

The Hydrogen Challenge: Where are we now?

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The Hydrogen Challenge

In 1998, Richard Harlow [1] remarked:

"I have a lot of confidence in structures where the hydrogen atoms were found and refined to reasonable positions (e.g. $0.85 < C-H < 1.05 \text{ \AA}$) and with reasonable thermal parameters (e.g. $2.0 < Biso < 6.0 \text{ \AA}^2$). The hydrogen atoms appear to be very sensitive indicators of a reliable structure and simply don't refine well if there are even modest errors in the data or the model, or if the data is insufficient for the structural analysis."

He went on to issue his famous Hydrogen Challenge":

"[the challenge is] to find a classic example ... of a published organic or organometallic structure where all of the hydrogen atoms have been found and refined ... and where the structure is demonstrably incorrect in some substantial way."

There appears to be no examples where the challenge has been defeated, which leads one to ask the opposite question.

"If the non-hydrogen atoms in a structure are well behaved and refine well, should we also refine the hydrogen atoms?"

The answer depends upon the quality of the diffraction data, which in turn depends upon the quality of the crystal.

Hydrogen Atoms in the CSD

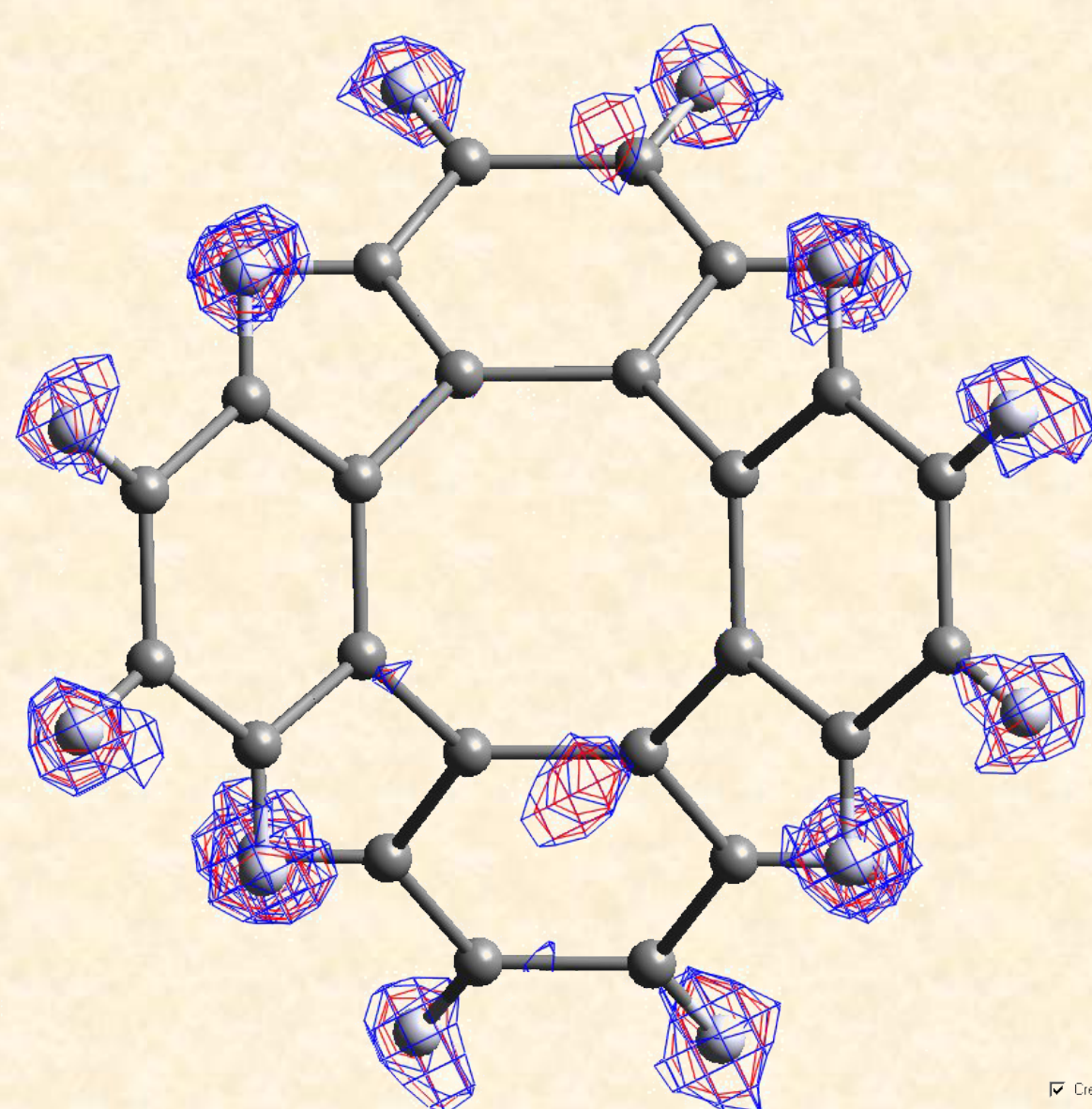
A survey of C-H and N-H distances in the 2010 release of the CSD suggests that the reported structures are heavily influenced by the default values commonly provided for riding restraints.

