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Conformational Analysis of Tyrosyl-Lysyl-Threonine Tripeptide Using MM, MD and QM Methods and Its Hyperpolarizability Study

Bilge BIÇAK*[1], Serda KECEL GÜNDÜZ[1]

Abstract

Peptides are important structures that offer important opportunities for therapeutic interventions in various diseases. Tyrosyl-Lysyl-Threonine is an important peptide structure that contains the antiviral, antioxidant, and anticancer properties of the amino acids in its structure. Examination of the conformational structure, which has great importance on both the ability of the molecule to fulfill its biological functions and electronic properties, is important for molecular studies. In this study, the determination of the stable conformations and optimization of the most stable structure of the Tyrosyl-Lysyl-Threonine molecule was carried out using molecular mechanical and quantum mechanical methods. With molecular dynamics simulation studies, the changes in conformational structure, RMSD, and Rg values in different environments were monitored for 10 ns. Additionally, the hyperpolarizability study of Tyrosyl-Lysyl-Threonine was carried out. As a result of this study, it was aimed to determine the optimized geometry of the tripeptide, its conformational changes, and nonlinear optical properties.

Keywords: Peptide, conformational analysis, hyperpolarizability

1. INTRODUCTION

Peptides are important structures that can be used as therapeutic compounds in the medicinal studies of diseases. Peptides that can trigger various biological activities such as anticancer, anti-inflammatory, immunomodulator, antidiabetic [1-4], are accepted internationally due to their therapeutic effects and are used effectively in different disease areas [5].

Tyrosyl-Lysyl-Threonine (YKT or Tyr-Lys-Thr) has $C_{19}H_{30}N_4O_6$ formula and 410.47 relative molecular mass. Structures containing tyrosine are neurotransmitter precursors [6,7] with the ability to increase the levels of plasma neurotransmitters. It also exhibits antioxidant properties [8,9]. Structures containing lysine also have antiviral effects as well as antioxidant properties like tyrosine [9,10]. In addition, it has been seen in studies in the literature that poly-lysine structures have antimicrobial, and antitumor properties [11]. It is known that

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structures containing threonine also have antibacterial properties [12], and support cardiovascular, hepatic, central nervous, and immune system functions. It has an important role in inhibiting apoptosis, synthesizing mucin, and maintaining the integrity of the intestinal barrier [13-15]. It is also an essential molecule for the synthesis of glycine and serine amino acids, which are important in collagen, elastin, and muscle tissue production [16]. Tyr-Lys dipeptide is an important peptide structure that has analgesic effects [17], and induces necrosis [18,19]. Considering both experimental and theoretical studies performed with Tyr-Lys-Thr, it was determined that Tyr-Lys-Thr tripeptide has a cytotoxic effect on prostate, breast and cervical cancer cells (Mat-LyLu, MCF-7, and HeLa cell lines) and has an anti-cancer potential in vitro studies. In molecular docking studies, it was determined that it made strong bindings with androgen, estrogen, progesterone, and EGFR receptors, supporting the experimental studies [20-22].

The conformations, which are of great importance in the estimation of biological activity and physicochemical properties of Tyr-Lys-Thr tripeptide with drug potential, were determined in this study. Different conformations of the tripeptide were investigated in depth by MM, MD and QM methods. Theoretical conformational analysis, optimization, molecular dynamics simulations and hyperpolarizability studies were realized to determine and evaluate the structural properties of YKT tripeptide.

2. MATERIAL METHODS

2.1. Theoretical Conformational Analysis

The conformational analysis of YKT tripeptide was realized with FORTRAN program [23]. The conformations having low energies of tripeptide were obtained with the help of the Ramachandran maps [24,25]. The conformational potential energies of YKT were obtained as the sum of Van der Waals, electrostatic, torsional, and hydrogen bond energies. The most stable conformation determined was accepted as the first data for geometry optimization performed by DFT method.

2.2. Optimization and Hyperpolarizability Analyses

Optimization in molecules provides to obtain a well-arranged structure by minimizing system energy. Different molecular geometries due to the arrays of atoms and the binding energies of the bonds affect the behavior of molecules (physical, chemical) [26]. Nonlinear-optical properties are important in the optoelectronic and laser technology areas [27]. The hyperpolarizability study of YKT tripeptide was achieved to predict the nonlinear-optical property. The optimization and hyperpolarizability studies of YKT were carried out using Gaussian09 software program [28] with the density functional theory method at B3LYP theory level and 6-311++G(d,p) basis set.

