

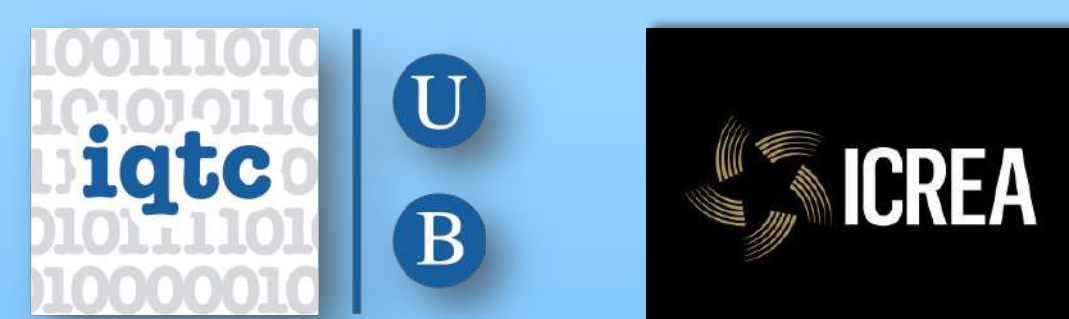
Selectivity in artificial DNA base pairs



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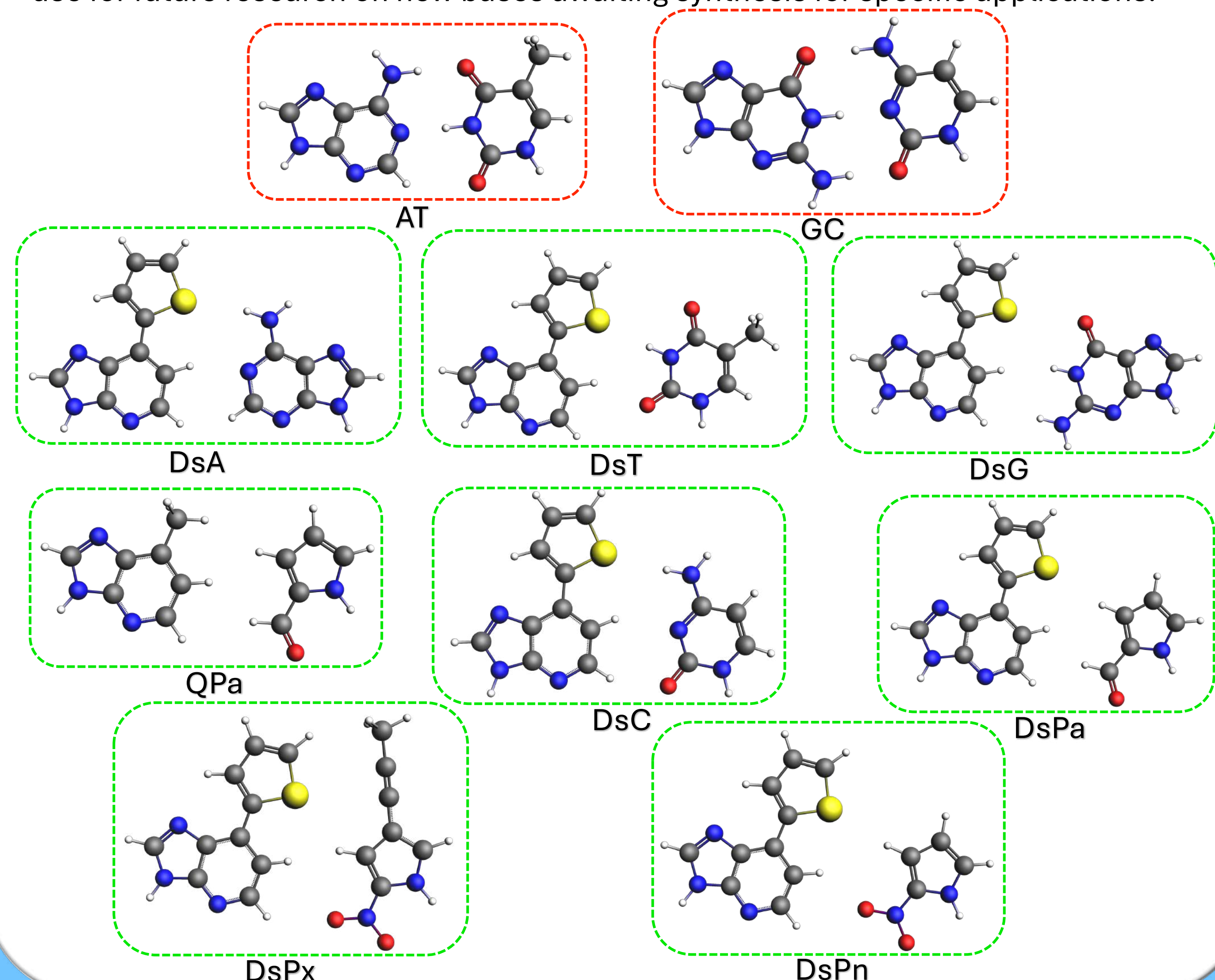


