ELECTRON DENSITY TOPOLOGICAL CRITERIA FOR HYDROGEN BONDING
AND THE NEED TO RE-DEFINE VDW ATOMIC RADIUS
WHEN IS A HYDROGEN BOND NOT A HYDROGEN BOND?
THE NEED FOR A QUANTUM-MECHANICALLY CONSISTENT DEFINITION

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Abstract

Hydrogen bonds are essential for life as we know it. Although considered weak by physical standards, and in comparison with covalent interactions, cooperative hydrogen bonding nonetheless results in the stabilisation of the three-dimensional structure of proteins, carbohydrates and nucleic acids. Enzyme-substrate interactions and drug-ligand binding are all strongly influenced by hydrogen bonding. The anomalous and essential physical properties of liquid water as a reaction medium for biological reactions, together with the hydration structure of solutes in aqueous solution, depend critically on the phenomenon of hydrogen bonding.

In this presentation I explore some recent theoretical quantum mechanical studies of the factors affecting hydrogen bonding in model systems and the light that these studies throw on the experimental methods used for 'detecting' this type of interaction. Our original interest was in the aqueous solution structure of complex carbohydrates and oligosaccharides, as studied by NMR and molecular mechanics / dynamics. During the course of this work it became clear that many standard MM/MD packages modelled long-range interactions, such as hydrogen bonds, rather badly. We thus decided to make extensive use of glycols and binary glycol-water systems as a computationally amenable model of carbohydrate hydration behaviour and hydrogen bonding in aqueous solution for detailed ab initio quantum mechanical studies. Detailed electron density topological analysis based on Bader's AIM theory, together with NBO natural population analysis and the application of density functional theory (DFT) methods, have led to the following conclusions:

i) vicinal 1,2-diols do not form intra-molecular hydrogen bonds, quite contrary to the widespread assumption made in the literature based on spectroscopic data;

ii) this finding can be extended to include complex organic structures, such as sugar ring systems and antibiotics, containing the 1,2-diol synthon - thus glucopyranose does not exhibit intra-molecular hydrogen bonds between adjacent ring OH groups, whereas the hydrated form shows enhanced hydrogen bond cooperativity;

iii) we have found it necessary to re-evaluate the usual experimental NMR and IR spectroscopic criteria used for detecting hydrogen bonds, especially where the observed NMR downfield or IR red-shifts are small;

iv) both the acceptor-donor distance and the geometry of the interaction are important for hydrogen bonding and our results have led to a re-interpretation of appropriate, modified VDW atomic radii suitable for determining whether hydrogen bonds are likely or not, based on electron density contours since the classical Bondi or Pauling values are in general far too large, leading to the over-optimistic assessment of whether hydrogen bonding is likely;

v) these findings have serious implications for the parameterisation of MM force-fields used for biological systems, for example, in drug-binding or receptor studies, since these frequently do not perform reliably for long-distance interactions and the parameter optimisation often uses a 'training set' which includes ethylene glycol as the archetypal -O-H...O-H hydrogen bond.

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Relevant bibliography:


