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Quantum Mechanical Study on the Conformational Properties of Antihistaminic Drugs

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SUMMARY

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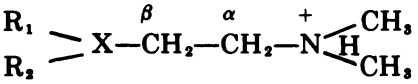
The method of perturbative configuration interaction using localized orbitals (PCILO) was applied to the study of the conformational properties of flexible antihistamines of the general formula

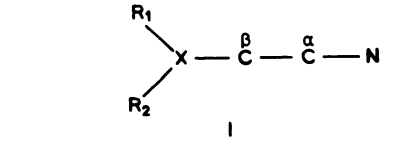


with X = N (ethylenediamine derivatives), CH—O (diphenhydramine), and saturated C (pheniramine). Conformational energy maps were constructed as a function of rotation about the X—C^{β} and C^{β}—C^{α} bonds for isolated protonated molecules (for two possible orientations of the cationic head) and for the hydrated derivatives carrying a hydrogen-bonded water molecule attached to $N^{+}H$. The computations predict a strong predominance of the *gauche* form for all the isolated molecules, owing to electrostatic interaction between the cationic head and the esteric oxygen in diphenhydramine, but resulting from hydrogen bonding between the cationic head and the pyridyl nitrogen in pheniramine and the ethylenediamine derivative. In water they predict the coexistence of *gauche* and *trans* conformers. Evaluation of the relative populations of these conformers indicates that the proportion of the *trans* conformer should vary inversely with the electronegativity of the X atom of the chain. The effect of flexibility was studied, using pheniramine as an example. The theoretical results were compared with the available experimental data from X-ray crystal structures and NMR and circular dichroism studies in solution.

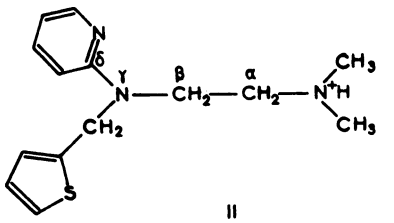
INTRODUCTION

A large number of fundamental antihistaminic compounds may be represented by the general structure I, where R_1 is an aryl (or heteroaryl) ring, R_2 an aryl or arylmethyl group, and X is N, CH—O, or a saturated C. X—C^{β} may be replaced by a C=C double bond. The terminal nitrogen atom is part of a tertiary acyclic or alicyclic basic grouping. Typical representatives of these different classes of antihistaminic drugs are ethylenediamine derivatives (such as histadyl, II), diphenhydramine (III), pheniramine (IV), triprolidine (V), and pyrrobutamine (VI).

Discussion of structure-activity relationships in this series of molecules has been dominated by the search for conformational analogies among these compounds and histamine. It has been postulated on the basis of similarities found in the crystal



I



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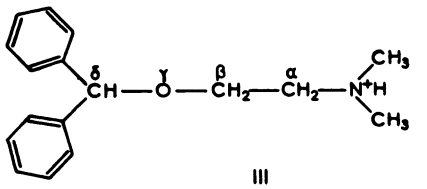

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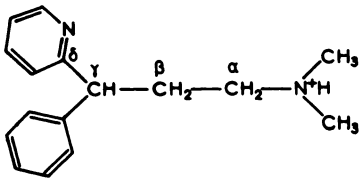

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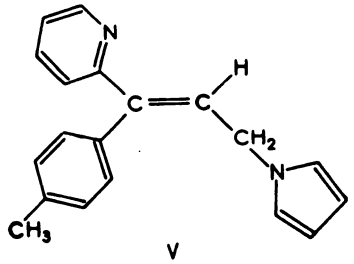
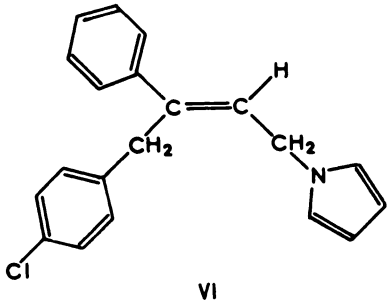


V



VI

structure of histamine (1), histadyl hydrochloride (2, 3), and brompheniramine and chlorpheniramine maleates (4, 5) that a fully extended *trans* conformation about the C^{α}—C^{β} bond is essential for antihistaminic activity. The demonstration that high antihistaminic activity in the conformationally restricted compounds V and VI requires a *trans* Ar—C = C—CH_2—N arrangement with the aromatic nucleus (α-pyridyl or phenyl) coplanar with the double bond (together with an aromatic function such as *p*-tolyl or *p*-chlorobenzyl in a position *cis* to the aminomethyl group) (6, 7) seemed to corroborate this point of view, the more so because a recent X-ray determination of the crystal structure of triprolidine hydrochloride monohydrate (8) indicated an essentially *trans* arrangement of the two nitrogen-containing rings. The belief that the crystallographically observed conformations are significant for antihistaminic activity may be considered to have culminated in the proposal (8) that because the distance between the saturated nitrogen atom and the centroid of the aromatic ring—a distance considered important for interaction with the antihistamine receptor site—is appreciably different in the fully extended forms of the antihistaminic drugs and of histamine, a flexible receptor protein must be involved in the interaction which adopts different conformations when histamine and antihistamine are bound.