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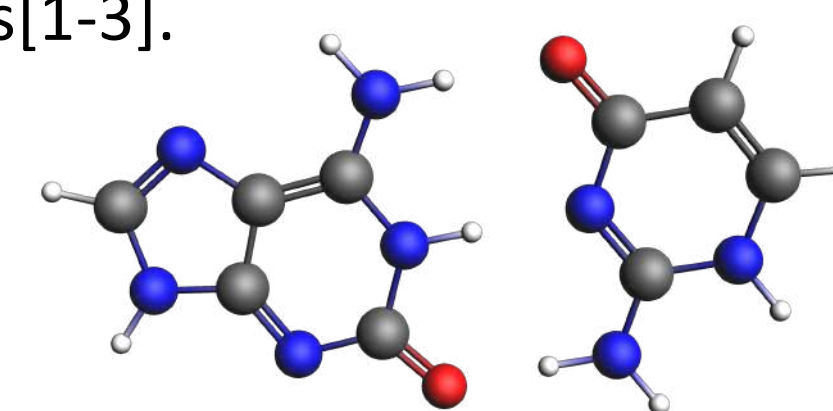
Abstract

We selected a group of previously proposed and experimentally tested artificial DNA base pairs. Our goal was to understand their selectivity and compare it to Watson-Crick base pairs. Despite lacking hydrogen bonds, their selectivity is determined by π - π stacking interactions with adjacent base pairs. Our computational model accurately replicates laboratory selectivity, supporting its use for future research on new bases awaiting synthesis for specific applications.