2.3. MD Analysis

The molecular dynamics (MD) simulations were carried out in the vacuum, water, and methanol environments for 10 ns using GROMOS96 43a1 force field [29] by GROningen MAchine for Chemical Simulations (GROMACS) software [30] to investigate the conformational change on the optimized structure. Before the MD production runs, further energy minimization calculations of the solvated systems were carried out and the systems were equilibrated with the help of NVT (for 50 ps) and NPT (for 500 ps) ensembles, employing the V-rescale thermostat [31] and the isotropic Parrinello-Rahman barostat [32] at 310 K and 1 bar. Only a simulation in an NVT ensemble was done for the vacuum medium for 100 ps. Molecular Dynamics (MD) simulations were conducted with 2 fs time steps and periodic boundary conditions. Root Mean Square Deviation (RMSD), Radius of Gyration (Rg), and H-bond information were obtained from the 10ns-long simulations.

YKT tripeptide was placed in the box and was adjusted as 3 x 3 x 3 nm. The cubic boxes were filled with 1061 moles of SPC (simple point charge) type water and 525 moles of methanol for solvent-containing environments. Na^+ and Cl^-

ions were included in the water and methanol systems to neutralize the systems. Energy minimization calculations using the steepest-descent algorithm were completed in 59 steps (for vacuum), 172 steps (for water), and 113 steps (for methanol). The NVT studies were carried out for 25,000 (for vacuum) and 50,000 (for water and methanol) steps with a 2-femtosecond time. For water and methanol environments, the NPT studies were realized for 250,000 steps with a 2 femtoseconds time. MD simulations were achieved for 5,000,000 steps with a 2 femtoseconds time in all environments.

Obtained graphics were plotted by Xmgrace plotting tool [33]. Images of conformational changes during 10 ns were obtained with VMD program [34].

3. RESULT AND DISCUSSION

3.1. Theoretical Conformational Analysis Result

The determination of the stable conformations of the YKT tripeptide was first started by performing the theoretical conformation analysis with the FORTRAN program. With this analysis, stable conformations of the tripeptide were tried to be determined. In the theoretical conformation analysis, the atoms forming the peptide, bond lengths, angles, angle values, and charge information were entered into the input file. The possible conformations and the energy values of these conformations were obtained by entering the dihedral angle values of the conformation regions with the help of the conformation regions formed by Ramachandran of the amino acids that make up the peptide (cf. Figure 1). 105462 conformations of YKT tripeptide were examined and it was observed that the conformation with the lowest energy was in the BBB (B1B3B1) region and had an energy value of 6.37 kcal/mol (cf. Table 1). While Van der Waals energy contributed the most to this energy value with -11.34 kcal/mol, the electrostatic and torsion energy values contributing to the total energy were calculated as 15.63 kcal/mol and 2.08 kcal/mol, respectively. When the most stable geometry was examined, it was seen that the biggest changes were in the χ_{13} (OH region in tyrosine side chain), φ_2 (between amino and Cα in lysine), and χ_{21} (between C_α and side chain in lysine) regions. When the input and output torsional angles were compared, it was seen that the biggest change was in the χ_{13} changed from -60.000 to -1.950 (cf. Table 2). The other changes were from 180.000 to 200.667 for χ_{21} and from -120.000 to -101.809 for φ_2.

Table 1 For the Tyr-Lys-Thr tripeptide, the conformation numbers examined for all conformation regions and the conformation region with the minimum energy (global energy)

Conformational Regions	Conformation numbers	Global energy (kcal/mol)
BBB	*13122*	***6.37***
BBR	*13122*	*6.99*
BRB	*13122*	*8.38*
BRL	*486*	*12.04*
BRR	*13122*	*9.21*
RRB	*13122*	*8.90*
RRR	*13122*	*9.53*
RBB	*13122*	*7.25*
RBR	*13122*	*8.08*
	Total: 105462	

