Single Selenium Atom to Control Nucleic Acid Conformation and Large Crystal Growth

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In general, crystallization is a bottleneck challenge in crystallography. Even worse, crystallization of DNA duplexes, normally existing in the B-form in solution, is much more challenging, as the high salt used in many crystallization processes favors their transformation to A-form DNA duplexes. To address crystallization challenges while avoiding structural perturbation, we explored the atom-specific incorporation of one selenium atom on the 2'-beta (arabino) position of the 2'-deoxyribose ring. This incorporation is expected to favor the B-form of a DNA duplex during crystallization. We have synthesized the first β-2'-MeSe-thymidine (SeT) nucleoside, the corresponding Se-phosphoramidite, and Se- containing DNA oligonucleotides. We have found that Se-DNAs and Se-DNA-protein complexes can form crystals that are larger, have higher quality, and give improved diffraction resolution when compared to crystals from the corresponding native oligonucleotides. Surprisingly, one duplex made from a self-complementary Se- oligonucleotide gave crystals 600 x 200 microns in size, approximately 100 times larger in volume than the corresponding native DNA crystals. Further, we discovered that the diffraction quality of the Se-DNA crystals was high (up to 1.15 Å resolution), and the Se- derivatized structure was virtually identical to the native structure. Furthermore, crystals of this size are especially important for neutron diffraction studies. Our discoveries represent a new and simple strategy to address many crystallization challenges in nucleic acid crystallography.

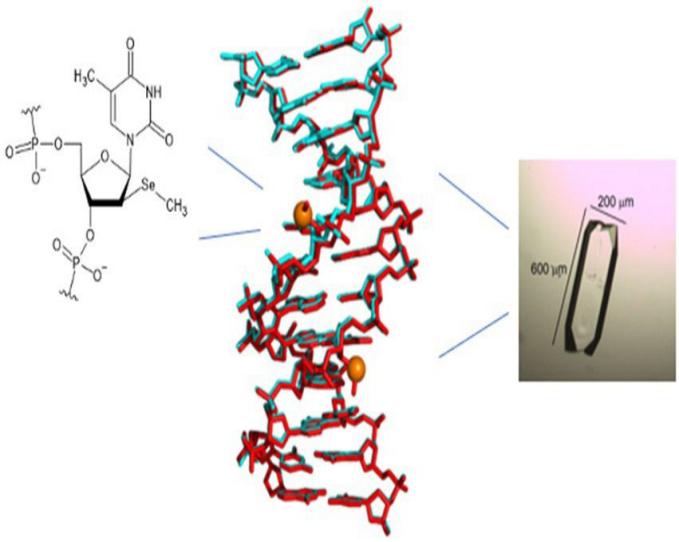

Figure 1