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A comparison of left and right handed DNA double-helix models.

Henry Rzepa[1]

[1]Affiliation not available

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HENRY RZEPA

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CORRESPONDENCE:
h.rzepa@imperial.ac.uk

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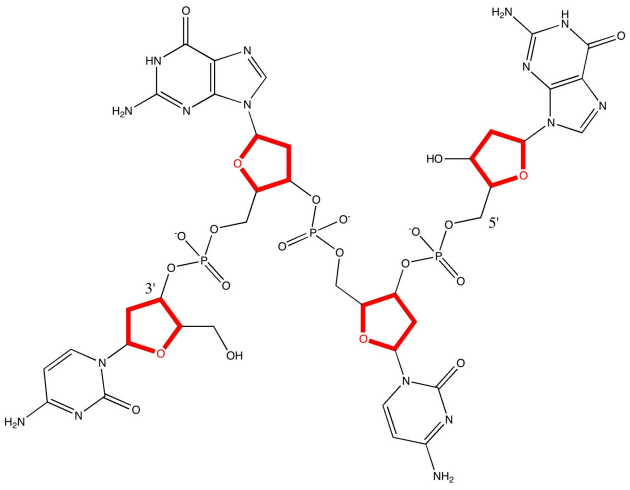
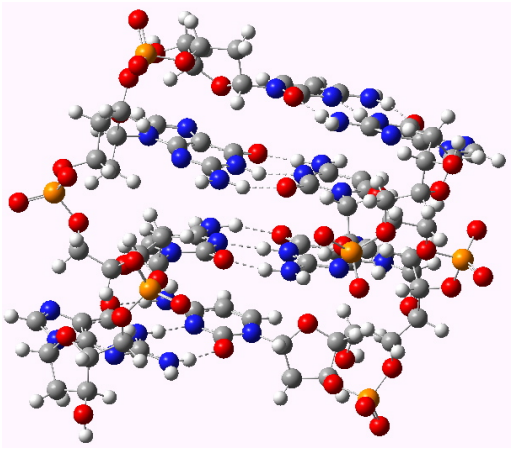
When Watson and Crick (WC) constructed their famous 3D model for DNA, they had to decide whether to make the double helix left or right handed. They chose a right-handed turn, on the grounds that their attempts at left-handed models all "*violated permissible van der Waals contacts*". No details of what these might have been were given in their original full article (or the particular base-pairs which led to the observation). This follow-up to my earlier post explores this aspect, using a computer model.



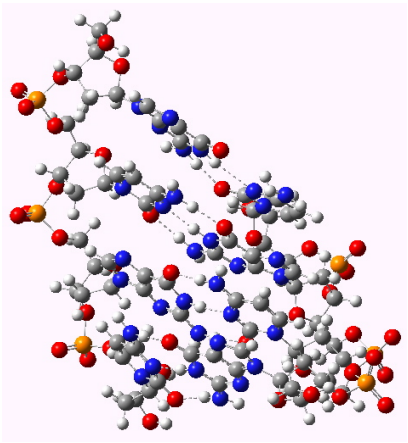
One half of a (CGCG) DNA strand

The DNA model used here is shown above; in shorthand it is d(CGCG)2. A crystal structure reveals it to form a (non-Watson-Crick) left-handed helix. If you open the 3D model below (based on a ωB97XD/6-31G(d)/SCRF=water optimisation), some of the short van der Waals contacts are measured. Most are around 2.25Å and the shortest is 2.1Å. It is worth noting that WC note in their article that a distance of 2.1Å for the B-form is acceptable (p92, bottom) and not a violation. All twelve hydrogen bond lengths H…O or H…N are normal, with lengths around 1.8Å. Given that a H…H distance is at its most **attractive** at ~2.4Å, and plenty of H…H distances of ~2.1Å are known from the crystal structures of organic molecules, one might conclude that (for the CG base pair), their hypothesis that the Z-form could be eliminated was wrong.



The DNA duplex d(CGCG) showing a left handed helix with short H...H contacts shown. Click for 3D

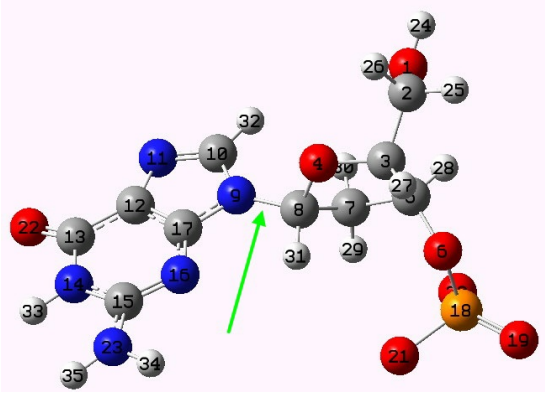
But might the original WC-right handed form for this system be at least competitive? There is one H…H of 2.05Å and quite a few at ~2.5Å (3D model below). The "violation" of van der Waals contacts is if anything slightly worse than with the left-handed helix. The total difference in the dispersion energy is a rather astonishing ~12 kcal/mol in **favour of the Z-form**. I will update this post (as a comment) when the relative free energies of the two forms are available (this calculation takes a while), but there is little doubt that the Z-form is indeed the more stable.



The DNA duplex d(CGCG) showing a right handed helix with short H...H contacts shown. Click for 3D

What can also be said about the Watson-Crick right handed form is that the hydrogen bonding is not so optimal. One of the twelve interactions between a (terminal) CG pair has some signs of being "*unzipped*", with an N-H…O=C distance of ~1.9Å (there is no sign of similar unzipping in the Z-form). One must wonder whether this difference in the Z- and B-helices for the CG pair has been exploited in nature.

One crucial aspect of DNA is the local conformation about the bond connecting the base and the ribose, N9-C8 in the diagram below(green arrow).



Conformation of the base-ribose unit

An analysis of this bond can be expressed in terms of NBO theory. This clearly shows a strong interaction energy (E2) between the lone pair on N9 and the C8-O4 antibonding orbital of 13.3 kcal/mol, a classical anomeric effect in fact. In this case, it promotes the local conformation of this unit, which has a significant effect on the final model.

What else can analysis of the wavefunction tell us? Well, curiously, the optical rotation of this particular small oligomer has never been reported in the literature, and an intriguing question is whether it might have proved useful to distinguish between B- and Z-forms of the duplex? To do this, one needs a reasonably reliable way of computing [α]D for **both** isomers. This is because optical rotations are not reliably additive, and it is difficult to estimate them accurately based purely on the fragments present in the molecule. In 2011, is is now perfectly possible to calculate this quantity quantum mechanically, even for 250 atoms, using a reasonable basis set and making allowance for solvation (which is known to affect the calculated rotation). The values (CAM-B3LYP/6-31G(d)/SCRF=water) for the Z-isomer are 66° and 32° for the B-isomer. Of course the model is not complete, lacking a counterion for the phosphate and explicit water molecules, but even so, it might appear that the reason optical rotations are not reported is that they truly are not useful!