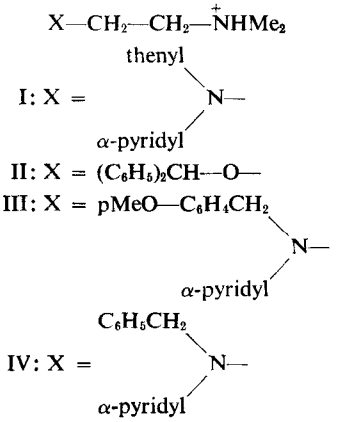
Solution Conformations of Antihistamines

Keyphrases ☐ Antihistamines—activity–conformation relationships ☐ Conformation, analysis—related to antihistamine activity ☐ Stereospecificity—antihistamine activity–*trans*-conformation relationships ☐ PMR spectroscopy—structure, conformation, antihistamines

Sir:

On the basis of similarities in the crystal structures of histamine and the antihistamine methapyrilene hydrochloride[1] (I), it was concluded that for $XCH_2CH_2N^+HMe_2$ compounds to show antihistaminic activity, it is essential that N^+ and X be in a *trans*-conformation (1). Many antihistamines have this general formula, in which the substituent X may be >N, —O, or saturated C, with a variety of groups attached.



Some support for this suggestion follows from the crystal structure of the physiologically inactive amino acid histidine, which has a *gauche*-arrangement of the NH_3^+ group and the imidazole ring (1, 2).

However, a number of assumptions are interposed between these structural observations and the deduction of a meaningful structure–activity relationship. For example, it is assumed that: (*a*) the receptors for the antihistamine and histamine are identical (3), and (*b*) the receptor-bound conformation of the drug is the same as that of the drug in solution or in the solid (3, 4). There is also the assumption, often unverified, that the solid-state conformation of the flexible $XCCN^+$ chain is preserved when the crystal lattice is destroyed in aqueous solution or *in vivo*. Indeed, it was recently shown (5) that the histamine univalent cation in D_2O does not have the *trans*-conformation found in the solid (6) but rather has approximately equal proportions of the *trans*-conformer and of each of the two *gauche*-conformers. In this communication, I present evidence, obtained from proton magnetic resonance (PMR) spectra, on the solution conformations of a number of antihistamines.

The PMR spectra were obtained at 60 and 100 MHz. (probe temperatures of 39 and 30°, respectively) on D_2O solutions of the salts of the antihistamines (approximately 40% by weight). The one free base studied was run as a 1:1 (by volume) solution in $CDCl_3$. The conformational information comes from an analysis of the *AA'BB'* system of the 1,2-disubstituted ethane fragment (7, 8).

For the $XCH_2—CH_2N^+$ chain, three conformations with respect to the C—C bond are possible: one with the substituents X and N^+ in a *trans*-disposition and two in which they are *gauche*. With the assumptions of 60° dihedral angles and only two vicinal proton–proton coupling constants, J_t and J_g, for a particular compound, Abraham and Pachler (8) showed that the rotationally averaged vicinal coupling constants, J_{AB} and $J_{AB'}$, are given by:

$$J_{AB} = n_t J_g + \tfrac{1}{2}(1 - n_t)(J_g + J_t) \quad \text{(Eq. 1)}$$

and:

$$J_{AB'} = n_t J_t + (1 - n_t) J_g \quad \text{(Eq. 2)}$$

where n_t is the proportion of *trans*-conformer. The *AA'BB'* spectral parameters, N and L, are defined by:

$$N = J_{AB} + J_{AB'} \quad \text{(Eq. 3)}$$

$$L = J_{AB} - J_{AB'} \quad \text{(Eq. 4)}$$

and it can be shown that:

$$N = \tfrac{1}{2}[J_t + 3J_g + n_t(J_t - J_g)] \quad \text{(Eq. 5)}$$

and:

$$L = (\tfrac{1}{2} - \tfrac{3}{2}n_t)(J_t - J_g) \quad \text{(Eq. 6)}$$

Furthermore, the parameter combination of $1/2N + 1/6L$ is independent of the proportions of the conformers present and is equal to the average of the vicinal coupling constants, since a little algebra shows that:

$$\tfrac{1}{2}N + \tfrac{1}{6}L = \tfrac{1}{3}(2J_{AB} + J_{AB'}) = J_{av} = \tfrac{1}{3}(J_t + 2J_g) \quad \text{(Eq. 7)}$$

