CONFORMATIONAL RECONSTRUCTIONS IN CREKA MOLECULE STRUCTURE IN MOLECULAR DYNAMICS PROCESS

G.J. ABBASOVA, E.Z. ALIYEV
Cafedra of optics and molecular physics
Baku State University

The spatial and electron structure of CREKA molecule which is new medicine possessing the antitumoral effect is investigated by molecular dynamics method. The geometric parameters and energy contributions of different types of interatomic interactions in stabilization of stable conformational molecule states are calculated, the quantitative evaluation of change limits of dihedral angles in main and side chains of amino-acid residuals in process of molecular dynamics is carried out.

Keywords: CREKA, peptide, conformational analysis, conformational state, molecular dynamics.
PACS: 31.15;33.15

INTRODUCTION

The more perspective directions in investigations of structure and properties of biological system on molecular and cell levels are connected with nanobiotechnology the aim of which is the control by the transport of medicinal and diagnostic agents. The loaded nanoparticle concentrates in itself the several decades of thousands and more molecules of medicinal agent that gives the possibility of effective transport of chemical compounds directly to the delivery place without affection of healthy cells of different organs and tissues.

The compound consisting of five amino-acid residuals Cys1-Arg2-Glu3-Lys4-Ala5 and called CREKA belongs to the number of such medicinal agents applied in tumor cell therapy using the nanoparticles. CREKA medicine possessing the strongly expressed anticancer effect in respect of prostate cancer had been firstly synthesized in 2006 by American scientists of Technical University of Massachusetts [1]. Further, its pharmacological properties had been studied [2-3]. The spatial structure and conformational properties of CREKA molecule are investigated in the given work by molecular mechanics method using the computer programs. The calculations are carried out by the method of theoretical conformational analysis by the technique which is given in detail in [4-5]. The conformational states of Arg2-Glu3, Cys1-Arg2-Glu3, Cys1-Arg2-Glu3-Lys4 fragments and further of whole CREKA molecule are gradually calculated on data based on mono-peptide molecules.

CALCULATION METHODS

The method of equilibrium molecular dynamics (MD) the progress, in development of which is based on achievements of computer technologies [6], is widely used under different conditions for description of dynamic behavior of peptide molecules. MD calculations are carried out in conditions of implicitly given water molecules with taking into consideration of (ε) medium dielectric constant. It is known that dielectric constant change influences on balance of electrostatic interactions of functional groups of amino-acid residuals in peptide molecules and essentially influences on hydrogen bond formation and its number. In all cases the calculated equilibrium geometry is used as the initial one for molecular-dynamic calculation carried out in potentials of semiemperical method MM+ without taking into consideration the symmetry. The optimization of molecule geometry is carried out with convergence parameter 0.01.

THE RESULTS AND THEIR DISCUSSION

The molecular dynamics of peptide in conditions modeling the implicitly water surrounding is studied for revealing of conformational stable and relatively labile parts of CREKA molecule. The collisional thermostat towards Berendsen one is used for keeping of temperature constancy. The time constant of velocity change in Berendsen thermostat is equal to τ=0,5. The periodic boundary conditions with cubic cell 100x100x100 Å are used. The cutoff radiuses are: a) for electrostatic interactions 21 Å; b) for Van-der-Waals interactions 16,8Å. It is known that change of torsion angles φ and ψ make the contribution in polypeptide chain flexibility, that's why the change limits of dihedral angles in molecule main chain at molecular dynamics process are given in table 8. The dihedral angles (grad) in low-energy conformations of CREKA molecules before (headline) and after (bottom line) molecular dynamics in MM+ force field are shown in table 1.

As it follows from the calculation results the state with minimal energy value (conformation 1, fig.1) undergoes the conformational reconstructions because of ψ angles, moreover, almost similarly for all amino-acid residuals. The molecule gains the more extended structure, in which only side chains of Arg2 and Glu3 residuals with opposite charged functional groups are connivent ones. In conformation 2 the reconstructions are related to main chains of Glu3, Lys4 and Ala5 residuals, the result of which is the closeness of Ala5 and Lys4 side chains. The changes in arginine residual structure are connected with insignificant conformational reconstructions in its side chain. 3 and 4 conformations keep the structure compactness and closeness of end residuals in spite of change of main chain step due to the change of angle ψ in Arg2 from value -63^0 to $+63^0$ and angle φ in Glu3 from -96^0 to 72^0.

