# THEORETICAL MODELLING OF CYS-ARG-GLN-LYS-ALA MOLECULE STRUCTURE COMPLEXES AND ITS ANALOGUES WITH IRON OXIDE (III)

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The complex structure of CREKA peptide and its 17 chemically modified analogues with $Fe_3O_4$ iron oxide are investigated by semiempirical methods of MM+ molecular mechanics and quantum chemistry in PM3 approximation. The comparative analysis of obtained results is carried out on the data base on geometric structure, electron parameters of stable complexes.

**Keywords:** stable complexes, chemically modified analogues, geometric structure
**PACS:** 31.15; 33.15

## INTRODUCTION

CREKA peptide in linear sequence of which there are five amino-acid residuals Cys1, Arg2, Glu3, Lys4 and Ala5, is related to number of unique natural compounds which accumulate in high concentrations near tumor cells in different organs and tissues [4,5]. The peptide was firstly obtained in 2006 by Ruoslahti with other authors from tissues affected by prostate cancer. Further, the analogues of this peptide were synthesized with the aim of their use in tumor cell therapy as transport for purposeful delivery of medicines to affected fields of constitution tissues. The complex theoretical model in which CREKA peptide covered by dextran contains the trivalent iron oxide as magnetic mark has been constructed by us earlier.

The spatial and electron structures of CREKA peptide complexes in various conformational states with $Fe_3O_4$ iron oxide and di-glucose are investigated, the geometric and energy parameters characterizing the stable low-energy complex states are established [1-3].

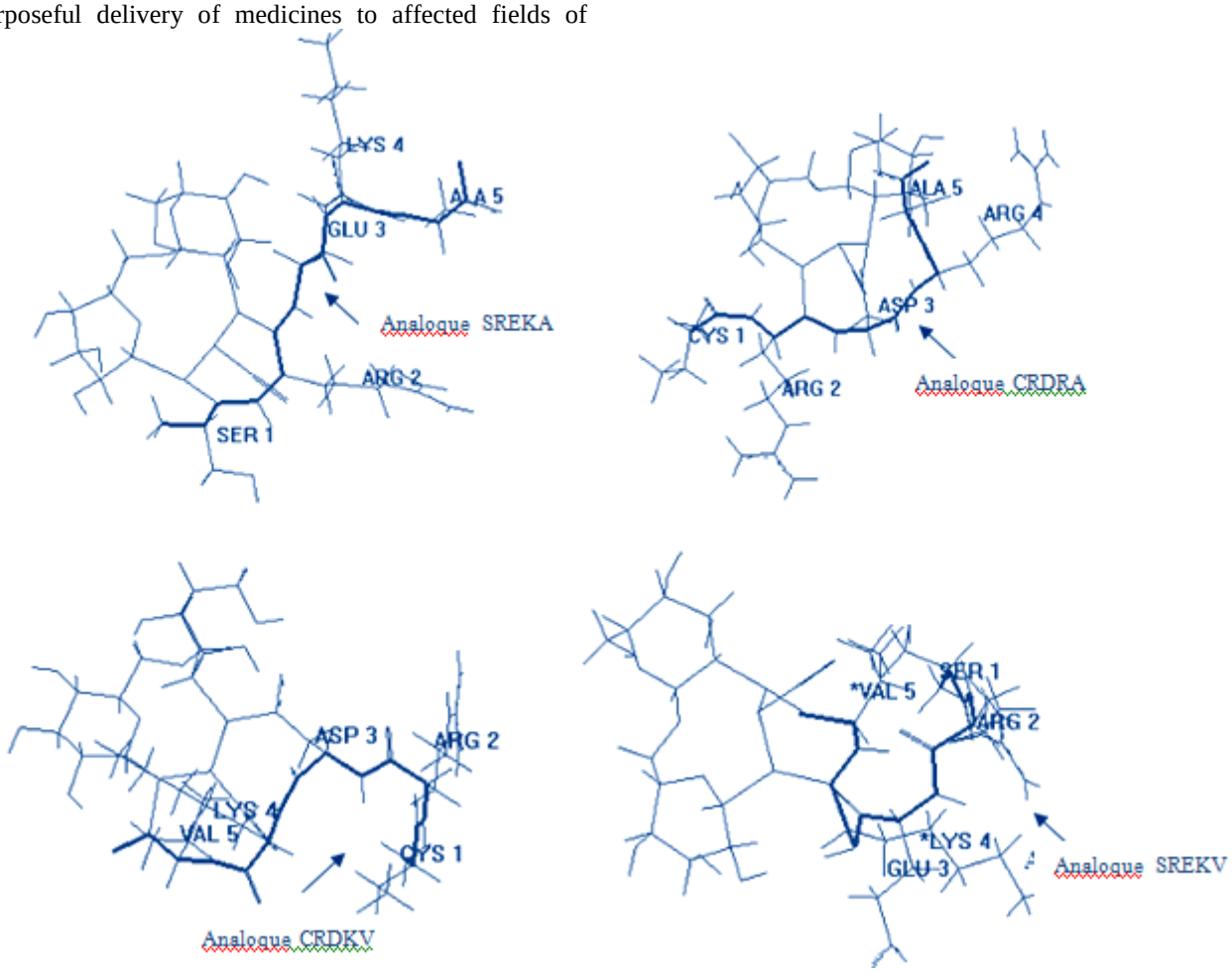


*Fig. 1.* The optimized complex structures including $Fe_3O_4$, di-glucose and CREKA peptide analogue.