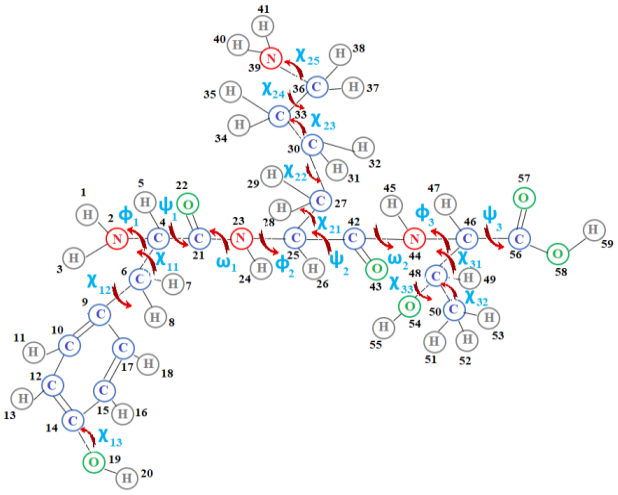

Figure 1 The structure of YKT

Table 2 For the Tyr-Lys-Thr tripeptide, the conformation numbers examined for all conformation regions and the conformation region with the minimum energy (global energy)

Angles (Y)	PHI_1	CH_{11}	CH_{12}	CH_{13}	PSI_1	W_2
In	-115.0	180.00	-90.00	-60.0	160.00	180.00
Out	-117.045	179.449	-98.51	-1.95	149.699	181.981

Ang. (K)	PHI_2	CH_{21}	CH_{22}	CH_{23}	CH_{24}	CH_{25}	PSI_2	W_3
In	-120.0	180.0	-60.0	180.0	180.0	180.0	100.0	180.0
Out	-101.809	200.667	-61.846	188.926	183.543	177.249	107.552	181.429

Ang. (T)	PHI_3	CH_{21}	CH_{22}	CH_{23}	PSI_2
In	-100.00	60.000	180.000	180.000	150.00
Out	-83.190	57.482	182.432	177.413	136.429

3.2. Optimization

Tyrosyl-Lysyl-Threonine (Tyr-Lys-Thr) tripeptide consists of 59 atoms and contains three different amino acids that are polar (tyr,thr) and positively charged (lys). The determined stable conformation with 6.37 kcal/mol energy obtained by Theoretical Conformation Analysis was introduced to the Gaussian09 program, and the optimization study was achieved using the DFT-B3LYP theory level and 6-311++G(d,p) basis set. The non-optimized (Figure 2a) and optimized (Figure 2b) geometries of YKT tripeptide were shown in Figure 2 with the names and numbers of the atoms and the energy values of the optimized geometry of YKT were given in Table 3. The parameters belonging to the bonds, angles, and dihedrals of the YKT tripeptide were obtained by Gaussian09 package program and given in Tables 4, 5, and 6. The bond lengths in the molecule structure take values from 0.96 Å to 1.56 Å. It was found that two of the peptide bonds in the tripeptide had a value of about 1.36 Å.

Table 3 The energy values of optimized geometry of YKT tripeptide

DFT/B3LYP		
Monomer	**Energy (a.u.)**	**Energy (kcal/mol)**
6-311++ G (d,p)	-1412.91298118	-886616.471001598

Table 4 Optimized bond lengths (Å) values of the Tyr-Lys-Thr tripeptide

Bond	**6-311++G(d,p)**
H1-N2	1.0134
N2-H3	1.016
N2-C4	1.4579
C4-H5	1.096
C4-C6	1.5642
C4-C21	1.5373
C6-H7	1.0953
C6-H8	1.0944
C6-C9	1.5121
C9-C10	1.3973
C9-C17	1.4026
C10-H11	1.0838
C10-C12	1.3928
C12-H13	1.0856
C12-C14	1.394
C14-C15	1.396
C14-O19	1.3697
C15-H16	1.0834
C15-C17	1.3902
C17-H18	1.086
O19-H20	0.963
C21-O22	1.2282
C21-N23	1.3555
N23-H24	1.0097
N23-C25	1.4659
C25-H26	1.0932
C25-C27	1.5377
C25-C42	1.5472
C27-H28	1.0951
C27-H29	1.0951
C27-C30	1.5376
C30-H31	1.098
C30-H32	1.0966
C30-C33	1.533
C33-H34	1.0973
C33-H35	1.0932
C33-C36	1.5364
C36-H37	1.0961
C36-H38	1.0962
C36-N39	1.4661
N39-H40	1.0156
N39-H41	1.0165
C42-O43	1.2236

