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Why Does Substitution of Thymine by 6-Ethynylpyridone Increase the Thermostability of DNA Double Helices?

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Efficiency of 6-ethynylpyridone (E), a potential Thymine (T) analogue, which forms high-fidelity base pairs with Adenine (A) and gives rise to stabler DNA duplexes, with stability comparable to those containing canonical Cytosine(C):Guanine(G) base pairs, has been reported recently. Estimates of the interaction energies, involving geometry optimization at the DFT level (including middle range dispersion interactions) followed by single point energy calculation at MP2 level, in excellent correlation with the experimentally observed trends, show that E binds more strongly and more discriminatively with A, than T does. Detailed analysis reveals that the increase in base-base interaction arises out of conjugation of acetylenic $\pi$ electrons with the ring $\pi$ system of E, which results in not only an extra stabilizing C–H $\cdots$ $\pi$ interaction in the EA pair, it also leads to a strengthening of the conventional hydrogen bonds.

However, the computed base-base interaction energy for the EA pair was found to be much less than that of the canonical CG pair implying that the difference in the TA versus EA base pairing interaction alone cannot explain the large experimentally observed increase in the thermostability of DNA duplexes, where a TA pair is replaced with an EA pair. Our computations show that the conjugation of acetylenic $\pi$ electrons with the ring $\pi$ system also possibly plays a role in increasing the stacking potential of the EA pair, which in turn, can explain its marked influence in the enhancement of duplex stability.

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