131 H.Javid ave, AZ-1143, Baku
ANAS, G.M.Abdullayev Institute of Physics
E-mail: jophphysics@gmail.com

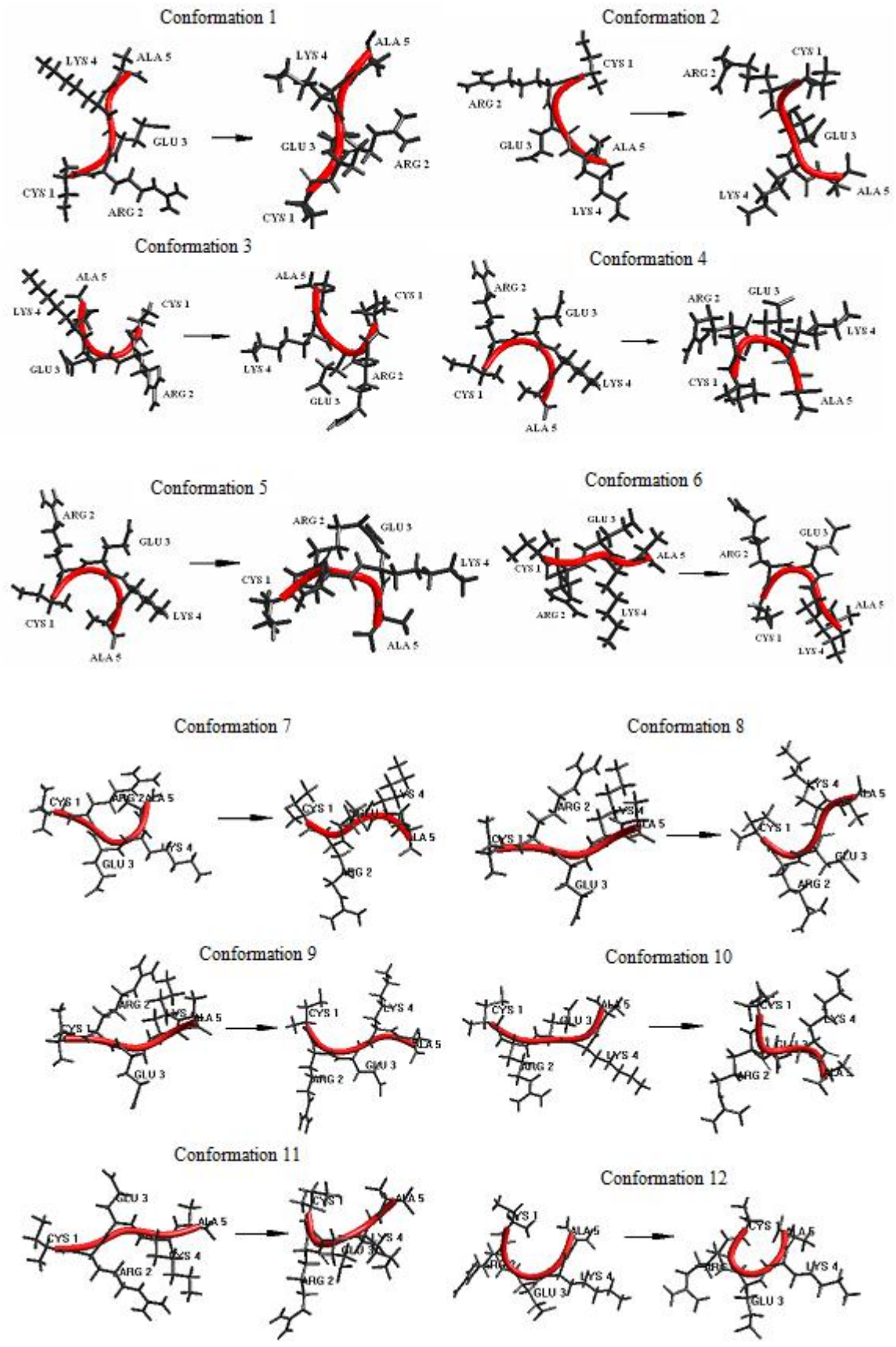

Fig.1. Conformational reconstructions in CREKA molecule structure.

Table 1.

The dihedral angles (grad) in low-energy conformations of CREKA molecules before (headline) and after (bottom line) molecular dynamics in MM+ force field

