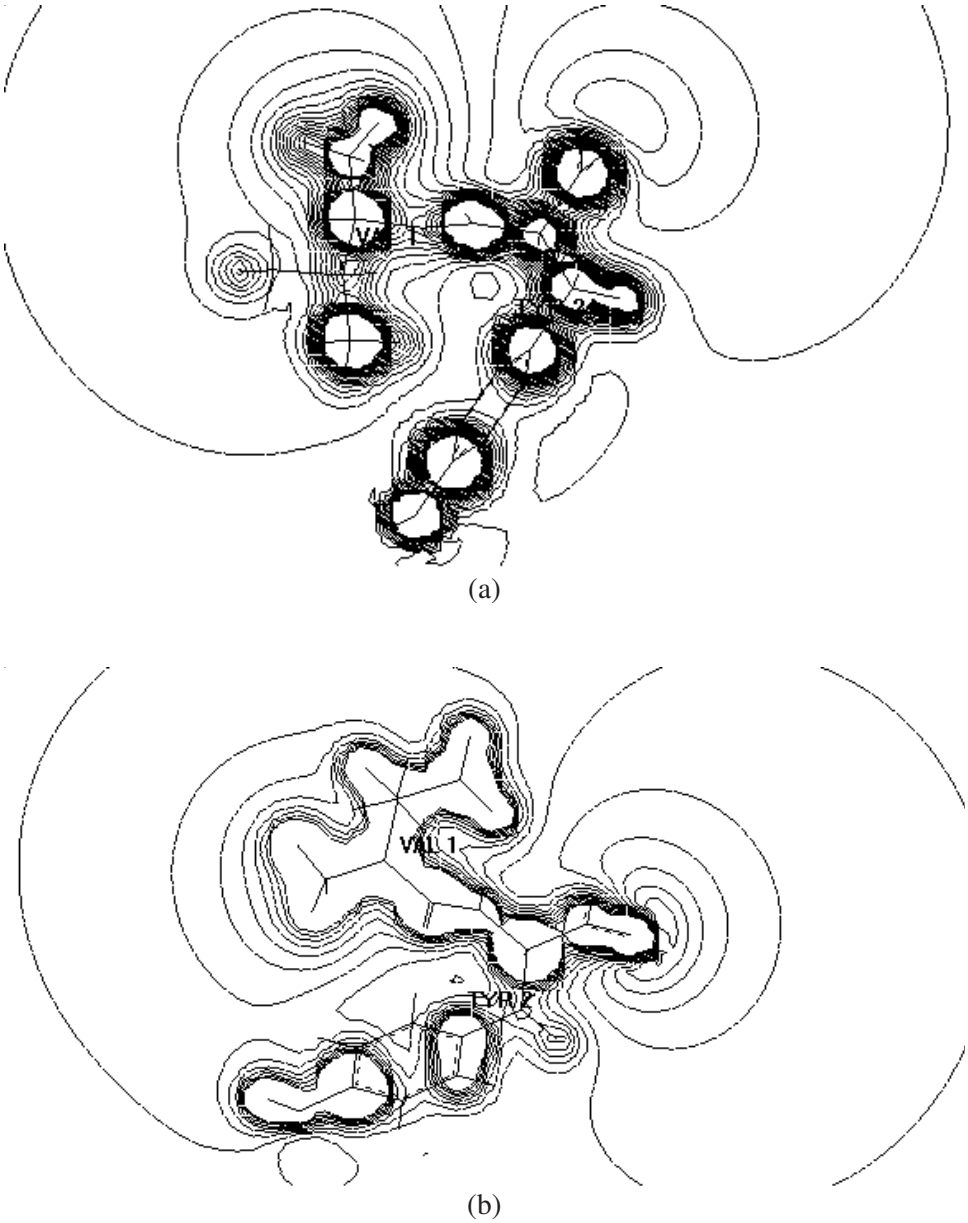
Fig. 1. Optimal folded (a) and extended (b) structures of Val-Tyr dipeptide

The distances from atom CG2 of side chain of Val to atom O of side chain of Tyr are 6.3 and 8.6 Å and the distances between N and C atoms of the opposite terminals of the molecules are 4.7 and 6.0 Å in the optimal folded and extended structures, respectively. The above data demonstrates that the mentioned distances in the optimal folded structure are shorter than those in the optimal extended structure and, thus, favours efficient interactions.