It is our belief that much modern diffraction data deserves a better fate than this, and that analysts should choose a refinement strategy appropriate for the data being processed.

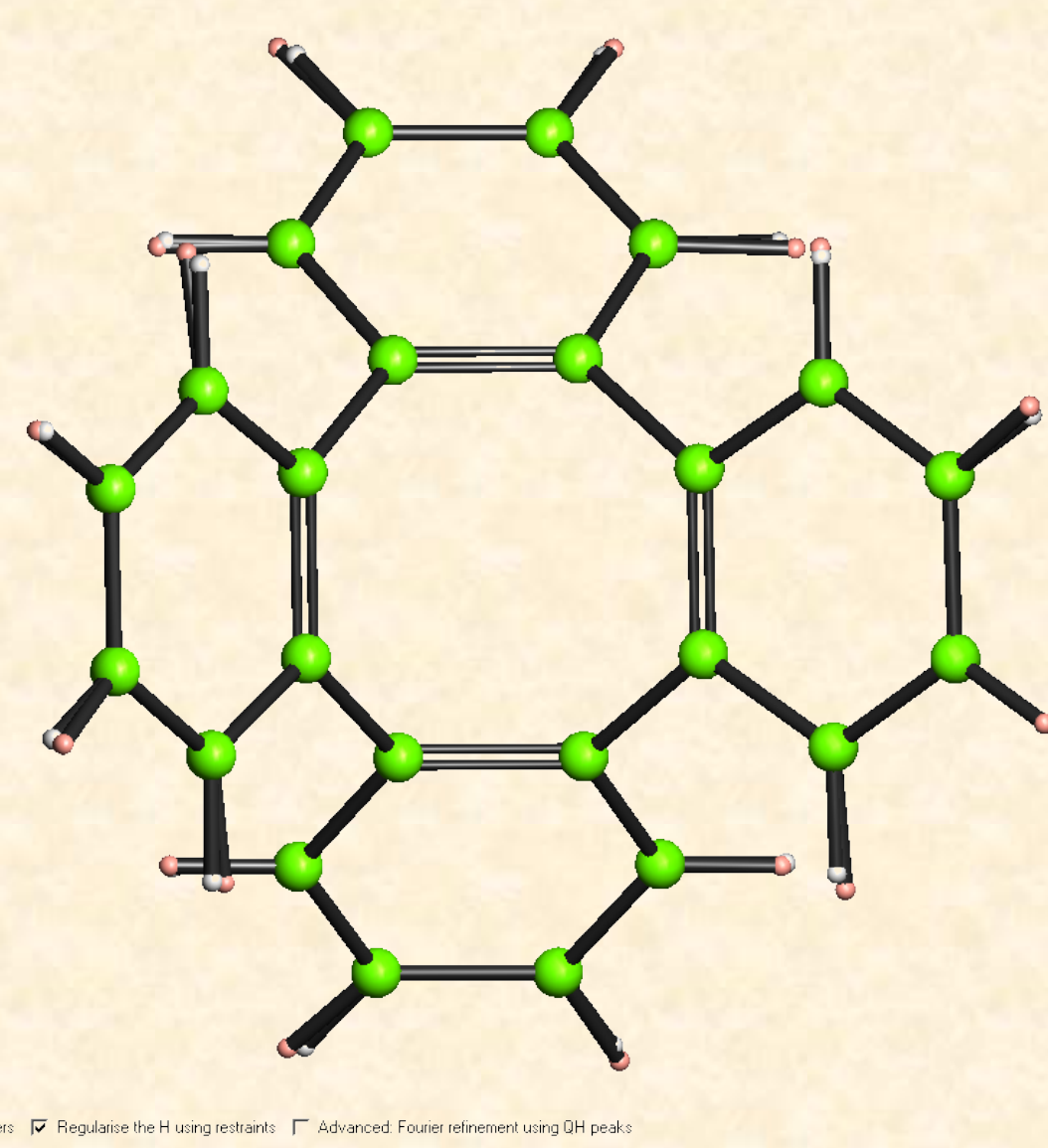
- **Poor Data:** Use calculated hydrogen positions and a riding model
- **Fair Data:** Use slack geometrical restraints
- **Good Data:** Refine the hydrogen atoms freely