The expressions for N and L show that, since $J_t - J_g$ is positive (9), the smaller the value of N the smaller the proportion of *trans*-conformer; and if L is positive, then n_t is less than 1/3 and the *gauche*-conformers are more stable. The sign of L cannot be determined from the spectrum; but in favorable cases, it can be obtained by using Abraham and Pachler's (8) correlation: $1/2N + 1/6L = 18.0 - 0.8\Sigma E$, where ΣE is the sum of the Huggins electronegativities (10) for the six atoms directly bonded to the C—C fragment.

Diphenhydramine hydrochloride (II)[2], an antihistamine of the dimethylaminoethyl ether type, gives a spectrum whose parameters have the following values (in Hz.): N, 10.1; L, ±3.5; K and M, which are, respectively, the sum and difference of the geminal coupling constants, −29.8 and ±2.1. The correlation between the average vicinal coupling constants and the substituent electronegativities, gives a calculated J_{av} of 5.7 Hz., whereas the experimental average is 5.6 Hz. ($L > 0$) or 4.5 Hz. ($L < 0$). I conclude that L is positive and, hence, that the *gauche*-forms are more stable and predominate in solution. This finding is in keeping with the anticholinergic properties of this substance (11) and the known *gauche*-$OCCN^+$ skeleton of acetylcholine in solution (12).

[1] Methapyrilene (I) is 2-[(2-dimethylaminoethyl)-2-thenylamino]-pyridine.

[2] Diphenhydramine (II) is 2-diphenylmethoxy-*N*,*N*-dimethylethylamine.

The three other antihistamines studied, pyrilamine maleate (III)[3], tripelennamine hydrochloride (IV)[4], and methapyrilene hydrochloride (I), are ethylenediamine derivatives. Their salts gave spectra which suggested that $L = 0$. This value is not expected, for it corresponds to equal proportions of all three conformers. Since the departure from $L = 0$ that can be recognized depends in part on the value of M, an attempt was made to estimate this parameter for the NCH_2CH_2N system by studying pyrilamine free base. Its spectrum showed $N = 14.6$ and $L = \pm 3.6$ with $M = \pm 2.0$ Hz.; the electronegativity relationship yields 6.1 Hz. for J_{av}, which is to be compared with the experimental value of 7.9 Hz. ($L > 0$) and 6.7 Hz. ($L < 0$). Thus, L is negative, *i.e.*, n_t is greater than 1/3 so that the *trans*-form is favored in solution and is more stable than the *gauche*-forms.

The N values for the salts, the species present at physiological pH, are 12.1 Hz. (pyrilamine), 12.0 Hz. (tripelennamine), and 11.8 Hz. (methapyrilene). By assuming an upper limit of $M = 2$ Hz. for these molecules, the observed spectra are consistent with L values between -1 and 1 Hz. If only the *trans*-form were present in solution, N and L values of approximately 16 and -6 Hz., respectively, would be expected (13, 14). Although there are experimental and theoretical uncertainties in deducing precise conformer proportions from the coupling constants, it is quite clear that the decreases in N and L, compared with pyrilamine free base, are accompanied by a decrease in the proportion of the *trans*-conformer. Attempts to allow for possible electronegativity effects of a substituent on the proton couplings only reinforce this decrease. Thus, in contrast to methapyrilene in the solid, these three closely related ethylenediamine antihistamines are not exclusively in the *trans*-conformation in solution; in fact, conformationally, they seem very similar to the histamine cation itself.

