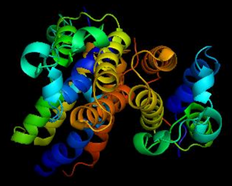
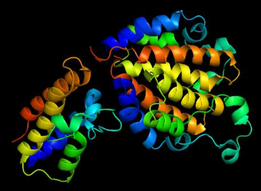


The Role of Dual Hydrogen Bonding in Biological and Medicinal Chemistry



Project by Luke Lewis-Borrell | Under the Supervision of Prof. Bernard Golding | School of Chemistry

Aims

- **Model** dual hydrogen bonding in suitable systems
- **Quantitatively** assess the contributon of dual hydrogen bonding in the chosen systems

Background

- Hydrogen Bonding is one of the most important phenomena in Biology and Chemistry, as without it life would not exist.
- **But, what is a Hydrogen Bond?** A hydrogen bond is a bond which occurs between two molecules or two groups in the same molecule resulting from an attraction between a proton in one entity and an electron-rich atom in the other.

  E.g. as in water, which due to strong hydrogen bonding between protons and oxygen is a liquid at room temperature and forms the basis for life on earth.

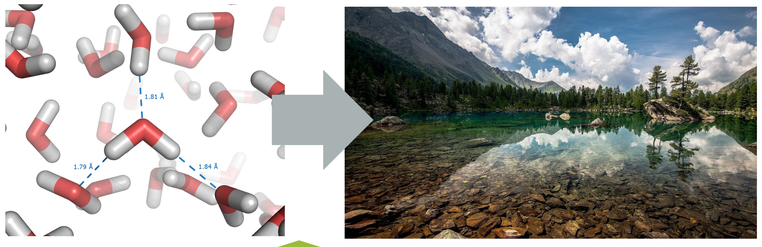
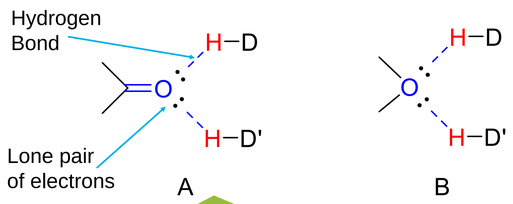


Figure 1: The real life consequences of hydrogen bonding in water molecules.

- **Dual Hydrogen Bonding** (shown in scheme 1) involves two hydrogen bond donors donating to one acceptor, usually an oxygen.
- This mode of hydrogen bonding could cause some interesting effects, for example: Increased reactivity of a carbonyl group (scheme 1A) through a process called partial protonation.[1]



Scheme 1: Dual hydrogen bonding with a carbonyl group (A) and ether oxygen (B) [D-H and D-H' are hydrogen bond donors]

Dual Hydrogen Bonding in Drug Discovery

- The importance of dual hydrogen bonding can be observed within bromodomains (BRDs), which are enzymes important for the treatment of cancer.
- The carbonyl oxygen of a *N*-acetyllysine residue of human lysine acetyltransferase enzyme forms hydrogen bonds to both an asparagine NH and a water molecule linked to a tyrosine hydroxyl group within the BRD (Figure 1).[2]
- Drugs targeting BRDs could be designed to mimic this double hydrogen bonding motif.

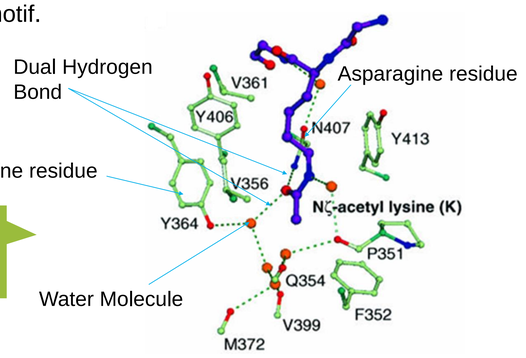


Figure 2: Bromodomain dual hydrogen bonding

Perspective

- There is a lack of quantitative understanding, in particular of the energetic benefit of two hydrogen bonds over one bond.
- We are therefore attempting to define the energetic contributions of dual hydrogen bonding and its impact on the reactivity of ethers, amides and thioesters (Figure 2), using techniques such as nuclear magnetic resonance (**NMR**)**, microwave spectroscopy** and **isothermal titration calorimetry (ITC)**.
- The study is therefore relevant to a vast array of chemistry and biochemistry with numerous downstream applications in prospect.