Although this hypothesis is in itself plausible, the argument is not, for a number of reasons, a rigorous one. First, the crystallographic results for histamine refer to a diprotonated form and may be different for the physiologically more significant monoprotonated one (9). Second, studies with other conformationally restricted potent antagonists of the histamine H_1 receptor, *trans*- and *cis*-1,5-diphenyl-3-dimethylaminopyrrolidines (10), which cannot attain a fully extended *trans* N—C—C—N^+ conformation, show that a range of values for the relevant torsional angle are acceptable for effective drug-receptor interactions. Similarly, although the crystallographic conformation of diphenhydramine is un-

known, results for related systems containing the O—C—C—N^+ chain, e.g., acetylcholine and derivatives (for a general discussion see refs. 11-13) or some phenylcholine ethers (14-16), show a variety of conformations with, moreover, a preference for a *gauche* arrangement. Last but not least, studies in solution, which are closer to physiological conditions than those relevant to the solid state, indicate the frequent coexistence of a number of *gauche* and *trans* forms both for histamine (17-21; for a general discussion see ref. 9) and for different antihistamines (22, 23) and related systems (e.g., refs. 24-27).

This situation raises the general problem of what the *intrinsic* conformational possibilities and preferences of the "flexible" antihistaminic drugs are, and to what extent they are influenced or modified by environmental factors and, in particular, by the solvent water. Interesting to know from that point of view are the nature of both the most stable and, if available the secondary stable conformations, and also the energy barrier between them.

The present paper is devoted to a quantum mechanical investigation of this problem, this work being an extension of our previous study on the conformation of histamine (9).

METHODS

The flexible antihistaminic compounds II, III, and IV possess five or six a priori important torsion angles corresponding to the principal single bonds of the backbone. We shall limit our study, however, essentially to the two torsion angles τ_1 and τ_2, which define the degree of extension or folding of this backbone. We recall that the torsion angle τ between the bonded atoms *A—B—C—D* is the angle through which the far bond CD is rotated relative to the near bond AB. Viewed from the direction of A, τ is positive for clockwise and negative for counterclockwise rotations. The value τ = 0° corresponds to the planar-*cis* arrangement of bonds *AB* and *CD*. More precisely, in the present cases $\tau_1 = \tau$ (C^δ—X^γ—C^β—C^α) and $\tau_2 = \tau$ (X^γ—C^β—C^α—N^+). The other torsion angles will be maintained in fixed, preselected values. For compounds II and IV they correspond to the crystallographically observed ones (3, 4). [τ (N—C^δ—N^γ—C^β) = 6°, τ (C_{aliph}—N^γ—C^β—C^α) 91°, τ (S—C_{arom}—C_{aliph}—N^γ) = −9° in II, and τ (C_{arom}—C_{arom}—C^δ—O^γ) = 33°, τ (C_{arom}—C^δ—O^γ—C^β) = 185° in III.] For III, for which no X-ray crystal data are available, plausible values have been adopted (see below). It may be added, however, that we have also considered two values for $\tau_3 = \tau$ (C^β—C^α—N^+—H). As it is obvious a priori that the interaction of the cationic head with the molecular skeleton will depend largely on its orientation about the C^α—N^+ bond, (e.g., ref. 28), computations have been carried out in addition to the crystallographic value of τ_3, which is generally close to 60° and permits the interaction of the N^+—H bond with the molecular skeleton, and also for τ_3 = 180°, in which such an interaction is precluded. The computations for τ_1 and τ_2 have been carried out in 30° increments. The method used for the construction of the conformational energy maps was the molecular oribital PCILO[1] procedure (29, 30), as used in the previous computations on histamine (9).

The influence of water on the conformation of the antihistamines was studied by the "microscopic supermolecular" approach, which consists of fixing water molecules at the most favorable hydration sites of the cation and calculating the conformational map of the new "supermolecule." The most favorable hydration sites are determined by studies *ab initio* on model compounds (alkylammonium, pyridine, ethers, etc.) by the procedure indicated in refs. 31-34 and recently reviewed (35). The conformational map of the new supermolecule, representing hydrated antihistamine, was computed again by the PCILO method. Although we do not expect that the entire solution behavior of the antihistamines can be elucidated by such a reduced treatment, we expect to obtain a reasonable indication of the direction and magnitude of changes in conformational preferences of the isolated molecule when

[1] The abbreviation used is: PCILO, perturbative configuration interaction using localized orbitals.

it enters aqueous solution. The success of this mode of approach has been strikingly illustrated in recent studies on histamine itself (9), indolealkylamines (28), phenethylamines (36, 37) and γ-aminobutyric acid (38).

Moreover, in one case, that of pheniramine, we have partially taken into account the flexibility of the attached water molecule.