Example

This structure [3] is from data collected on a CCD diffractometer at room temperature (low temperature data was also collected). The final R factor is 4% for all data.



Difference electron density.



Predicted hydrogen atoms (white) and peaks found in the difference map (pink)

Simply computing the positions of the hydrogen atoms, refining them with restraints or refining them freely has almost no effect on the final R factor, or the final non-hydrogen atom parameters.

			C-H calc	C-O Obs	Delta Q-H	C-H free refinement	C-H Restrained	Delta Free-Rest
C(2) - Q(12)	H(21)	0.95	1.04	0.21	1.01	1.00	0.01	
C(3) - Q(3)	H(31)	0.95	0.97	0.05	0.98	0.97	0.01	
C(4) - Q(7)	H(41)	0.95	1.00	0.13	0.95	0.94	0.01	
C(5) - Q(13)	H(51)	0.95	0.97	0.13	1.02	0.99	0.03	
C(8) - Q(14)	H(81)	0.95	0.95	0.07	1.01	0.99	0.02	
C(9) - Q(17)	H(91)	0.95	0.99	0.15	1.00	0.98	0.02	
C(10) - Q(11)	H(101)	0.95	1.09	0.14	0.98	0.97	0.01	
C(11) - Q(4)	H(111)	0.95	0.92	0.04	1.00	0.98	0.02	
C(14) - Q(5)	H(141)	0.95	1.06	0.11	0.99	0.97	0.02	
C(15) - Q(2)	H(151)	0.95	1.01	0.10	1.00	0.99	0.01	
C(16) - Q(15)	H(161)	0.95	1.07	0.17	0.98	0.97	0.01	
C(17) - Q(10)	H(171)	0.95	1.01	0.06	1.00	0.98	0.02	
C(20) - Q(1)	H(201)	0.95	1.07	0.16	1.01	0.99	0.02	
C(21) - Q(9)	H(211)	0.95	1.05	0.11	0.98	0.97	0.01	
C(22) - Q(8)	H(221)	0.95	1.13	0.19	0.99	0.97	0.02	
C(23) - Q(5)	H(231)	0.95	1.00	0.06	1.01	0.99	0.02	
Mean esd					0.014	0.011		

Why Bother With Hydrogen Atoms?

The structure factor is a complex number (has both magnitude and phase). The magnitude can be represented by:

$$F^2 = A^2 + B^2$$

where A is the real and B the imaginary part.
and

$$A_{hkl} = \sum_j f_j \cos 2\pi(hx+ky+lz)$$

with B given by similar sin terms.

This equation can be factored into the hydrogen and non-hydrogen atoms.