Conformation	Cys1	Arg2	Glu3	Lys4	Ala5
1	*-73, -55, 180 -145, -67, 182	-104, -59, 178 -96, 56, -172	-99, 137, 185 -82, 35, 164	-117, -61, 184 -99, 60, -171	-88, -52, 178 -58, 180, 179
2	-76, -52, 180 161, -164, 189	-92, -56, 178 -102, -28, -175	-147,173,180 -101,107,-168	-90, 95, 180 -67, 30, -175	-84, -55, 179 -119,172, 164
3	-83, 72, 181 -53, 93, 176	-116,-63,177 -96, 63, 169	-96,-52,183 72, -40, -172	-114,123,175 -83, 57, -161	-83,-54, 180 -42, 146,174
4	-83, 76, 181 -50, 93, 177	-119, -63, 179 -88, 31, 171	-94, 140, 187 80, -44, -165	54, 65, 184 -74, -52, 159	50, 56, 188 -88, 118, 169
5	-77,-57,179 -90, -73, 185	-108,-61,178 -86, 45, -176	-98,143,186 -73, 55, 178	55, 68, 181 87, -72, -166	-113, 141, 183 -162,-168,-173
6	-87, -62, 180 174, -176, 181	-136, -63, 180 -98, 70, -164	53, 62, 183 70, 12, 173	-117, 96, 182 -95, 68, 171	-89, -56, 180 -63, -38, 169
7	-88, -63, 180 -74,104,182	-137, -62, 180 -103,11,179	53, 68, 180 72,-18,-173	60, 68, 183 65,39,174	-111, 141, 177 -165,-85,-168
8	-89,-62,180 161,72,179	-138,-63,179 -73,59,-176	53,59,183 79,53,-178	-113,-61,182 -88,71,173	-86,-54,179 -101,99,-161
9	-82,85,181 81,82,186	-105,-62,179 69,-31,179	-98,139,188 -103,68,-179	-116,-60,181 -72,-57,173	-87,-52,178 -167,48,-177
10	-79,84,181 106,159,182	-103,101,181 -90,-23,-170	-107,167,189 -86,75,164	-83,-53,177 -156,-48,180	-83,-53,176 -160,-19,173
11	-79,83,181 170,73,188	-113,-62,180 -75,54,168	50,62,179 72,40,-180	-120,94,181 -84,82,-176	-89,-56,180 120,27,177
12	80,-58,180 53,-78,184	-113,-58,178 -71,-64,180	-104,-74,176 -118,-54,177	-128,-68,193 174,-47, 171	189,-51,189 -151,- 68,174

*Note: The values of dihedral angles of the main chain are given in consistency: φ, ψ, ω.

The essential reconstructions are revealed in molecular dynamics processes in 5 and 7 conformations in difference on the conformations above mentioned.

The changes in angle ψ in Arg2 from -61^0 to $+45^0$ and also changes of angle ψ in Lys4 from $+68^0$ to -72^0 lead to the formation of more disordered structure.

The hydrogen bond rupture between atoms of peptide group NH in Cys1 and COO in Glu3 takes place in conformations 6,8-11 because of formation of strong intramolecular interactions between atoms of side chain of Cys1 and Lys4 residuals.

The sum energy of such interactions is higher on 0,8 kcal/mol than formation energy of hydrogen bond.

The conformation 12 is more stable one in respect of main chain angles. The insignificant changes in Arg2 main chain leads to formation of more compact structure with connivent final sections.

The interatomic spacing between C^{α}-atoms of Cys1 and Ala5 residuals decreases from 6.4 up to 4.2 Å.

CONCLUSION

Thus, summarizing the investigation results one can conclude the following: in spite of the data of molecular mechanics method the conformation 12 is less on 3,4 kcal/mol than other low-energy conformational states.

It is more stable one in respect of intramolecular interactions in molecular dynamics process.

This allows us to conclude that especially this conformational state of CREKA molecule is the more stable one to surrounding action and can keep the spatial structure elements to realize its biological functions.

The obtained results will be used for molecular modeling of CREKA molecule analogues and study of their structural-functional interaction with the aim of revealing of common elements of spatial structure which are responsible for pharmacological effects of investigated compound. Such investigations can be the basis for further synthesis of new medicinal agents with controlling therapeutic effect.

[1] *O.C. Farokhzad, J.J. Cheng, B.A. Teply, I. Sherifi, S. Jon, P.W. Kantoff, J.P. Ritchie, R. Langer.* 2006. Targeted nanoparticles–aptamer bioconjugates for cancer chemotherapy in vivo. *Proc. Nat. Acad. Sci.* **103,** 6315-6320.

[2] *A. Fleischmann, U. Laderach, H. Friess, M.W. Buechler, J.C. Reubi.* 2000. Bombensin

receptors in distinct tissue compartments of human pancreatic diseases. *Laboratory Investigation*, **80**, 1807-1817.

[3] *X. Montet, R. Weissleder, L. Josephson.* 2006. Imaging pancreatic cancer with a peptide–nanoparticle conjugate targeted to normal pancreas. *Bioconjugate Chemistry*. **17**, 905-911.

[4] *P. Couvreur, C. Vauthier.* 2006. Nanotechnology: intelligent design to treat complex disease. *Pharm.Res*., **23** (7), 1417-1450.

[5] *Q.M. Lipkind, S.F. Arxipova, E.M. Popov.* 1970. Jurnal structurnoy ximii. **11**, 121-126. (In Russian).

[6] *K.B. Shaytan.* Molekulyarnaya dinamika peptidov. (In Russian).

[7] (www.moldyn.ru/bioinzhenerija/doc/stat/moldyn.htm)

Received: 14.03.2016