Quantifying Nucleic Acid Base Pairing Free Energy

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The free energy of base pairing and base stacking makes an important contribution to the stability of double-stranded DNA. Different models have been proposed to attribute this free energy to their various sources. Pairing interactions are of special interest because of their importance in controlling DNA complementarity. The entropy cost of forming hydrogen bonds between base pairs is offset by the concomitant release of water molecules originally hydrogen-bonded to the individual bases and this has been suggested as an important determinant of base pairing stability, but so far these entropic factors not been carefully quantified. Here we study a pair of nucleobases (A:T or G:C) in an aqueous solvent with up to 5,000 TIP3P water molecules using Monte Carlo simulations and umbrella sampling with full electrostatics and Ewald summation. The free energy of an A:T or a G:C pair is calculated to be stable by 7 to 8 kcal/mol. Calculating the entropic contributions separately, we find that the majority of this stability is due to the release of water as hydrogen bonds between the bases are made. Using these results, we are able to quantify for the first time how solvent entropy dominates DNA base-pairing complementarity.