Conformation and Histamine Activity

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AN explanation for the diverse behaviour of histamine and histidine has been suggested by our X-ray crystal structure study of histamine acid phosphate monohydrate. Although histamine has the same basic skeleton as histidine, the latter exhibits neither the adverse biological reactions of histamine nor the beneficial effects of an antihistamine. Many of the common antihistamines are believed to function because of a structural similarity to histamine, but this hypothesis has yet to be proved.

The acicular crystals of histamine acid phosphate monohydrate are monoclinic, space group $P2_1/n$ with $a = 12{\cdot}692 \pm 0{\cdot}011$, $b = 13{\cdot}193 \pm 0{\cdot}006$, $c = 7{\cdot}790 \pm 0{\cdot}002$ Å, $\beta = 104{\cdot}74 \pm 0{\cdot}04°$; $D_m = 1{\cdot}671$, $Z = 4$, and $D_c = 1{\cdot}673$; 2104 reflections with counts $> 1{\cdot}2$ times background were considered to be observed and were used in the analysis.

The structure was solved by locating the two phosphorus atoms in the three-dimensional Patterson and calculating a minimum function based on one phosphorus–phosphorus vector. The two PO_4 units were easily located and the positions of the remaining atoms were found from subsequent Fourier syntheses. The structure was refined by least-squares methods, first with isotropic and then with anisotropic thermal parameters to a final R of 0·060. The hydrogen atoms were located from a difference Fourier; two further cycles of least-squares further reduced R to 0·044.

The distances and angles in the histamine cation are in excellent agreement with the values reported by Donohue and Caron[1] for the structurally similar molecule histidine, the average difference between chemically equivalent bonds being 0·012 Å. However, a view down the carbon–carbon bond in the side chain in each of the two molecules given in the Figure suggests a possible difference for the radically different physiological activity of the two compounds. In the case of histamine the quaternary nitrogen is *trans* to the imidazole ring but in histidine the configuration is *cis*. Whether this difference in configuration persists in solution and accounts for the difference in the biological activity may be confirmed by studies currently in progress.

A second feature of interest is the two acid phosphate groups, $H_2PO_4^-$. In each anion there are two long P–O distances of an average $1{\cdot}562 \pm 0{\cdot}002$ Å and two shorter P–O distances of an average $1{\cdot}500 \pm 0{\cdot}002$ Å. The difference Fourier demonstrated that the long P–O bonds each contain the hydrogen atom required in the acid

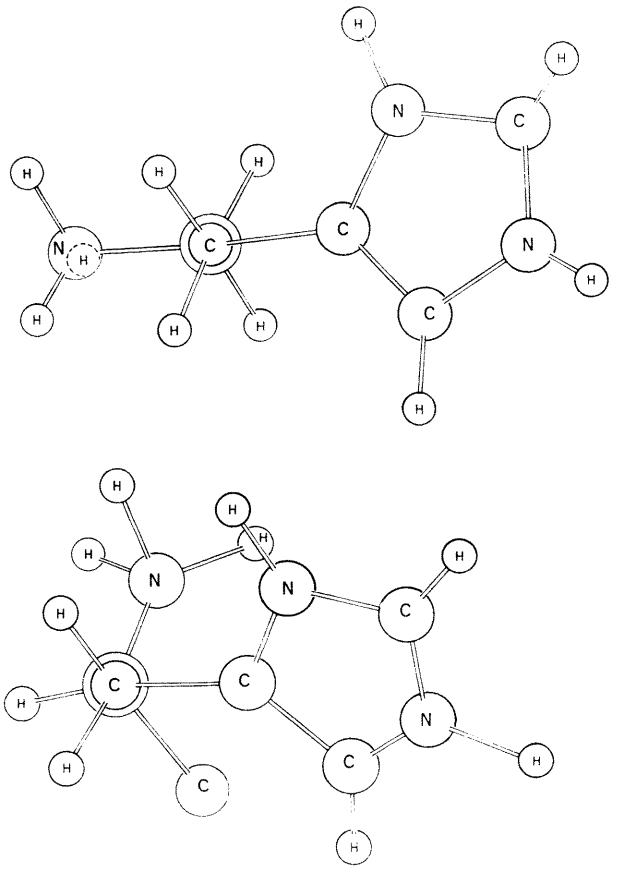

FIGURE. *The upper molecule is a view down the* C–C *bond in the histamine cation. The lower molecule represents a view down the corresponding* C–C *bond in the histidine cation.*

phosphate group. In both cases the P–O bonds are shorter than the sum of the single-bond covalent radii, indicating some double-bond character.

[1] J. Donohue and A. Caron, *Acta Cryst.*, **1964**, **17**, 1178.

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