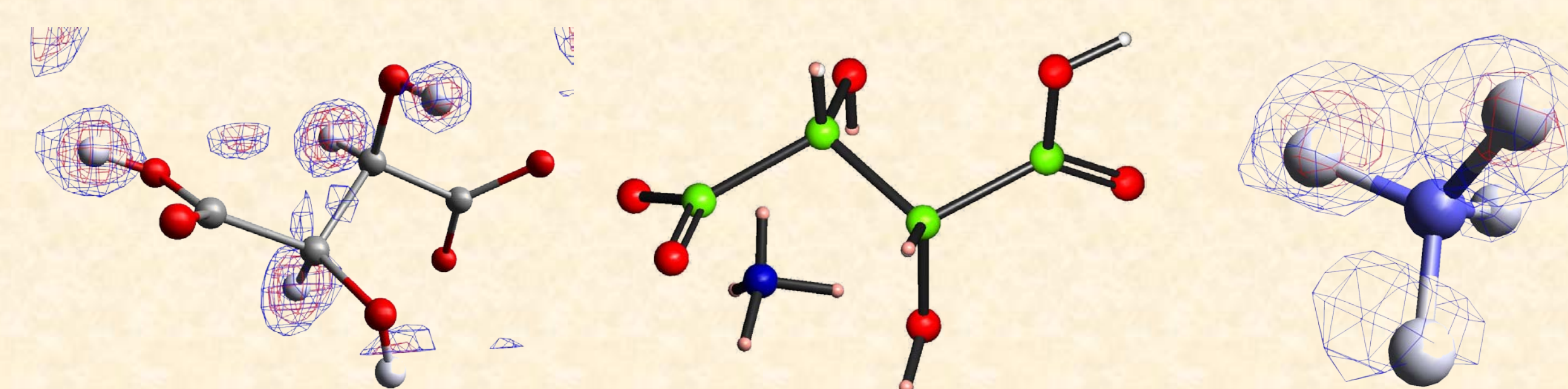
$$A_{hkl} = \sum_j^{non-H} f_j \cos 2\pi(hx+ky+lz) + \sum_j^H f_j \cos 2\pi(hx+ky+lz)$$

The hydrogen atoms must be included in the model at something like their 'true' position [2].

$$M = \sum (F_o - F_c)^2$$

$$M = \sum (|F_o| - |F_{c_{nonH}} + F_{c_H}|)^2$$

**Leaving H atoms out leads to a systematic error in F_c ,
and thus to a systematic error in the other refined parameters.**



CRYSTALS makes no attempt to automatically compute (white) positions for hydrogen atoms bound to N or O, but they can generally be located in difference maps (pink), even on ammonium ions. If they cannot be located or positioned automatically, CRYSTALS contains tools for manually placing (and then refining) them.

Who Cares?

Generally, not single crystal crystallographers. So long as the hydrogen atoms are there, their exact position is not important for routine structure determination.

However, there is continuing interest in solving structures from powders, and proton NMR provides additional information to help resolve the degeneracy of the data. Dependable predicted hydrogen positions are needed in order to reliably predict the chemical shifts. In the absence of reliable published hydrogen geometries, people working on structure prediction from NMR data are "optimising" hydrogen positions using DFT programs such as CASTEP. It's a great pity they need to do this since Nature has already optimised the positions during crystal growth.

Hydrogen distances (right) as deposited in the CSD, and as optimised in CASTEP (for FLUBIP, structure shown below).

"Chemical shift computations on a crystallographic basis: some reflections and comments" [4]

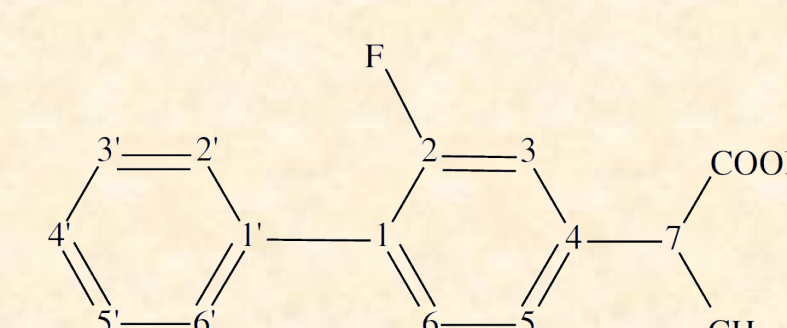


Table 1. Bond lengths involving hydrogen atoms for X-ray, H-optimised and fully-optimised structures of flurbiprofen²⁰

Bond	Bond length/Å	
	X-ray	Calculated (all atoms relaxed)
O-H	1.286	1.023
O...H	1.358	1.618
O-H...O	2.641	2.641
Methyl C-H	1.128	1.091
Aromatic C-H	1.132	1.083
C7-H	1.149	1.090

Magn. Reson. Chem. 2007, 45, S174-S186

1. Richard Harlow. The Hydrogen Challenge. <http://www.pitt.edu/~geib/challenge.html> (1998).
2. David J. Watkin, *J. Appl. Cryst.*, 41, 491-522, (2008).

3. Alice Williams, Part II Thesis, Oxford (2002).
4. Robin K. Harris, Paul Hodgkinson, Chris J. Pickard, Jonathan R. Yates and Vadim Zorin, *Magn. Reson. Chem.*, 45, S174-S186 (2007).