

# Molecular recognition properties of “general” fluorobases – Unveiling the Janus face of organic fluorine

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Fluorine-substituted base analogues have proven invaluable as nonpolar nucleoside isosteres (NNI) to probe the physical forces that govern the stability of nucleic acids. When paired against natural bases, fluorinated analogues destabilize DNA and RNA helices and exhibit little binding sequence specificity. When paired opposite themselves, a considerable degree of stability is regained, and a selective pairing of fluorinated bases in the context of nucleic acids is observed. Apparently, the role of fluorine in molecular recognition strongly depends on the surrounding molecular environment.

Towards the goal of addressing the influence of the environment on the molecular recognition thermodynamics of organic fluorine, we, first, have undertaken a combined experimental/computational free energy study of fluorobenzene *self-pairing* in the context of duplex RNA.<sup>1</sup> The study reveals the determinants of the surprising stability of fluorobenzene self-pairs with increasing fluorine-substitution and demonstrates that it may generally not be sufficient to discuss molecular recognition properties of organic fluorine in terms of global molecular properties. Instead, analyses at an atomic level are required.

Second, potentials of mean force have been calculated for planar configurations of *NNIs with natural bases*. No differences in base pairing interactions between difluorobases and different natural bases are found, in agreement with experiment. Base pairing involving difluorobases is disfavored compared to Watson-Crick base pairing, but more favorable than if toluene is used as NNI. This is the result of similar desolvation costs of the NNIs, but decreased attractive base-base interactions involving toluene compared to difluorobases. Based on isosteric considerations, we proposed a 7-*N*-linked purine as a new “general base”, which was confirmed experimentally. A modified 7-*N*-linked 9-deaza-purine finally emerged to be the least destabilizing general base in the context of duplex RNA known to date.

1. Kopitz, H.; Zivkovic, A.; Engels, J. W.; Gohlke, H., Determinants of the unexpected stability of RNA fluorobenzene self pairs. *ChemBioChem* **2008**, 9, (16), 2619-22.