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Conformational Analysis of Cyclo(Tyr-Cys) and Cyclo(Phe-Cys) Dipeptides

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Abstract: In this study, eight possible stable conformers of the Cyclo(Tyr-Cys) and Cyclo(Phe-Cys) dipeptides, which show the most significant inhibition in cervical carcinoma cells opposite to HT-29 and MCF-7 cells, performed depending on the obtained conformational analysis. The possible stable geometries were determined with the aid of φ, Ψ backbone and χ chain dihedral angles. Available all conformers and their energies were calculated and made comparison with the quantum chemical ab-initio results. The Van der Waals, electrostatic , torsional , interaction energies between side and main chains of aminoacids and total energies of cysteine containing dipeptides were computed by using Fortran program.

Cyclo(Tyr-Cys) ve Cyclo(Phe-Cys) Dipeptitlerinin Konformasyon Analizi

Anahtar Kelimeler
Halka dipeptitler, Konformasyon analizi, DFT

Özet: Bu çalışmada HT-29 ve MCF-7 hücrelerine karşı servikal kanser hücrelerinde önemli antikanser etki gösteren Cyclo(Tyr-Cys) ve Cyclo(Phe-Cys) dipeptitlerinin olası sekiz kararlı konformasyonu konformasyon analizine bağlı olarak elde edilmiştir. Olası kararlı geometriler φ, Ψ ana zincir ve χ yan zincir dihedral açılarının yardımıyla belirlenmiştir. Mevcut tüm konformerler ve onların enerjileri hesaplanmıştır ve kuantum kimyasal ab-inito sonuçlarla karşılaştırılmıştır. Sistein içeren dipeptitlerin Van der Waals, elektrostatik, torsiyonal, yan ve ana zincirleri arasındaki etkileşme enerjileri ve toplam enerjileri Fortran programı kullanılarak hesaplanmıştır.

1. Introduction

Cyclic peptides, which are consisted of diketopiperazines, are extensively used as an antibiotics, toxins, hormones thanks to their anti-tumor, antibacterial and antifungal characteristics [1]. The structural rigidity, biochemical stability, cytotoxic and antithrombotic features of cyclic peptides enable target cancer cell without damaging normal cells [2] made them possible to use in cancer therapy [3-5]. The cyclic peptides which are used as targeting ligands have also been achieved when tested on various cancer therapy such as **breast** [6]**, colon** [7] and **prostate cancers** [8].

Cysteine-containing dipeptides that have thiol (-SH) group in side chain are also potential anticancer factors against **HeLa** (cervical carcinoma), **HT-29** (colon carcinoma) and **MCF-7**(breast carcinoma) [9].

Their spatial structures and the full of low-energy conformational states should be known to understand the anticancer function. Conformational possibilities of cysteine-containing dipeptides have not been studied in the literature. Theoretical conformational analysis method, which is made up of Molecular Mechanics approach, is essential conformational compatibility. This method utilizes Ramanchandran maps (φ, Ψ backbone and χ chain dihedral angles) and identifies possible stable conformation energies with structural geometry. The aim of this study is to determine the structural geometry with energies (Van der Waals, electrostatic, torsional interaction energies) and made comparison with the quantum chemical ab-initio results of eight conformers of two cysteine-containing dipeptides (cyclo(tyr-cys) and cyclo(phe-cys)). The present study introduces comprehensive investigations of structural geometry of anticancer peptide molecules.

2. Method

Stable conformers of cyclic dipeptides were determined by using theoretical conformational analysis following DFT calculations. This computational method calculates all nonbonded interactions of molecular system. This method consists of nonbonded and electrostatic interactions,

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intramolecular hydrogen bonds, and limited rotation about single bonds of side chains. The Lennard-Jones potential was used to calculate non bonded interactions with output proposed by Scott and Scheraga[10]. Electrostatic energy was computed in a monopole approximation with consist of atom centered charges[10]. Torsional potential and barrier energies which were about to rotate side chain bonds were given by Scheraga[11]. Bonding lengths, angles and dihedrals are taken as suggested by Corey and Pauling [11], and are kept stable; peptide bond angle was taken 180°. Conformational analysis of the cyclic dipeptides was determined, by using program proposed by Godjayev et al.[12]. To investigate the orientation of side chains within the possible conformations with low energy which are acquired by using theoretical conformational analysis, the conformational maps were obtained around the χ dihedral angles of Tyr,Phe,Cys residues. The conformation of cyclo(tyr-cys) and cyclo(phe-cys) dipeptides with lowest energy were optimized and the mulliken charges of optimized geometry were computed by using DFT/B3LYP/ 6-31++G(d,p) [13,14].