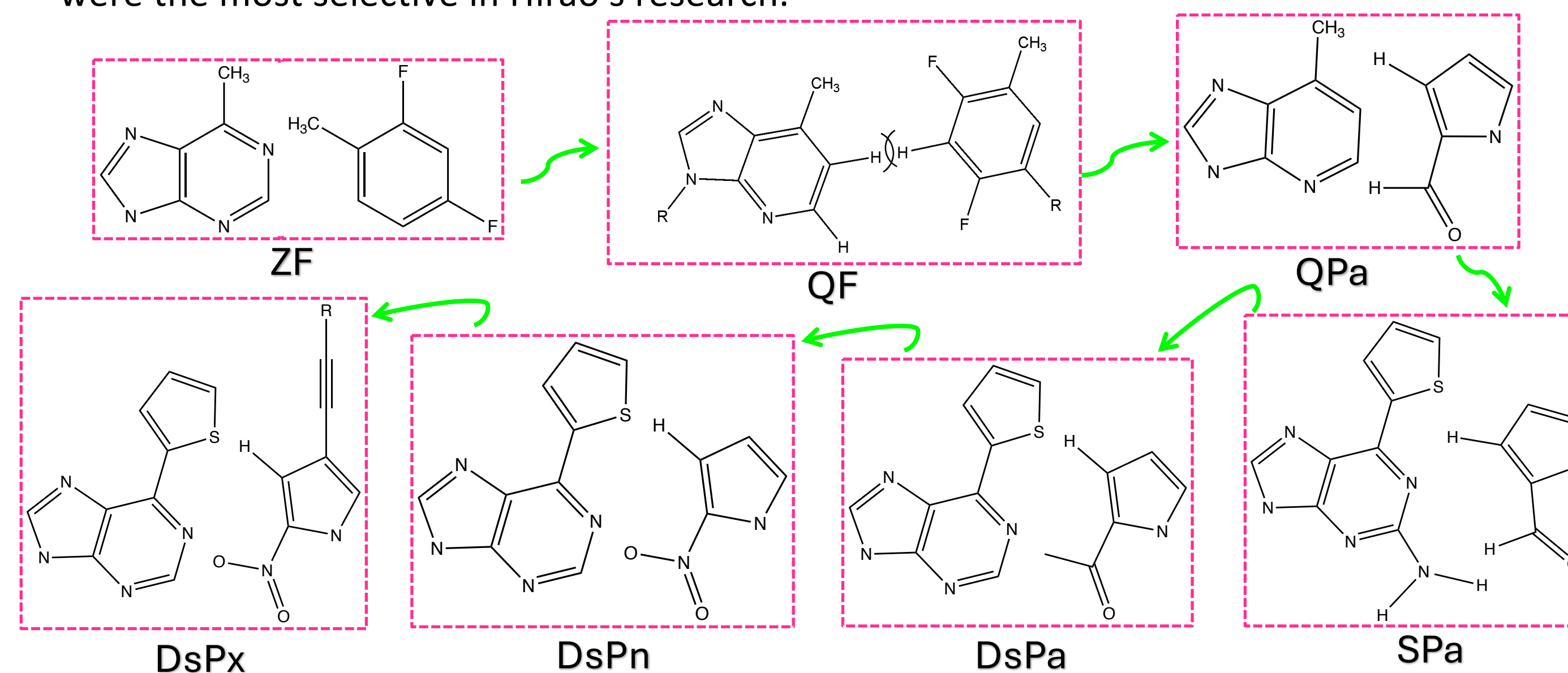


Introduction

In 1962, Alexander Rich proposed the development of the first artificial base pairs. He suggested the isoG-isoC pair, which had hydrogen bonds but differed in geometry from the natural G-C and A-T pairs[1-3].