C42-N44	1.3584
N44-H45	1.0105
N44-C46	1.4426
C46-H47	1.0934
C46-C48	1.5421
C46-C56	1.5337
C48-H49	1.0953
C48-C50	1.5247
C48-O54	1.4341
C50-H51	1.0948
C50-H52	1.0938
C50-H53	1.0918
O54-H55	0.9623
C56-O57	1.202
C56-O58	1.3543
O58-H59	0.9691

Table 5 Optimized angle values (degrees) of the Tyr-Lys-Thr tripeptide

Angle	**6-311++G(d,p)**
H1-N2-H3	109.0402
H1-N2-C4	111.5289
H3-N2-C4	109.6419
N2-C4-H5	108.7168
N2-C4-C6	114.1771
N2-C4-C21	106.7859
H5-C4-C6	107.497
H5-C4-C21	108.6947
C6-C4-C21	110.8524
C4-C6-H7	106.2763
C4-C6-H8	108.6473
C4-C6-C9	114.9046
H7-C6-H8	106.6946
H7-C6-C9	108.9465
H8-C6-C9	110.963
C6-C9-C10	121.8126
C6-C9-C17	120.5854
C10-C9-C17	117.5767
C9-C10-H11	119.9932
C9-C10-C12	121.5093
H11-C10-C12	118.4907
C10-C12-H13	119.7226
C10-C12-C14	119.8385
H13-C12-C14	120.4301
C12-C14-C15	119.7762
C12-C14-O19	122.7269
C15-C14-O19	117.4969
C14-C15-H16	119.1497
C14-C15-C17	119.6097
H16-C15-C17	121.2404
C9-C17-C15	121.688
C9-C17-H18	119.5106
C15-C17-H18	118.799
C14-O19-H20	109.6253
C4-C21-O22	121.1574
C4-C21-N23	116.4264
O22-C21-N23	122.4161
C21-N23-H24	118.9176
C21-N23-C25	122.6811
H24-N23-C25	118.0877
N23-C25-H26	106.467
N23-C25-C27	109.2816
N23-C25-C42	109.4584
H26-C25-C27	109.7535
H26-C25-C42	109.3118
C27-C25-C42	112.3924
C25-C27-H28	106.7791
C25-C27-H29	108.5171
C25-C27-C30	115.3374
H28-C27-H29	107.4238
H28-C27-C30	108.1394
H29-C27-C30	110.3151
C27-C30-H31	108.879
C27-C30-H32	107.4403
C27-C30-C33	115.969
H31-C30-H32	105.7544
H31-C30-C33	109.4353
H32-C30-C33	108.8686
C30-C33-H34	109.536
C30-C33-H35	110.6931
C30-C33-C36	112.9308
H34-C33-H35	106.462
H34-C33-C36	109.3515
H35-C33-C36	107.6457
C33-C36-H37	109.2229
C33-C36-H38	110.01
C33-C36-N39	115.5531
H37-C36-H38	106.1393
H37-C36-N39	107.5508
H38-C36-N39	107.9313
C36-N39-H40	110.4995
C36-N39-H41	109.9592
H40-N39-H41	106.7414
C25-C42-O43	121.7987
C25-C42-N44	114.8015
O43-C42-N44	123.3873
C42-N44-H45	119.5286
C42-N44-C46	122.8268
H45-N44-C46	117.3628
N44-C46-H47	107.8202
N44-C46-C48	111.2584
N44-C46-C56	111.3009
H47-C46-C48	108.8582
H47-C46-C56	106.4297
C48-C46-C56	110.974
C46-C48-H49	107.3631
C46-C48-C50	112.9346
C46-C48-O54	104.9393
H49-C48-C50	109.8307
H49-C48-O54	109.5859
C50-C48-O54	111.9751
C48-C50-H51	109.8952
C48-C50-H52	110.5358
C48-C50-H53	111.162
H51-C50-H52	107.3302

H51-C50-H53	108.5576
H52-C50-H53	109.2601
C48-O54-H55	109.363
C46-C56-O57	126.2832
C46-C56-O58	110.6868
O57-C56-O58	123.0141
C56-O58-H59	107.3715

