The Conformation of Histamine in Solution: ^{1}H Nuclear Magnetic Resonance Study

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Summary In contrast to the solid-state, the ^{1}H n.m.r. spectrum in D_2O solution of the histamine univalent cation indicates that the $-CH_2CH_2N^+$ side-chain has approximately equal proportions of the *trans*-rotamer and both *gauche*-rotamers.

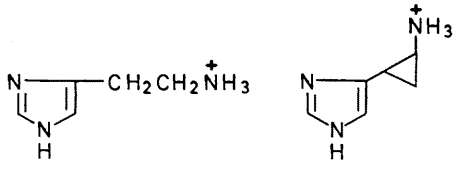
CURRENT interest in the solid-state and solution conformations of molecules of pharmacological importance[1] has prompted this magnetic resonance study in aqueous solution of the histamine univalent cation (I), the form expected to predominate at physiological pH.

At 100 MHz the ^{1}H n.m.r. spectrum shows a long-range coupling (*ortho*-benzylic type) of $-0{\cdot}8$ Hz between the upfield ring-proton and the first side-chain methylene group. The decoupled methylene multiplet was analysed as an AA'BB' system and is superficially a situation in which L (defined as $J_{AB} - J_{AB'}$) could be zero. Comparison of calculated and experimental spectra indicate that L may have a maximum value (sign undetermined) of *ca.* 1 Hz, in which case the individual vicinal coupling constants become 7·75 and 6·75 Hz.

The $-CH_2CH_2N^+$ side-chain of histamine can have three possible conformations, one *trans* (II) and two *gauche* (IIIa, IIIb). Under the assumption of 60° dihedral angles and only two vicinal coupling constants, J_T and J_G, the value of L is given by

$$L = (\tfrac{1}{2} - \tfrac{3}{2}n_T)(J_T - J_G)$$

where n_T is the fraction of the *trans*-conformer.[2] Within the range 7·5—15 Hz for $J_T - J_G$ and with L equal to ± 1 Hz, the proportion of *trans*-conformer is between 0·25 and 0·45 while the proportion of each *gauche*-conformer is between 0·375 and 0·275.

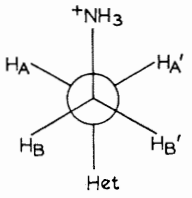


(I) (IV)

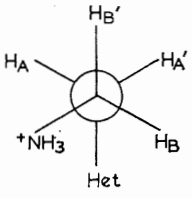
The long-range benzylic coupling of $-0{\cdot}8$ Hz (negative sign with respect to the cross-ring coupling, assumed positive) seems to be typical of an alkyl side-chain (values quoted $-0{\cdot}6$ to $-0{\cdot}9$ Hz for benzene derivatives[3]).

We conclude that the n.m.r. spectra indicate that for the histamine univalent cation in D_2O, the $-CH_2CH_2N^+$ side-chain has approximately equal proportions of the *trans*-rotamer (II) and both the *gauche*-rotamers (IIIa, IIIb) and that there is little conformational preference about the ring to side-chain bond. This result supports Kier's conclusion based on extended Hückel molecular orbital calculations, that the *trans*- and *gauche*-forms have very nearly equal total energies.[4] Our conclusion contrasts with the recent

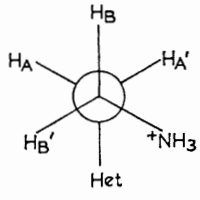
X-ray study of crystalline histamine acid phosphate, which showed that it exists entirely in the *trans*-conformation.[5]



(II)



(IIIa)



(IIIb)

The solid-state conformation of histamine acid phosphate (*trans*) also was different from that of histidine (*gauche*) and it was suggested[5] that, if this conformation difference persists in solution, it may be of significance in regard to the lack of histaminic and antihistaminic properties of histidine. This suggestion seems unlikely in the light of the present findings and recent reports that the *trans*-analogue, 2-(4-imidazolyl)cyclopropylamine (VI), with a fixed imidazolyl–amino relative orientation, is only a very feeble histamine agonist.[6]

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