

Pseudo-Complementary Base-Pairing Involving Sulfur as a Robust Design Element in Crystal Engineering

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Pseudo-complementary base-pairing as in the 2-thiothymine–2-aminoadenine base-pair is shown to be a reliable interaction motif and thus a robust supramolecular synthon^[1] for the formation of co-crystals.^[2] The synthon comprises three hydrogen bonds, *viz.* an N—H \cdots O and an N—H \cdots N hydrogen bond, as in the Watson-Crick adenine–thymine base pair, plus an additional N—H \cdots S hydrogen bond. On the basis of the results of co-crystallization experiments^[4] and statistical searches of the Cambridge Structural Database, a detailed analysis of the interaction geometry of the N—H \cdots O/N—H \cdots N/N—H \cdots S interaction motif, denoted synthon $3s_{N:S;N:N;N:O}$, is performed. The results reveal significant differences compared to the interaction geometry of the related triply hydrogen-bonded N—H \cdots O/N—H \cdots N/N—H \cdots O interaction motif, *i.e.* synthon $3s_{N:O;N:N;N:O}$, which is applied for the preparation of anti-sense oligonucleotides.^[3] *Via* dispersion-corrected DFT calculations it is shown that synthon $3s_{N:S;N:N;N:O}$ is less stable than synthon $3s_{N:O;N:N;N:O}$ but still favorable enough to be a reliable synthon. The results are not only valuable for the application in crystal engineering but also for the understanding of the intermolecular interactions of 2-thiouracil in antisense oligonucleotides since structural data for that interaction was not accessible so far.

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