Table 6 Optimized dihedral values (degrees) of the Tyr-Lys-Thr tripeptide

Dihedral	**6-311++G(d,p)**
H1-N2-C4-H5	-83.5707
H1-N2-C4-C6	36.4338
H1-N2-C4-C21	159.3202
H3-N2-C4-H5	155.5545
H3-N2-C4-C6	-84.4409
H3-N2-C4-C21	38.4455
N2-C4-C6-H7	-43.5887
N2-C4-C6-H8	70.8911
N2-C4-C6-C9	-164.151
H5-C4-C6-H7	77.0972
H5-C4-C6-H8	-168.423
H5-C4-C6-C9	-43.4652
C21-C4-C6-H7	-164.2365
C21-C4-C6-H8	-49.7566
C21-C4-C6-C9	75.2012
N2-C4-C21-O22	-34.3865
N2-C4-C21-N23	145.6829
H5-C4-C21-O22	-151.5101
H5-C4-C21-N23	28.5593
C6-C4-C21-O22	90.5503
C6-C4-C21-N23	-89.3803
C4-C6-C9-C10	-94.5552
C4-C6-C9-C17	83.5711
H7-C6-C9-C10	146.3614
H7-C6-C9-C17	-35.5124
H8-C6-C9-C10	29.1822
H8-C6-C9-C17	-152.6915
C6-C9-C10-H11	-1.274
C6-C9-C10-C12	177.7612
C17-C9-C10-H11	-179.4542
C17-C9-C10-C12	-0.419
C6-C9-C17-C15	-178.0405
C6-C9-C17-H18	2.5285
C10-C9-C17-C15	0.1632
C10-C9-C17-H18	-179.2679
C9-C10-C12-H13	-178.6091
C9-C10-C12-C14	0.3171
H11-C10-C12-H13	0.4401
H11-C10-C12-C14	179.3663
C10-C12-C14-C15	0.0522
C10-C12-C14-O19	-179.9301
H13-C12-C14-C15	178.9707
H13-C12-C14-O19	-1.0116
C12-C14-C15-H16	179.5174
C12-C14-C15-C17	-0.3013
O19-C14-C15-H16	-0.4994
O19-C14-C15-C17	179.6819
C12-C14-O19-H20	1.2508
C15-C14-O19-H20	-178.7318
C14-C15-C17-C9	0.1927
C14-C15-C17-H18	179.6277
H16-C15-C17-C9	-179.6222
H16-C15-C17-H18	-0.1872
C4-C21-N23-H24	7.678
C4-C21-N23-C25	-178.88
O22-C21-N23-H24	-172.2517
O22-C21-N23-C25	1.1903
C21-N23-C25-H26	39.6895
C21-N23-C25-C27	158.1649
C21-N23-C25-C42	-78.3561
H24-N23-C25-H26	-146.8169
H24-N23-C25-C27	-28.3415
H24-N23-C25-C42	95.1375
N23-C25-C27-H28	-39.5693
N23-C25-C27-H29	75.95
N23-C25-C27-C30	-159.7383
H26-C25-C27-H28	76.8356
H26-C25-C27-H29	-167.6451
H26-C25-C27-C30	-43.3334
C42-C25-C27-H28	-161.2939
C42-C25-C27-H29	-45.7746
C42-C25-C27-C30	78.5371
N23-C25-C42-O43	-74.6105
N23-C25-C42-N44	104.145
H26-C25-C42-O43	169.1347
H26-C25-C42-N44	-12.1098
C27-C25-C42-O43	47.0134
C27-C25-C42-N44	-134.2311
C25-C27-C30-H31	54.8175
C25-C27-C30-H32	168.9098
C25-C27-C30-C33	-69.0804
H28-C27-C30-H31	-64.6043
H28-C27-C30-H32	49.4881
H28-C27-C30-C33	171.4978
H29-C27-C30-H31	178.1839
H29-C27-C30-H32	-67.7238
H29-C27-C30-C33	54.286
C27-C30-C33-H34	-56.4681
C27-C30-C33-H35	60.6261
C27-C30-C33-C36	-178.6009
H31-C30-C33-H34	179.9232
H31-C30-C33-H35	-62.9826
H31-C30-C33-C36	57.7904
H32-C30-C33-H34	64.7812
H32-C30-C33-H35	-178.1245
H32-C30-C33-C36	-57.3515
C30-C33-C36-H37	-55.8643
C30-C33-C36-H38	60.2574
C30-C33-C36-N39	-177.243
H34-C33-C36-H37	-178.1006
H34-C33-C36-H38	-61.9788
H34-C33-C36-N39	60.5208
H35-C33-C36-H37	66.6287
H35-C33-C36-H38	-177.2495

