

Calculated circular dichroism spectra of homo- and heteropolar G-quadruplexes

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Abstract. Circular dichroism spectra of model homo- and heteropolar quadruplex structures are calculated using quantum mechanics methods and classical dipole-dipole interaction model. Quantum chemical calculation yielded CD shapes that closely resemble experimental ones. Classical model allows for fast qualitative theoretical estimate of CD spectrum of an arbitrary quadruplex structure and can be utilized for tracking molecular dynamics trajectories. The dependence of CD spectrum on geometrical parameters is investigated.

Keywords: circular dichroism, g-quadruplex, molecular dynamics

Secondary structure of nucleic acids always attracts considerable attention. Among the diversity of DNA and RNA forms, the specific kind of secondary structures, G-quadruplexes, has raised constantly increasing interest. From one hand, they occur in telomeres, IgG switch regions, c-myc oncogene and other natural sequences. From another hand, they represent the basic structure in aptamers, a novel type of pharmaceuticals. Functional activity of aptamers is completely determined by its ability to bind sterically target molecule; thus, studying of their spatial structure, and G-quadruplexes as its main element, is of the highest importance. G-quadruplex represents two or more stacked guanine quartets each of which, in turn, consists of four guanines arranged roughly in the same plane and connected by hydrogen bonds in a circle. X-ray crystallography and nuclear magnetic resonance techniques are commonly used to resolve the quadruplex structure, yielding high-resolution data. However, these complicated methods take quite a long time to lead to result so they cannot be used for fast batch analyses. In contrast, circular dichroism (CD) spectroscopy is fast and relatively simple method which is highly sensitive to 3D-structure of quadruplexes. Despite being widely used, the appropriate interpretation of CD spectrum in terms of spatial structure is still controversial. Early models based on dipole-dipole interaction approach provided some qualitative description for CD spectra of quadruplexes but never gave perfect coincidence with experimental CD signals.

Recently developed quantum chemistry techniques such as HF-3c basis set [4] and sTDA-DFT approach for excited states [5] have filled the gap between quantum chemistry and large systems. Combination of this approaches allows to calculate optical properties (absorption and CD spectra) of whole quadruplex systems in terms of hours.

Calculated spectra reproduce the most prominent features of experimental spectra such as bands at 260 and 290 nm. Based on this result, we performed thorough investigation of CD lineshape and amplitude dependency on quadruplex structure and for the first time showed their high sensitivity to geometrical parameters such as stacking mode and rotational angle between quartets. Remarkably, the common paradigm stating that the sign and intensities of extrema at 260 and 290 nm are determined by topology of nucleic acid chain(s), appeared to be not universal. Instead, we have shown that the overall CD lineshape is determined by stacking mode rather than topology. While the calculation scheme presented here provides previously unavailable level of accuracy and computational speed, it is still far from desirable performance for such promising applications as tracking conformational changes during molecular dynamics simulation with CD verification.

For that reason we compared our quantum mechanical results with CD spectra calculated within the framework of dipole-dipole interaction approximation which is commonly used as a fastest and simplest way to describe CD spectra of quadruplex structures [1]. The model treats quadruplex unit as a set of oscillating dipoles corresponding to electronic transitions in guanines. As nitrogenous bases have planar structure, magnetic transition dipoles can be neglected and only electric dipoles are considered. Dipole directions coincide with electric transition dipoles, band intensities are proportional to oscillator strengths and natural frequencies are determined by corresponding transition energies. So given that parameters for guanine electronic transitions are known, calculated CD spectrum is determined solely by mutual orientation of guanines in space.

In our calculation we used two sets of parameters for guanine transitions: one determined experimentally on 9-ethylguanine crystals by Clark [2] commonly used in the literature [1][3] and those obtained in our calculations. With these parameters we calculated dipole-dipole interaction CD spectra for the same model structures that were used in quantum mechanics calculations. Spectra calculated with experimental parameters showed qualitative rather than quantitative description of the main quadruplex CD features but the general trend in dependence on geometrical parameters was the same as in quantum chemical calculations results. However, introducing the computationally derived transition parameters into model lead to more realistic picture. Thus, the common dipole-dipole interaction model can be used for fast, though qualitative, description of particular quadruplex conformation. It can serve as a useful tool in tracking molecular dynamics trajectories.

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