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Table 1

Energy characteristics (kcal/mol) and dipole moments (μ, Debye) of stable complexes of CREKA peptide and its analogues with di-glucose and $Fe_3O_4$ (according to data of PM3 method)

| № | Complex of peptide with $Fe_3O_4$ | $E_t$ | $E_{el}$ | $E_{rep}$ | $E_b$ | $E_h$ | μ |
|---|---|---|---|---|---|---|---|
| **1** | AREKA | -303739 | -4204709 | 3900970 | -12521 | -877 | **34.2** |
| **2** | CPEKA | -292035 | -3966233 | 3674197 | -11865 | -977 | **39.6** |
| **3** | CKEKA | -313740 | -7204710 | 6900970 | -12771 | -988 | **32.6** |
| **4** | CRERA | -334141 | -4769214 | 4435073 | -12606 | -762 | **32.8** |
| **5** | SREKA | -334163 | -4447260 | 4113097 | -12627 | -784 | **20.4** |
| **6** | CKEKA | -310393 | -4266874 | 3956481 | -12503 | -800 | **36.4** |
| **7** | CRDKA | -300572 | -4005438 | 3704866 | -12393 | -910 | **47.8** |
| **8** | CREKV | -314880 | -4418098 | 4103218 | -13095 | -836 | **48.5** |
| **9** | SKEKA | -303049 | -4285393 | 3982344 | -12428 | -951 | **23.7** |
| **10** | SRDKA | -177912 | -1877926 | 1700013 | -11058 | -488 | **28.1** |
| **11** | SRERA | -317979 | -4547334 | 4229354 | -12819 | -891 | **46.3** |
| **12** | SREKV | -317128 | -4591095 | 4273966 | -12902 | -649 | **44.7** |
| **13** | CKDKA | -296829 | -3835584 | 3538755 | -11818 | -609 | **40.9** |
| **14** | CKEKV | -169491 | -1768304 | 1598813 | -10632 | -131 | **35.2** |
| **15** | CRDRA | -320183 | -4412944 | 4100762 | -12633 | -972 | **37.2** |
| **16** | CRDKV | -314880 | -4418098 | 4103218 | -13095 | -836 | **36.4** |
| **17** | **CRERV** | **-195452** | **-1990742** | **1845290** | **-7998** | **-135** | **36.5** |

$E_t$ is total energy; $E_{el}$ is electron energy; $E_{rep}$ is repultion energy of atomic cores; $E_b$ is bond energy; $E_h$ is heat energy.

## METHODS AND CALCULATION RESULTS

In the given work the models of 17 CREKA peptide analogues with di-glucose and $Fe_3O_4$ iron oxide are constructed on the base of investigation of their spatial and electron structures, the optimization of complex structure in order to establish the more stable structures is carried out. The investigation of complex electron structure is carried out in framework of semiempirical method PM3 parametrizated for transition metal atoms is carried out. CREKA peptide analogues are obtained in the result of consistent point exchanges. Cys1 residual exchanges by alanine or serine, arginine residual in second position exchanges by proline or lysine, Glu3 residual exchanges by asparaginic acid, Lys4 residual exchanges by positively charged arginine amino-acid and exchanges by nonpolar valine amino-acid.

The comparison of values of electric density and effective charges on amino-acid residual atoms including into peptide molecule shows that the essential changes of charge density in strongly defined atom groups, in particular, in the side chain of arginine amino-acid residual in positions 2 and 4 of peptide chain and also in side chain of Glu3 glutaminic acid take place. The highest electric density is revealed on atoms of peptide groups of carbonyl oxygen for all analogues of CREKA peptide. The peptide molecule parts relatively sensitive ones to conformational reconstructions are revealed on the base of analysis of concrete atom effective charge changes. The dipeptide fragments Lys4-Ala5 and Arg4-Val5 in different analogues of CREKA peptide are related to them. Gly1-Glu3 fragments in analogues of CREKA and CRERA are characterized by relatively less changes in effective charge values that confirms their stability because of the presence of profitable atom interactions (both non-valent and electrostatic ones) obtained on the base of data of theoretic conformational analysis method. The energy contributions of total energy, bond energy, energy of nuclear interactions, heat energy and also values of dipole moments of complexes formed by these

analogues with di-glucose and $Fe_3O_4$, are given in table 1. The optimized structures of more stable complexes formed by some analogues of CREKA peptide are given in fig.1.

## CONCLUSION

The comparative analysis of results carried out for complexes of CREKA peptide analogues with di-glucose and $Fe_3O_4$ shows that the complexes formed by analogues of SREKA, CRERA, CREKV, SRERA, SREKV, CRDRA and CRDKV peptides are the more stable ones.

The complexes formed by analogues of SRDKA, CKEKV, CRERV peptides are the less stable ones.

The change regularities of spatial and electron structures of peptide analogue revealed in the given paper, are necessary for prediction of stability and reactivity of investigated compounds.

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*Recevied: 24.04.2017*