H35-C33-C36-N39	-54.7499
C33-C36-N39-H40	-62.4679
C33-C36-N39-H41	55.1101
H37-C36-N39-H40	175.258
H37-C36-N39-H41	-67.1641
H38-C36-N39-H40	61.1301
H38-C36-N39-H41	178.708
C25-C42-N44-H45	-4.5522
C25-C42-N44-C46	-178.2907
O43-C42-N44-H45	174.181
O43-C42-N44-C46	0.4426
C42-N44-C46-H47	16.5177
C42-N44-C46-C48	135.8167
C42-N44-C46-C56	-99.8552
H45-N44-C46-H47	-157.3482
H45-N44-C46-C48	-38.0492
H45-N44-C46-C56	86.2789
N44-C46-C48-H49	177.2415
N44-C46-C48-C50	-61.5436
N44-C46-C48-O54	60.6942
H47-C46-C48-H49	-64.0806
H47-C46-C48-C50	57.1343
H47-C46-C48-O54	179.3721
C56-C46-C48-H49	52.729
C56-C46-C48-C50	173.9439
C56-C46-C48-O54	-63.8184
N44-C46-C56-O57	-2.2479
N44-C46-C56-O58	176.325
H47-C46-C56-O57	-119.4691
H47-C46-C56-O58	59.1038
C48-C46-C56-O57	122.2406
C48-C46-C56-O58	-59.1866
C46-C48-C50-H51	-179.511
C46-C48-C50-H52	-61.2267
C46-C48-C50-H53	60.2885
H49-C48-C50-H51	-59.7052
H49-C48-C50-H52	58.5791
H49-C48-C50-H53	-179.9057
O54-C48-C50-H51	62.2861
O54-C48-C50-H52	-179.4296
O54-C48-C50-H53	-57.9144
C46-C48-O54-H55	-170.2305
H49-C48-O54-H55	74.76
C50-C48-O54-H55	-47.3714
C46-C56-O58-H59	179.977
O57-C56-O58-H59	-1.395

Additionally, intramolecular hydrogen bonds of YKT were determined as a result of MM, and QM calculations, shown in Figure 2 and Table 7.

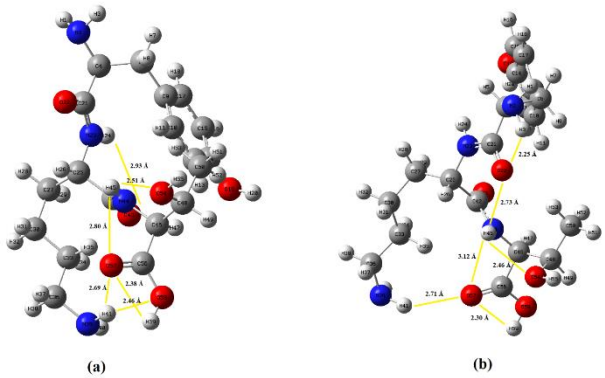

Figure 2 The structure of YKT

Table 7 Intramolecular hydrogen bond lengths of YKT

(a) as a result of MM calculations (non-optimized geometry)	
Atoms	**Bond Lengths (Å)**
O43-H24	2.93
O54-H45	2.51
O57-H41	2.69
O57-H45	2.80
O57-H59	2.38
O58-H41	2.46
(b) as a result of QM calculations (optimized geometry)	
Atoms	**Bond Lengths (Å)**
O22-H3	2.25
O22-H45	2.73
O54-H45	2.46
O57-H41	2.71
O57-H45	3.12
O57-H59	2.30

3.3. MD Results

Molecular dynamics simulations were successfully achieved in the vacuum, water, and methanol. Potential energies were converged to -2.1324930 x 10^2 kJ/mol (for vacuum), -5.2986488 x 10^4 kJ/mol (for water) and -1.9647314 x 10^4 kJ/mol (for methanol), shown in Figure 3. MD simulations were achieved in the vacuum, water, and methanol environment, and kinetic, potential, and total energies for 10 ns were shown in Figure 4.