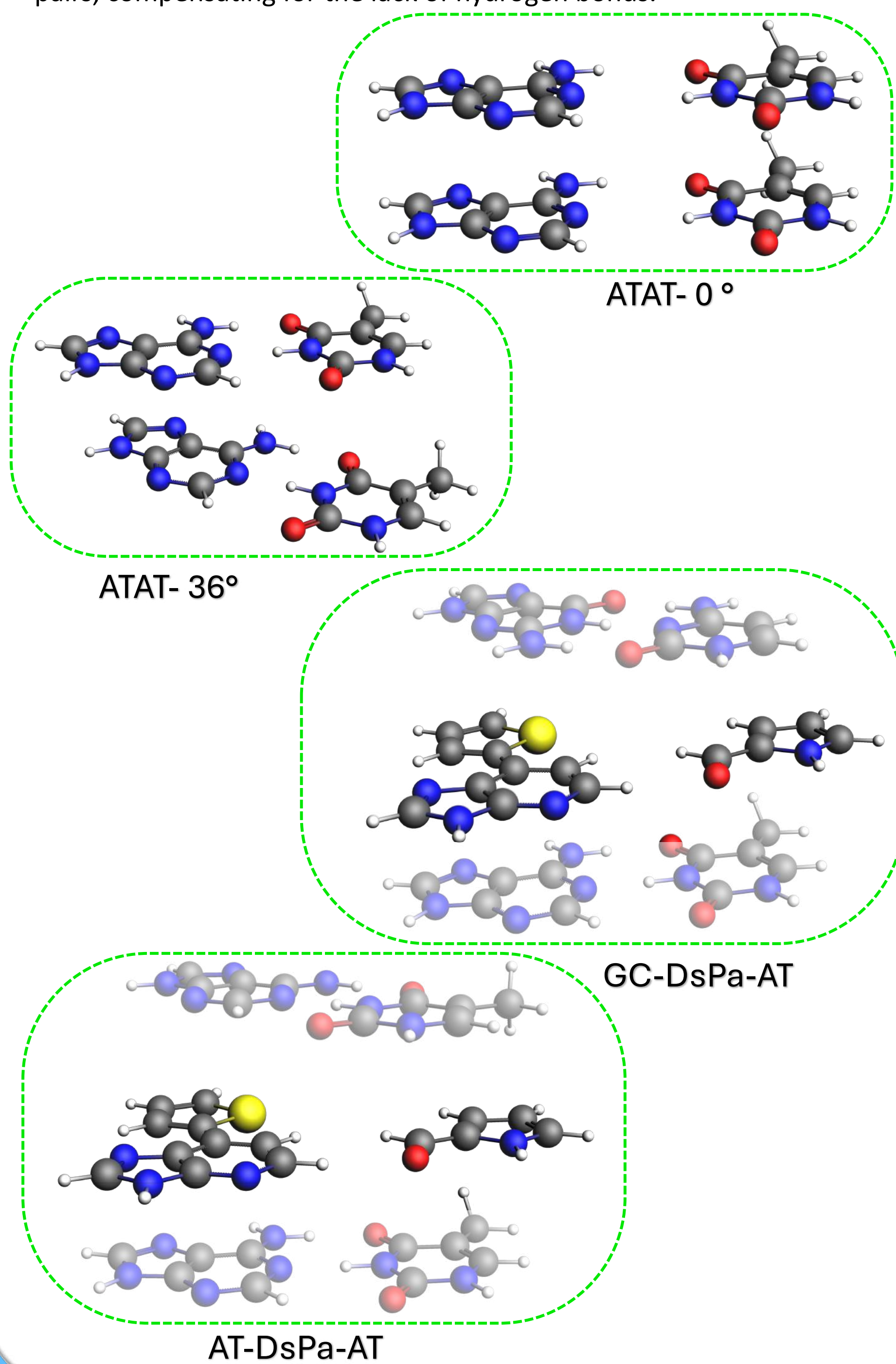


In 1998, Eric Kool's team reported the Z-F pair, a non-hydrogen bonding isostere of the A-T pair, which did not interact well with polymerase. They improved Z to Q, but the QF pair had hydrogen clashes. Hirano's team then modified F to create the Pa base, which paired well with Q. Pa paired with S to form a hydrophobic unnatural base pair (UBP). To improve shape complementarity, Hirao's team synthesized DsPa, but it had low PCR efficiency. Replacing the aldehyde group with a nitro group led to the Pn base, which improved this issue. They later designed Px, more hydrophobic than Pn. Ultimately, the Ds-Px pair showed the highest selectivity. Following Ds-Px, the pairs DsPn, QPa, and DsPa were the most selective in Hirao's research.



