Comparison small nucleic acids derivatives hybridization parameters obtained by molecular dynamics and experimentally .

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Oligonucleotides - small synthetic fragments of nucleic acids are widely uses for investigations of molecular-biological processes, in biosensors and in antisense therapy. Nowadays there are some different types of nucleic acids derivatives. Successful implementation of the modified oligonucleotides requires characterization of physicochemical and molecular-biology properties. The one of the crucial attributes of nucleic acids analogues are the possibility and efficiency of complex formation with DNA and/or RNA. Quantitatively it can be characterized by the entropy and enthalpy changes at complex formation. Recently it was shown that hybridization properties of native complexes of nucleic acids can be predicted using MD simulation [1]. At the same time there are still no efficient methods for prediction physic-chemical properties of new derivatives. The development of the techniques for efficient prediction complex formation for nucleic acid analogues is essential task at rational design of new compounds. The goal of the work is to develop approaches for determination hybridization properties of new nucleic acids analogues using experimental and *in silico* methods. For this purpose we chose new glycine-morpholine derivatives invented recently [2]. The properties of these new compounds was not studied in details yet. The typical problem is small size of oligomers and not enough amounts because of the difficulties in chemical synthesis. This lead to the extremely low thermodynamic stability of the complexes with complementary chain. Here we proposed to use tandem complex of pentameric native and morpholine adeninenes. Due to the efficient stacking interaction at the helix-helix interface the thermal stability significantly increases at complex formrd by two or more short oligomers at long DNA matrix chain. To determine

thermodynamic parameters (enthalpy and enthalpy changes) of the low thermal stability nucleic acid complexes new approaches based on the experimental method of thermal denaturation with optical registration of signal. We propose original approaches for obtaining thermodynamic parameters of binding and cooperative interaction in the nick. In this method small oligonucleotides (pentamers of adenine or morhpholine derivative of adenine) binds with long complementary DNA/RNA matrix (oligothymidines 15, 20, 25 or ~300 nucleobase in lenth). The analysis of the denaturation curves of complexes different molecularity (with 15, 20, 25 basebair) alowes to determine the binding and cooperative interaction thermodynamic parameters. Alternatively, the concentration method was proposed for this purpose. The analysis of the thermodynamic parameters determined for native and modified complexes of different molecularity shows the model reliability.

Based on molecular dynamics (MD) simulation methods we developed a procedure for calculation enthalpy of complex formation and cooperative interactions at helix-helix interface. MD simulations were performed using AMBER12 software package using recently developed BSC1 force field. The 1 μs trajectories were obtained in the explicit solvent in periodic condition (TIP3P water model, 10Å cuboid box) and NPT ensemble (1 bar, 300K). MD data we analyzed using MMGBSA calculation. The values of hybridization enthalpy were obtained by analysis of MD trajectories for both native and modified oligomers.

The thermodynamics data obtained by MD simulation and experimental thermal denaturation approaches are well correlate both for native and morpholine oligonucleotides.

In conclusion, we have developed new procedures for determination of binding and cooperative interaction energies for complexes with low thermal stability. The thermodynamic parameters obtained experimentally and by computer simulations are well correlate.

The work was supported by RFBR (grant # 16-04-01029) and government assignment on 2017-2020 years (project VI.62.1.4, 0309-2016-0004). Molecular Modeling were performed using the computing facility of the Siberian Supercomputer Center (www2.sscc.ru).

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