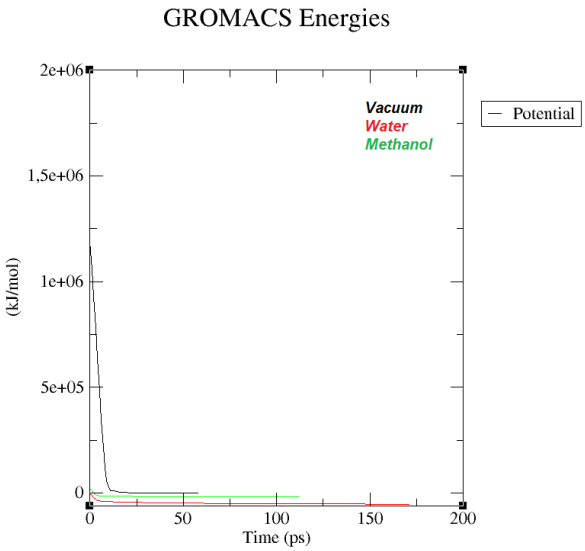

Figure 3 The potential energies of the system as a function of the minimization step using Steepest Descent algorithm

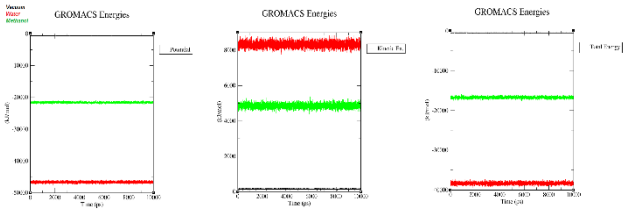

Figure 4 The potential, kinetic and total energies of all systems

For the changes in the molecular structure, using the trajectory files, the conformation of the molecule in each nanosecond was determined in the vacuum, water, and methanol environment, shown in Figure 5.

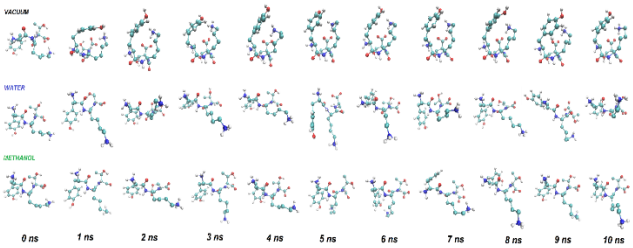

Figure 5 The conformation of the YKT in each nanosecond in the vacuum, water and methanol environment

RMSD, Rg, and hydrogen bond values of all systems were determined as a result of MD studies. RMSD values provide information on how much the system deviates from the initial structure [35]. Values less than 0.2 nm indicate that the structure is not subjected to a major structural change compared to the first structure. Looking at the RMSD values for all systems, the highest RMSD value was obtained in the vacuum environment and its value is 0.15 nm. In the water and methanol environments, these values are 0.12 nm and 0.11 nm, respectively. According to these values, it was observed that the structure tended to retain its first structure for 10 ns in all environments shown in Figure 6a.

Rg of the peptide is a measure of its compactness. When Figure 5 and Figure 6 were interpreted together, Figure 5 showed that the peptide is quite stable with folded structure in the vacuum environment, and it was seen in the RMSD and radius of gyration graphs (Figure 6) that this stable structure remains stable from 2 ns to 10 ns. In the water and methanol environment, extended structures clearly showed the reason for the fluctuation of the radius of gyration graph within the simulation period.

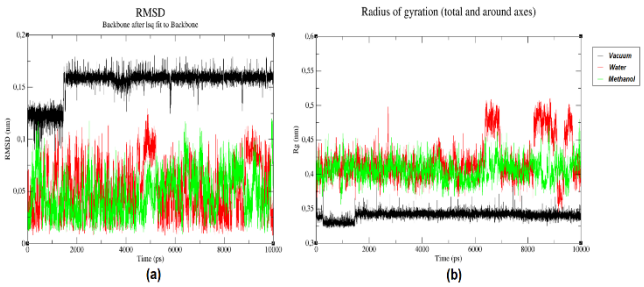

Figure 6 RMSD values (a) and Radius of gyration values (b) of YKT tripeptide in different environments

In the vacuum medium, due to the folded structure of the peptide (cf. Figure 5), atoms with high electronegativity and hydrogens bound to these atoms have more interactions and tended to make intramolecular H-bonds. It is observed in Figure 7 that the tendency to make hydrogen bonds is mostly in the vacuum medium.