Although none of the salts studied here is exclusively in the *trans*-form in solution, the ethylenediamine derivatives are among the most active antihistamines. These $NCCN^+$ types have pA_2 values approximately 1 unit higher than the $OCCN^+$ type (15). While it is probably an oversimplification to ascribe all of this difference in activity to conformational preference, the order of decreasing activity is also the order of decreasing N values and, hence, decreasing proportion of the *trans*-conformer. This observation is consistent with the stereospecificity observed in antihistamines of the allylamine type (16), where UV spectra indicate that the more active geometric isomer has the basic N atom and the α-pyridyl ring in a *trans*-arrangement.

(1) G. R. Clark and G. J. Palenik, *J. Amer. Chem. Soc.*, **92**, 1777(1970).

(2) J. Donahue and A. Caron, *Acta Crystallogr.*, **17**, 1178 (1964).

(3) E. J. Ariens, *Advan. Drug Res.*, **3**, 235(1966).

(4) B. Belleau, *ibid.*, **2**, 89(1965).

(5) A. F. Casy, R. R. Ison, and N. S. Ham, *Chem. Commun.*, **1970**, 1343.

(6) M. V. Veidis, G. J. Palenik, R. Schaffrin, and J. Trotter, *J. Chem. Soc. A*, **1969**, 2659.

(7) E. W. Garbisch, Jr., *J. Chem. Ed.* **45**, 480(1968).

(8) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1964).

(9) M. Karplus, *J. Chem. Phys.*, **30**, 11(1959).

(10) M. L. Huggins, *J. Amer. Chem. Soc.*, **75**, 4123(1953).

(11) H. O. Schild, *Brit. J. Pharmacol.*, **2**, 189(1947).

(12) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, **1966**, 537.

(13) R. J. Abraham, L. Cavelli, and K. G. R. Pachler, *Mol. Phys.*, **11**, 471(1966).

(14) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, **1970**, 1242.

(15) R. B. Barlow, "Introduction to Chemical Pharmacology," Methuen, London, England, 1968, p. 357.

(16) *Ibid.*, pp. 368, 371.

NORMAN S. HAM

Division of Chemical Physics
CSIRO
Clayton, Victoria 3168
Australia

Received April 5, 1971.

Accepted for publication August 9, 1971.

I thank J. L. Little and R. I. Willing for recording spectra and the following for generously providing samples: Eli Lilly and Co. (methapyrilene hydrochloride), Parke, Davis & Co. (diphenhydramine hydrochloride), May & Baker (Australia) (pyrilamine maleate), and Ciba Co. (tripelennamine hydrochloride).

[3] Pyrilamine (III) is 2-[(2-dimethylaminoethyl)(*p*-methoxybenzyl)-amino]pyridine.

[4] Tripelennamine (IV) is 2-[benzyl(2-dimethylaminoethyl)amino]-pyridine.

BOOKS

REVIEWS

Handbook of Experimental Pharmacology, Volume 28, Part 1, Concepts in Biochemical Pharmacology, Edited by B. B. BRODIE and J. R. GILLETTE. Springer-Verlag New York, Inc., 175 Fifth Ave., New York, NY 10010, 1971. xvi + 471 pp., 16.5 × 25 cm. Price $50.40.

This volume continues the high tradition of the Handbook series for breadth of coverage and criticality in the review of specialized aspects of pharmacology.

Part 1 of Volume 28 presents a detailed critique of current information on drug absorption, transport, and disposition in tissues and drug disposition *via* several excretory routes. Part 2 will cover the topics of microsomal and nonmicrosomal biotransformation of drugs as well as bioanalytical methodology for the study of drug metabolism and the isolation and identification of drug metabolites. When complete, this volume will likely become the standard reference work on all aspects of drug absorption, transport, and disposition.

The book is divided into three sections. Section One is entitled Routes of Drug Administration and contains chapters on Absorp-