3. Results and Discussion

3.1. Cyclo(tyr-cys)

Corey, Degeilh and Dorset found crystal structure of diketopiperazine (DKP) [15-17]. The investigators found DKP ring with a planar geometry.Thus in our investigation, we have supposed the DKP ring is planar. Energy of conformations for cyclo(tyr-cys) was calculated as a function of χ_{11}, χ_{12}, χ_{13}, χ_{21} and χ_{22}. Dihedral angles of the eight possible stable conformations before and after energy optimization and relative energies are showed in Table 1. The possible eight conformers which have low energy are demonstrated in Figure 1. The most stable structure is obtained by near χ_{11}=60°, χ_{13}=180°, χ_{21}=-60° and χ_{22}=180°. Figure 2. shows charge distribution of lowest energy conformation of cyclo(Tyr–Cys) dipeptide. Van der Waals, electrostatic, torsional and total energies of the conformers are given Table 2. Interaction energies between side and main chains of aminoacids are calculated and presented in Table 3.

Table 1. Total energy(kcal/mol) and geometrical parameters of the stable calculated conformations of Cyclo(Tyr-Cys)

NO		Dihedral angles of side chain for Tyr and Cys					E_{total}	$E_{rel.}$
		X_{11}	X_{12}	X_{13}	X_{21}	X_{22}		
1	IN	60	-90	180	-60	180	-2.9	0
	OUT	64.8	-0.4	196.6	-65.3	180		
2	IN	60	90	180	-60	60	-2.89	0.01
	OUT	65.3	179.8	197.7	-63.2	60		
3	IN	-60	-90	180	-60	60	-2.32	0.58
	OUT	-115.2	-0.3	74.2	-63	60		
4	IN	180	-90	180	-60	60	-2.31	0.59
	OUT	245.3	-0.2	74.5	-67.3	60		
5	IN	180	-90	60	-60	60	-2.14	0.76
	OUT	244.1	-0.4	66.9	-18	60		
6	IN	-60	-90	60	-60	60	-2.12	0.78
	OUT	-116.8	-0.3	67.2	-17.4	60		
7	IN	60	-90	-60	60	60	-1.93	0.97
	OUT	65.2	-0.5	-50.7	82.1	60		
8	IN	180	-90	-60	60	60	-1.92	0.98
	OUT	245.7	-0.5	-51.6	83.1	60		

Table 2. Energetical parameters(kcal/mol) of the stable calculated conformations of Cyclo(Tyr-Cys)

NO	Evwalls	Eelec.	Etor.	E_{total}	$E_{relative}$
1	-2.1	-0.98	0.18	**-2.9**	**0**
2	-2.15	-0.93	0.2	**-2.89**	**0.01**
3	-1.5	-0.95	0.13	**-2.32**	**0.58**
4	-1.49	-0.95	0.14	**-2.31**	**0.59**
5	-1.21	-0.96	0.03	**-2.14**	**0.76**
6	-1.19	-0.96	0.04	**-2.12**	**0.78**
7	-1.02	-0.96	0.06	**-1.93**	**0.97**
8	-1.01	-0.96	0.05	**-1.92**	**0.98**

Table 3. Interaction energies (kcal/mol) between side and main chains of aminoacids.

NO	E_{total}	$E_{relative}$	Tyr side Tyr side	Cys side Cys side	Tyr side Tyr main	Cys main Tyr side	Cys side Cys main	Cys side Tyr side	Cys side Tyr main
1	-2.9	0	1.01	-0.09	-1.29	-0.28	-1.5	-0.04	-0.89
2	-2.89	0.01	1.04	-0.1	-1.29	-0.28	-1.54	-0.04	-0.89
3	-2.32	0.58	1.01	-0.1	-1.28	-0.27	-0.6	-0.24	-0.97
4	-2.31	0.59	1.01	-0.09	-1.28	-0.28	-0.6	-0.23	-0.97
5	-2.14	0.76	1.01	-0.08	-1.28	-0.27	-0.26	-0.23	-1.07
6	-2.12	0.78	1.01	-0.8	-1.26	-0.28	-0.26	-0.22	-1.07
7	-1.93	0.97	1.01	-0.8	-1.29	-0.28	-0.39	-0.06	-0.9
8	-1.92	0.98	1.01	-0.8	-1.28	-0.28	-0.38	-0.06	-0.9