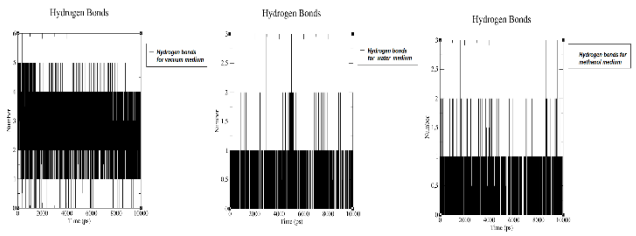

Figure 7 Hydrogen bond values of YKT tripeptide in different environments

As a result of all structural analyzes performed using MM, MD, and QM methods, the energy values of YKT tripeptide were calculated as -6.37 kcal/mol, -117.26 kcal/mol, and -886616.47 kcal/mol, respectively.

3.4. Hyperpolarizability

First-order hyperpolarizability (β_0), polarizability (α), and dipole moment (μ) data of Tyr-Lys-Thr (YKT) tripeptide were obtained with DFT/B3LYP method using 6-311++G(d,p) basis set.

The dipole moment, polarizability, and hyperpolarization values obtained in the studies using the DFT / B3LYP / 6-311 ++ G (d, p) basis set in the Gaussian 09 program are given in the following Table 8.

The dipole moment value obtained is 1.6968023 D and the hyperpolarization value is $2.6114151629 \times 10^{-30}$ esu. Urea values of μ, α, and β in the literature were obtained as 1.373D, 3.8312×10^{-24} esu, and 0.37289×10^{-30} esu using the B3LYP / 6-31G (d) basis set [36-38]. When the values of YKT tripeptide were compared with the literature data, μ, α, and β_0 values of the tripeptide were obtained 1.2358, 10.775, and 7.0031 times that of urine, respectively.

Table 8 First-order hyperpolarizability (β_0), polarizability (α), and dipole moment (μ) table of YKT tripeptide

Parameters			
μ_x	-0.7736091	β_{xxx}	-45.1187173
μ_y	1.1058228	β_{xxy}	3.9859085
μ_z	-1.0285052	β_{xyy}	-107.2066633
μ	**1.6968023**	β_{yyy}	205.1883547
α_{xx}	301.183032	β_{xxz}	-29.7750615
α_{xy}	4.5501607	β_{xyz}	3.3650559
α_{yy}	280.3586188	β_{yyz}	56.0279763
α_{xz}	-13.5298548	β_{xzz}	-15.1125743
α_{yz}	18.6290357	β_{yzz}	40.1568576
α_{zz}	254.1346634	β_{zzz}	7.9961513
$<\alpha_o>$	**278.5587714**	β_o	302.2821117
$<\alpha_{top(esu)}>$	41.28241×10^{-24}	$\beta_{o(esu)}$	$2611.4151629 \times 10^{-33}$
		$\beta_{o(esu)}$	$2.6114151629 \times 10^{-30}$
(α:1 a.u. = 0.1482×10^{-24} esu ; β:1 a.u. = 8.639×10^{-33} esu)			

4. CONCLUSIONS

In this study, the stable conformations of Tyrosyl-Lysyl-Threonine were obtained by the theoretical conformational analysis, firstly. And then, the optimized geometry and energy values of the determined structure as the most stable conformation of YKT tripeptide by theoretical conformational analysis were obtained and bond, angle, and dihedral data of tripeptide were determined and shared. Additionally, the intramolecular H-bonds of the structure obtained from MM and QM calculations were determined. The conformational change of YKT tripeptide in the vacuum, water, and methanol environments was investigated by molecular dynamics methods for 10 ns. Additionally, the energy values obtained using MM, MD, and QM methods are presented comparatively. μ, α, and β_0 values of YKT were calculated by Gaussian09 software program. With this study, a study about the structural properties of YKT tripeptide was brought to the literature.

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The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by the authors.

Authors' Contribution

The authors contributed equally to the study. B.B: data collection, literature research, writing. S.K.G: writing, editing, literature research.

The Declaration of Ethics Committee Approval

This study does not require ethics committee permission or any special permission.

The Declaration of Research and Publication Ethics

The authors of the paper declare that they comply with the scientific, ethical and quotation rules of SAUJS in all processes of the paper and that they do not make any falsification on the data collected. In addition, they declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

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