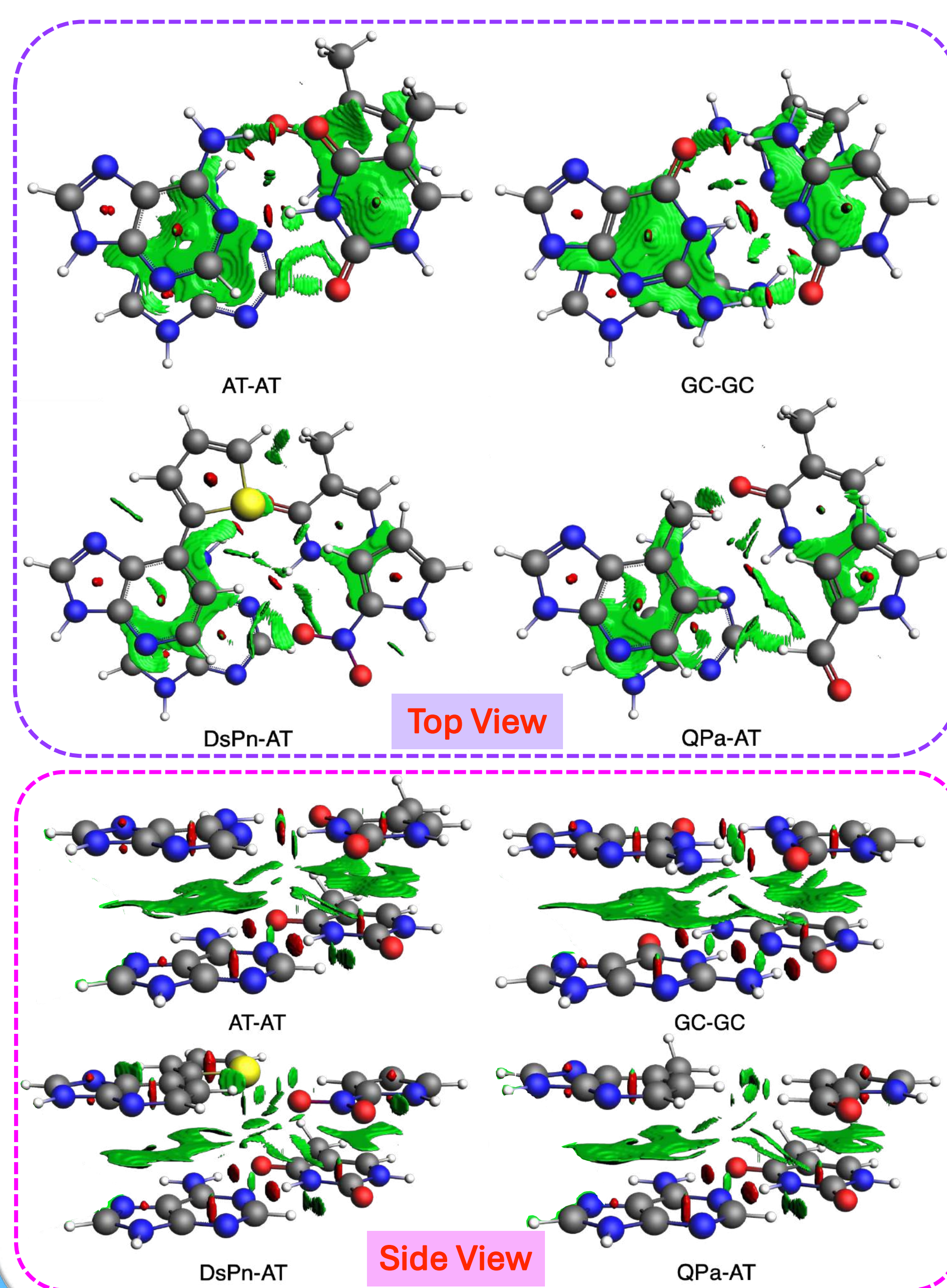
π - π stacking interactions

The analysis of π - π stacking interaction energies shows that such interactions significantly contribute to the selectivity of all our base pairs, compensating for the lack of hydrogen bonds.