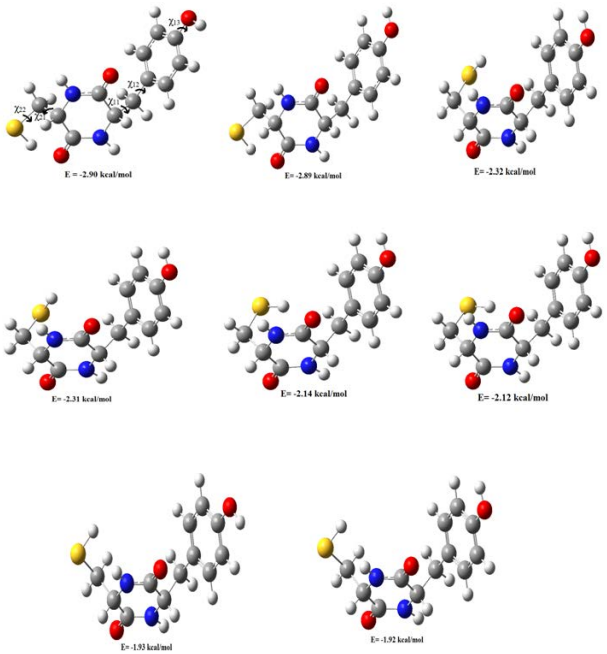

Figure 1. The possible eight conformers with low energy of Cyclo(Tyr-Cys)

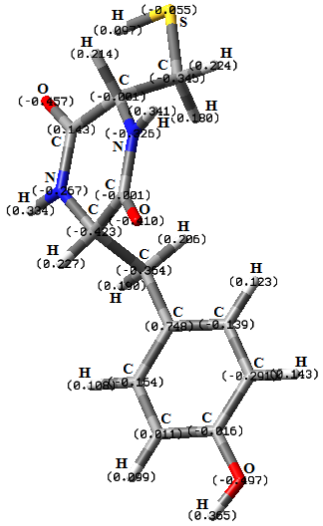

Figure 2. Charge distribution using B3LYP 6-31++G(d,p) for the cyclo(Tyr-Cys) molecule

3.2. Cyclo(phe-cys)

To determine the action of the side chains within the energy , specific geometry was get the conformational maps around dihedral angles χ_{11}, χ_{12} and χ_{21}, χ_{22} for Phe and Cys residue, respectively. The dihedral angles were calculated as initial value parameters for minimization. The minimization results which were obtained by changing of dihedral angles were given in Table 4.

Dihedral angles of eight conformers for cyclo(phe-cys) determined as 1 (χ_{11}=180°, χ_{12}=90° and χ_{21}= -60° , χ_{22}= 60°), 2 (χ_{11}=60°, χ_{12}=90° and χ_{21}= -60° , χ_{22}= 60°), 3 (χ_{11}=60°, χ_{12}=90° and χ_{21}= 60° , χ_{22}= 60°), 4 (χ_{11}=180°, χ_{12}=90° and χ_{21}= 60° , χ_{22}= 60°), 5(χ_{11}=-60°, χ_{12}=90° and χ_{21}= 180° , χ_{22}= 60°), 6 (χ_{11}=60°, χ_{12}=90° and χ_{21}= 180° , χ_{22}= 60°),7 (χ_{11}=180°, χ_{12}= -90° and χ_{21}= 60° , χ_{22}= 60°) and 8 (χ_{11}=60°, χ_{12}= -90° and χ_{21}= 60° , χ_{22}= 60°) have an comparable relative energy 0, 0.03, 0.20, 0.21, 0.45, 0.46, 0.5 and 0.51 kcal/mol, respectively.

The eight conformers with lowest energy are given in Figure 3. The atomic charge of conformation which has the lowest energy of cyclo(Phe-Cys) dipeptide is demonstrated in Figure 4. Table 5 shows the energy of Van der Waals, electrostatic interaction, torsion potential of all possible conformers.

