B-DNA structure and stability: the role of nucleotide composition and order

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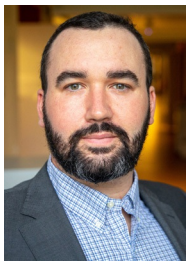


Celine Nieuwland | Trevor A. Hamlin | Célia Fonseca Guerra | Giampaolo Barone | F. Matthias Bickelhaupt

Invited for this month's cover are the groups of Célia Fonseca Guerra at the Vrije Universiteit Amsterdam and Leiden University, Giampaolo Barone from the Università degli Studi di Palermo, and F. Matthias Bickelhaupt at Vrije Universiteit Amsterdam and Radboud University Nijmegen. The cover picture shows the four primary interaction components (hydrogen bonding, cross-terms, base stacking, and solvation) that determine the stability of B-DNA duplexes. Quantum chemical analyses identify an interplay between the stabilizing hydrogen bonds between nucleotides that drive the formation of the DNA double-strand, and the destabilizing loss of stacking interactions within individual strands combined with partial desolvation. The sequence-dependence in the duplex stability originates mainly from the cross-terms, which can be attractive or repulsive. Read the full text of their Research Article at 10.1002/open.202100231.

What is the most significant result of this study?

The stability of duplex DNA does not solely depend on the base pair composition, but also on the order in which the nucleobases occur. In this work, we pinpoint the origin of these effects and provide guidelines for predicting the stability of DNA duplexes relative to their single-stranded counterparts. Our quantum chemical analyses unexpectedly identify the loss of stacking interactions within individual strands as a destabilizing factor in the duplex formation, in addition to the better-known effects of partial desolvation. We show that, and how, the sequence-dependence of the duplex stability originates mainly from the so-called diagonal interactions or cross-terms between nucleobases of two adjacent Watson-Crick pairs. These cross-terms can be stabilizing or destabilizing, depending on the attractive or repulsive nature of the diagonal electrostatic interactions.

What aspects of this project do you find most exciting?

It is exciting that both the structure and stability of large biomolecules such as DNA, can not only be simulated by quantum chemical computations but also understood and traced back to simple and intuitive physical principles.

What was the biggest challenge?

Biological systems are the product of ages of evolution, involving energy differences that are often tiny and yet, literally, of

vital importance. These circumstances constitute a challenge for elucidating the key physical principles behind the sequence-dependent differences in DNA stability. Nevertheless, through extensive analyses of the geometric and electronic structure of the single strands, we succeeded in developing a unified model to rationalize the stability of DNA duplexes.

What future opportunities do you see?

Our newly developed rules for the quantitative prediction of DNA duplex stabilities have the potential to contribute to a better understanding of all kinds of problems related to the function of DNA, gene expression, and genome stability.