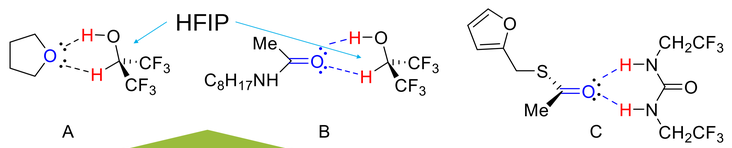
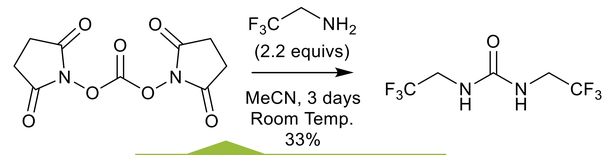


Figure 3: Representative complexes exhibiting the possibility of dual hydrogen bonding. Complex in B is designed to model the *N*-acetyllysine within the BRD while C models acetyl-coenzyme A.

Studies of Varying Molecular Systems

- A proposed dual hydrogen bonding urea was synthesised (Scheme 2)



Scheme 2: Synthesis of Dual Hydrogen Bonding Urea

- A crystal structure of the synthesised urea showed the presence of a 'urea tape' which dual hydrogen bonded to itself (Figure 4)

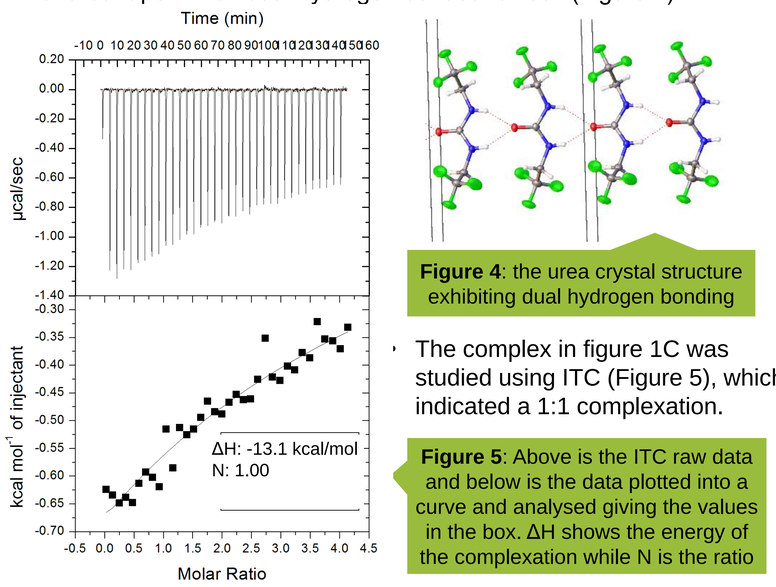


Figure 4: the urea crystal structure exhibiting dual hydrogen bonding

- The complex in figure 1C was studied using ITC (Figure 5), which indicated a 1:1 complexation.

Figure 5: Above is the ITC raw data and below is the data plotted into a curve and analysed giving the values in the box. ΔH shows the energy of the complexation while N is the ratio

Conclusion

- We have found that for the systems studied with hexafluoroisopropanol (HFIP) as hydrogen bond donor, 1:1 complexes are formed with no evidence of 2:1 complexation at higher concentrations of HFIP.
- Work is continuing to determine whether a C-H hydrogen bond is present. An alternative possibility is that a C-F bond interacts with N-H in *N*-acetyloctylamine or C2-H in tetrahydrofuran.

References and Acknowledgments

[1] e.g. Acyl dehydrogenases: W Buckel, B M Martins, A Messerschmidt, B T Golding, *Biol Chem*, 2005, **386**, 951 [2] D J Owen *et al*, *EMBO J*, 2000, **19**, 6141

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