Table 6 demonstrates the calculated energies between side and main chains of aminoacids.

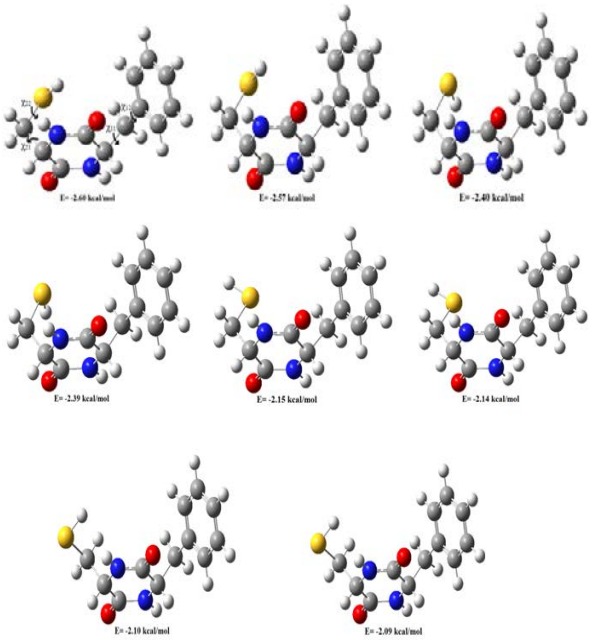

Figure 3. The possible eight conformers with low energy of Cyclo(Phe-Cys)

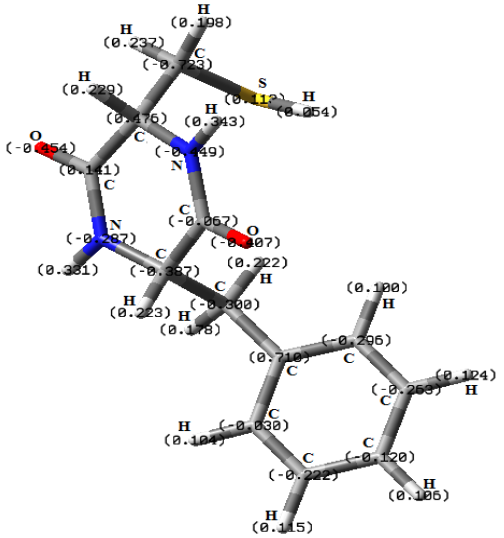

Figure 4. Charge distribution using DFT/B3LYP 6-31++G (d,p) for the cyclo(Phe-Cys) molecule

Table 4. Total energy (kcal/mol) and geometrical parameters of the stable calculated conformations of Cyclo (Phe-Cys)

NO		Dihedral angles of side chain for Phe and Cys				E_{total}	$E_{rel.}$
		X_{11}	X_{12}	X_{21}	X_{22}		
1	IN	180	90	-60	60	**-2.6**	**0**
	OUT	246.3	71.8	-57.3	60		
2	IN	60	90	-60	60	**-2.57**	**0.03**
	OUT	66.6	71.9	-61.3	60		
3	IN	60	90	60	60	**-2.4**	**0.2**
	OUT	66.1	71.6	76.4	60		
4	IN	180	90	60	60	**-2.39**	**0.21**
	OUT	245.8	71.3	81.6	60		
5	IN	-60	90	180	60	**-2.15**	**0.45**
	OUT	-115.1	70.7	179.8	60		
6	IN	60	90	180	60	**-2.14**	**0.46**
	OUT	66.4	72.1	179.8	59.9		
7	IN	180	-90	60	60	**-2.1**	**0.5**
	OUT	244.4	-52.4	77.6	60		
8	IN	60	-90	60	60	**-2.09**	**0.51**
	OUT	65	-53.5	76.5	60		

Table 5. Energetical parameters(kcal/mol) of the stable calculated conformations of Cyclo(Phe-Cys)

NO	Evwalls	Eelec.	Etor.	E_{total}	$E_{relative}$
1	-2.63	-0.06	0.09	**-2.6**	**0**
2	-2.61	-0.06	0.09	**-2.57**	**0.03**
3	-2.43	-0.06	0.09	**-2.4**	**0.2**
4	-2.44	-0.06	0.11	**-2.39**	**0.21**
5	-2.17	-0.06	0.08	**-2.15**	**0.45**
6	-2.18	-0.06	0.1	**-2.14**	**0.46**
7	-2.08	-0.06	0.04	**-2.1**	**0.5**
8	-2.06	-0.06	0.03	**-2.09**	**0.51**

Table 6. Interaction energies(kcal/mol) between side and main chains of aminoacids.

