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Molecular Chameleon: How a Ligand Adapts to Double-Stranded and G4 DNA with Distinct Fluorescence Signatures

DNA can adopt a variety of secondary structures beyond the canonical double-stranded form (dsDNA). Among these, the guanine quadruplex (G4) has been widely studied for its role in gene expression and cancer, as G4s are found in many oncogenic promoters and at telomeres [1]. This has driven efforts to detect and track G4s in cells using near-infrared fluorescent probes [2]. A key example is the tripodal quinone-cyanine dye [QCy(MeBT)$_3$], featuring three N-methylbenzothiazolium cations linked by dimethine chains, which was the first reported switch-on fluorescent probe able to distinguish between dsDNA and G4 through different fluorescence colors [3]. However, the mechanisms behind this unique behavior remain largely unclear.

In this study, multiscale modeling is employed to rationalize the photophysical properties of QCy(MeBT)$_3$. Different conformers, generated by rotation around flexible bonds, were first identified, and a PCM corrected linear response study revealed a wide range of emission wavelengths depending on their conformation. Rigid molecular docking was then performed to obtain unbiased starting structures for molecular dynamics (MD) simulations, with the force field parametrized through ab-initio calculations. Binding affinities were estimated using MMPBSA, and the photophysics of the best-binding conformers was investigated at the QM/MM TDDFT level by extracting a statistically significant number of MD snapshots. Notably, the best dsDNA-interacting conformers showed lower emission wavelengths than G4-interacting ones, in excellent agreement with experiments. Moreover, the minor groove binding mode observed with dsDNA matched previous studies on an analogous ligand [4]. Finally, MD trajectory analysis is used to investigate the origins of the conformers' differential stability between dsDNA and G4, potentially helping the design of new ligands.

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