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Misplaced hydrogen atoms and undetected disorder in imidazoles and pyrazoles

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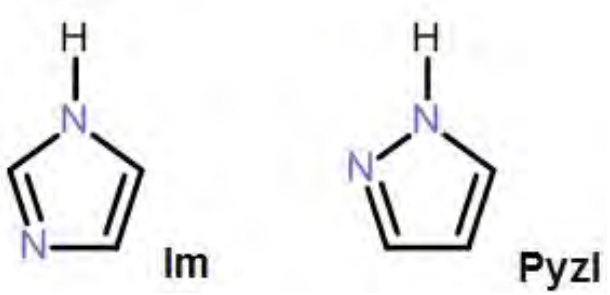
Imidazole (Im) and pyrazole (Pyzl) rings occur in drugs such as cimetidine and celecoxib. The Im ring of histidine is important in biological systems since it often participates in proton relays. The NH group of one neutral Im or Pyzl ring frequently hydrogen bonds to N of an adjacent ring; the similarity of electron density between NH…:N and N:…HN muddles the assignment of protonation sites. Geometrical criteria can be more reliable.

Malinska et al. [1] developed 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 were most significant. A precise neutron diffraction study at 103 K of Im [2] gave 1.347, 1.322 Å and 107.1, 105.1°. A search of the 2018 version of the CSD for non-fused neutral Im rings in organic structures with R <= 10% and no recognized disorder yielded 547 hits with 478 unique refcodes. The mean difference DISDIF between C-NH and C=N bond distances was 0.024(12) Å; between C-NH-C and C=N-C angles (ANGDIF), 2.3(8)°. In 5 structures both differences are < -0.01 Å and < -0.8°, implying that the H atom has been misplaced. Alterations are suggested. For a sizeable number of structures both differences have small absolute values, suggesting previously undetected NH/N disorder.

A similar search for Pyzl structures yielded 723 hits, 635 unique. Pyzl itself with Z' = 2 is not a totally reliable guide to geometry: a comprehensive variable-temperature study [3] showed small amounts of charge transfer from one ring to another and NH/N disorder. Their structure determination at 100 K gave, for the independent molecules, C-NH and C=N distances of 1.338, 1.334 and 1.347, 1.330 Å, C-NH-N and C=N-NH angles of 112.2, 104.2 and 112.2, 104.5°. Notwithstanding the closeness of bond distances, the differences in bond angles are unmistakeable. Nine structures have DISDIF < -0.01 Å and ANGDIF < -3.3°, implying that the wrong N atom has been protonated; 5 are corroborated by CheckCIF Alerts for clashes. Most symmetrically substituted Pyzl structures have 50:50 NH/N disorder, and the prevalence of smaller ANGDIF values suggests widespread partial disorder.



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