NO	E_{total}	$E_{relative}$	Phe side Phe side	Cys side Cys side	Phe side Phe main	Cys main Phe side	Cys side Cys main	Cys side Phe side	Cys side Phe main
1	-2.6	0	-0,18	-0,1	-0,91	-0,26	-0,5	-0,32	-0,43
2	-2.57	0.03	-0,18	-0,1	-0,91	-0,26	-0,51	-0,3	-0,42
3	-2.4	0.2	-0,18	-0,09	-0,92	-0,26	-0,49	-0,17	-0,39
4	-2.39	0.21	-0,18	-0,08	-0,92	-0,25	-0,53	-0,16	-0,38
5	-2.15	0.45	-0,17	-0,14	-0,92	-0,25	-0,32	-0,13	-0,29
6	-2.14	0.46	-0,18	-0,14	-0,91	-0,26	-0,34	-0,13	-0,29
7	-2.1	0.5	-0,17	-0,09	-0,92	-0,25	-0,26	-0,11	-0,34
8	-2.09	0.51	-0,17	-0,09	-0,92	-0,25	-0,23	-0,11	-0,34

When the orientation of the side chains in these two dipeptides was investigated in theoretical conformational analysis, it is seen that these side chains approached to each other in stable conformation of Cyclo(Phe-Cys) (folded form) and moved away from each other in Cyclo(Tyr–Cys) (extended form). The powerful interaction on global conformation for Cyclo(Tyr–Cys) was Van der Waals interaction with -2.10 kcal/mol and this interaction for Cyclo(Phe-Cys) was calculated -2.63 kcal/mol. The electrostatic interaction is less effective for global conformation. The calculated values are -0.98 kcal/mol and -0.06 kcal/mol for Cyclo(Tyr–Cys) and Cyclo(Phe-Cys), respectively.

A hydrogen bond between the hydrogen atom of the Cys side chain and the oxygen atom of the diketopiperazines ensure stable conformation of the dipeptide. The hydrogen atom in the Cys side chain for Cyclo(Phe-Cys) rotated reverse direction in accordance with oxygen atom of the diketopiperazine group, therefor not consist of intra-hydrogen bond. As we can see side chains interactions for Cyclo(Tyr–Cys) and Cyclo(Phe-Cys), Cys side and main chain interaction was calculated -1.50 kcal/mol and -0.50 kcal/mol.

In conclusion, the conformational analysis of both dipeptides which was evaluated and the conformation which has the acquired lowest energy were optimized by using Gaussian program consists of DFT-B3LYP/6-31++G(d,p) method. The molecular structures which were obtained from quantum chemical calculation and theoretical conformational analysis of both cyclic dipeptides were given comparatively in Figure 5-6.

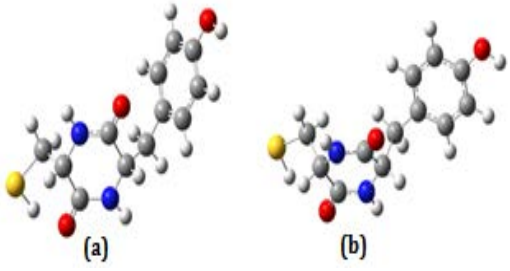

Figure 5. Comparison of theoretical conformational analysis (a) and DFT/B3LYP 6-31++G(d,p) (b) optimized results of cyclo(Tyr-Cys)

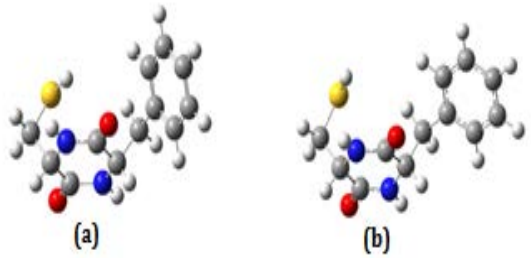

Figure 6. Comparison of theoretical conformational analysis (a) and DFT/B3LYP 6-31++G(d,p) (b) optimized results of cyclo(Phe-Cys)

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