

Iffy imidazoles: misplaced hydrogen atoms and undetected disorder

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The imidazole ring occurs in drugs such as cimetidine. Its protonation state in histidine is important in biological systems since this amino acid often participates in proton relays. The NH group of one neutral imidazole ring frequently hydrogen bonds to N of an adjacent ring; the similarity of electron density between NH...N and N:...HN muddles the assignment of protonation sites. Malinska et al. [1] developed geometrical criteria for the protonation state of histidine: differences in bond length between C-NH and C=N, along with differences in bond angle between C-NH-C and C=N-C. A precise neutron diffraction study at 103 K of imidazole itself [2] gave 1.347 and 1.322 Å, 107.1, 105.1°.

A search of the 2018 version of the CSD for non-fused neutral imidazole rings in organic structures with R ≤ 10% and no recognized disorder yielded 547 hits. The mean difference between C-NH and C=N bond distances was 0.024(12) Å, and between C-NH-C and C=N-C angles it was 2.3(8)°. In 5 structures both differences are sizeably negative, implying that the H atom has been misplaced. In two of these, swapping NH for N would necessitate rearrangement of other H atoms. Based on deposited structure factors for 4,5-bis(1H-tetrazol-5-yl)-1H-imidazole monohydrate, refcode YOTYOW [3], a difference map made after omitting hydrogen atoms prompted the conjecture that instead of a neutral hydrate, the structure is an ammonium salt with one anionic tetrazole moiety. Re-refinement lowered R(obs) from 7.1 % to 4.9 %. For a sizeable number of structures the absolute values of both differences are small, suggesting previously undetected disorder of H atom placement, even though Drew and colleagues [4] had presented a structure where packing required 50:50 disorder and analysed 3 similar cases.

[1] M. Malinska et al. (2015) *Acta Cryst. D*, **71**, 1444-1454.

[2] R. K. McMullan et al. (1979) *Acta Cryst. B*, **33**, 688-691.

[3] M. Guo (2009) *Acta Cryst. E*, **65**, o1403.

[4] M. G. B. Drew et al. (2008) *J. Chem. Cryst.* **38**, 507-512.