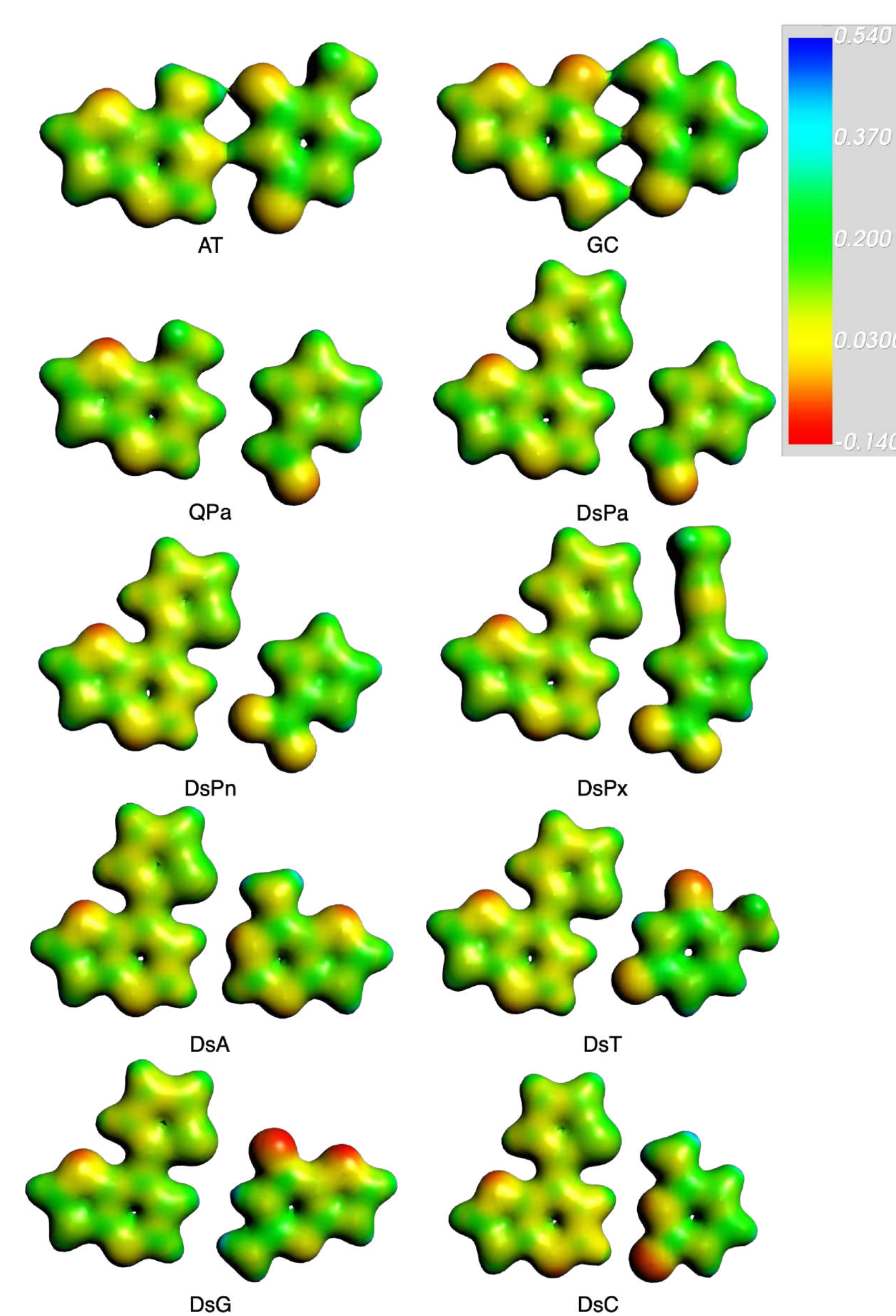
Non-Covalent Interactions (NCI)

NCI was calculated to identify non-covalent interactions, such as hydrogen bonds, van der Waals interactions, and π - π interactions. The red regions between the oxygen and hydrogen atoms indicate strong hydrogen bonding, which is crucial for the stability of the base pair. Additionally, green regions between the aromatic rings suggest the presence of van der Waals forces.



Molecular Electrostatic Potential (MEP)

The variation of electronic density can be illustrated through the MEP. In these base pairs, dispersion interactions are crucial for maintaining stability; without these interactions, the system would become unstable, causing the bases to separate. These values are relatively minor, and from a selectivity perspective, it is evident that such interactions will not significantly influence the behavior of these bases.



Electrostatic potential surfaces (at 0.01 au) from -0.140 (red, δ^-) to 0.540 (blue, δ^+) a.u. of the studied base pairs.

Conclusion

We examined a group of previously proposed and experimentally tested artificial DNA base pairs to understand their selectivity in comparison to Watson-Crick base pairs. Despite the absence of hydrogen bonds, we found that their selectivity is governed by π - π stacking interactions with adjacent base pairs. Our computational model successfully replicated the selectivity observed in laboratory experiments.

References

- [1] Kimoto, M., & Hirao, I. (2020).. *Chemical Society Reviews*, 49(21), 7602-7626
- [2] Kimoto, M., & Hirao, I. (2022). *Frontiers in molecular biosciences*, 9, 851646.
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