TABLE-2
GEOMETRICAL PARAMETERS (degrees) FOR OPTIMAL FOLDED AND EXTENDED STRUCTURES OF VAL-TYR DIPEPTIDE

Conformation	Angles	
	Val	Tyr
Folded	φ = -153 ψ = -57 ω = 182 χ_1 = 179 χ_2 = 183 χ_3 = 181	φ = -118 ψ = -54 χ_1 = -53 χ_2 = 110 χ_3 = 180
Extended	φ = -80, ψ = 147 ω = 181, χ_1 = 61 χ_2 = 176, χ_3 = 181	φ = -142, ψ = 148 χ_1 = -58, χ_2 = 87 χ_3 = 180

Since each particular conformation is characterized by its own electronic distribution, it was interested to study the electronic structures of the optimal conformations of both shapes and, thus, to try to reveal qualitative and quantitative estimates of their differences. The electronic characteristics of the structures were calculated by the semi-empirical quantum-mechanic method AM1, parameterized for calculating the electronic structures of biopolymers using Program[10] HyperChem 7.5. The calculations were performed in the valence electron approximation. The total number of electrons in the calculation model was 110, pairwise occupied 55 energy levels. The number of considered orbitals was 100. The total charge of the molecule in the ground state was taken to be zero. Self-consistency was attained at the 13-th iteration for both structures. The calculated electronic characteristics are listed in Table-3 and the 2D contours of the electrostatic potential for these structures are illustrated in Fig. 2. As seen from Table-3, the total, binding isolated atomic energies and heat of formation of the mentioned conformations are not different. However, their electronic energies differ appreciably: E_{el} = -603410 and -599284 kcal/mol for folded and extended structures, respectively and the nuclear interaction energies: E_{el} = 526677 and 512550 kcal/mol for folded and extended structures, respectively. The conformational differences cause the electron redistribution and consequently, affect the electron population, the orbital energies and, as result, the effective charges on the atoms. These parameters proved to differ noticeably for the two structures. As seen from Table-4, changes are in the charges of both atoms of the backbone and of the side chains of the amino acids (Table-4). The result can be explained if we take into account the atomic distances; the atoms of the side chains of the two residues in the folded structure are closer with one another and also with the backbone atoms than in the extended structure. The noticeable differences are in the charges of O atoms of the COO^- group, N and H atoms of the backbone chain of the Tyr and HG atoms of the side chain of Val. Small changes take place in the charges of carbon atoms of the side chains of both residues, also in the charges of H atoms of $^+NH_3$ group. As seen from the Table-3 the dipole moment of the folded structure is 3 D lower than that of the extended structure owing to the approach of the charged terminal groups of the molecule.



(a)

(b)

Fig. 2. 2D contours of the electrostatic potential in the optimal folded (a) and extended (b) structures of Val-Tyr dipeptide

Thus, the calculation revealed the differences in electronic structure between the two optimal characteristic conformations of Val-Tyr dipeptide. Probably, the realization of a concrete structure this dipeptide depends on the conditions of interaction with the receptor and also on the polarity of the environment.

TABLE-3
ELECTRONIC CHARACTERISTICS OF THE OPTIMAL FOLDED AND EXTENDED STRUCTURES OF VAL-TYR DIPEPTIDE

Total Energy (kcal/mol)	Binding energy (kcal/mol)	Isolated atomic energy (kcal/mol)	Electronic energy (kcal/mol)	Core-Core interaction energy (kcal/mol)	Heat of formation (kcal/mol)	Dipole moment, debyes (D)
-86733	-3977	-82756	-603410	526677	-79	21
-86733	-3977	-82756	-599284	512550	-79	24

TABLE-4
DISTINGUISH ATOMIC CHARGES IN OPTIMAL FOLDED AND EXTENDED STRUCTURES OF VAL-TYR DIPEPTIDE

Atoms	Folded	Extended
2H (NH_3)	0.247813	0.237651
3H (NH_3)	0.239509	0.247073
C (CO) Val	0.262896	0.271420
O (CO) Val	-0.320516	-0.388686
HA Val	0.162724	0.141488
CB Val	-0.133569	-0.129438
HB Val	0.111983	0.088591
CG1 Val	-0.206504	-0.230031
1HG1 Val	0.125010	0.044290
1HG3 Val	0.087419	0.131973
2HG2 Val	0.091313	0.132914
3HG2 Val	0.045620	0.088218
N (NH) Tyr	-0.309697	-0.283673
H (NH) Tyr	0.213594	0.250234
HA Tyr	0.130631	0.124411
CD1 Tyr	-0.109431	-0.119973
CD2 Tyr	-0.084340	-0.068728
CG2 Tyr	-0.108820	-0.085314
CE1 Tyr	-0.240574	-0.262834
HE1 Tyr	0.122898	0.106283
CE2 Tyr	-0.158187	-0.146927
O (COO^-)	-0.513488	-0.563327
O (COO^-)	-0.571865	-0.515517

Conclusion

In this study, the spatial structure and electronic characteristics of antihypertensive dipeptide, Val-Tyr, which is known an as ACE inhibitory peptide *in vitro*, were investigated. The energy of dipeptide is found to be very sensitive to the conformations of the side chains of the amino acid residues (Val and Tyr). The calculated results indicated that the molecule has such a structural organization which does not exclude the realization of two types of conformation: folded and extended. The calculated electronic characteristics revealed the differences in electronic structure between the two optimal characteristic conformations of Val-Tyr dipeptide.

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