Finally, the computations on the stability contours of the energy minima have been extended to an examination of the probability of occurence of the compounds in the different allowed conformational states through the construction of probability maps and the evaluation of the populations of the principal rotamers considered.

Toward this goal, the partition function for the compound was approximated as the sum of Boltzmann factors taken at equal intervals of τ_1 and τ_2 throughout their range (e.g., ref. 30); that is,

$$Z = \sum_{\tau_1} \sum_{\tau_2} e^{-E(\tau_i, \tau_j)/RT}$$

These intervals correspond in our work to the 144 points obtained from the grid of the conformational energy map built with 30° increments. Thus the partition function is established on the basis of 144 states i in the angle configurational space:

$$Z = \sum_{i=1}^{i=144} e^{-E(\tau_i, \tau_j)/RT}$$

Now to each point i we assign a statistical weight Z_i and a probability P_i defined by

$$Z_i = e^{-E(\tau_i, \tau_j)/RT}$$

$$P_i = \frac{Z_i}{Z}$$

In this way we can build a probability map picturing the probabilities P_i as a function of the rotational angles τ_1 and τ_2. Clearly the absolute value of Z is subject to the arbitrariness inherent in the choice of the increment in (τ_1 τ_2), but as we are interested only in the relative probabilities of the different regions of the map, this procedure may be considered a satisfactory first approximation to an exact statistical treatment of the problem.

From these results the populations of the different rotamers have been evaluated with respect to τ_2, as this is the essential information furnished by NMR experiments in solution. In order to be able to compare the theoretical results with the experimental ones, which are generally expressed in terms of the relative population of the *trans* ($\tau_2 \approx 180°$) and *gauche* ($\tau_2 \approx 60°$ and 300°) rotamers, the whole range of τ_2 has been subdivided into three areas (0–120°, 120–240°, and 240–360°) and the probabilities that the conformers will be within these area have been evaluated. The choice of the above boundaries is somewhat problematic but in practice is not very important: the greatest contributions to the different rotamers come generally from regions located rather close to the classical values of 60°, 180°, and 300°, transitional forms giving a much lower contribution. This type of calculation implicitly includes an estimate of the entropic contributions to the stability of each rotamer, since it takes into account not only the depths of the minima on the potential surfaces but also their curvatures and widths. We are thus closer to dealing with free energy. (For related examples, see refs. 30, 39–41.)

RESULTS AND DISCUSSION

Figures 1–3 present the conformational energy maps of protonated histadyl (II), diphenhydramine (III), and pheniramine (IV) as a function of the torsion angles τ_1 and τ_2. The remaining geometrical input data (bond length, valence angles, remaining torsion angles) correspond to the X-ray crystal results for II (3) and IV (4). In particular the preselected value of the torsion angle τ_3 is close to 60° (41.4° in II and 51.8° in IV)—a situation which enables the N^+H bond of the cationic head to be oriented toward the backbone of these molecules. For III, for which no X-ray results are yet available, the input data were taken as a combination of those for acetylcholine (42) as concerns the O—C—C—N chain, and for adiphenine (43) as concerns the aromatic rings. The values adopted for the torsion angles not

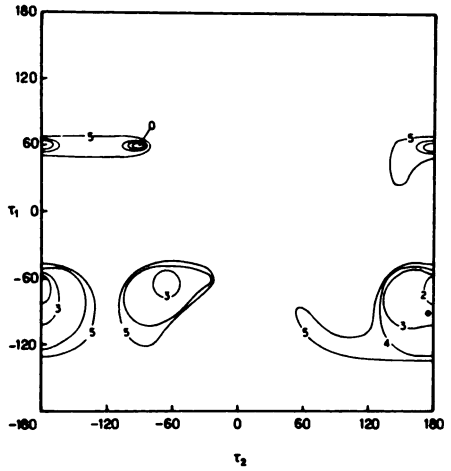


FIG. 1. *Conformational energy map for protonated histadyl with τ_3 = 41.4° (crystallographic value)*
Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy. ●, X-ray crystallographic conformation (3).

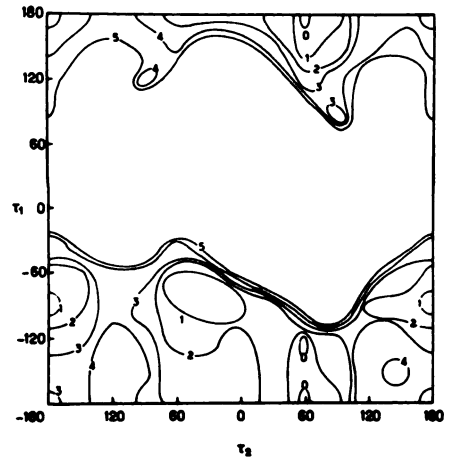


FIG. 2. *Conformational energy map for protonated diphenhydramine with τ_3 = 51.8°*
Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy.

involved in the computations are τ(N—C$^\delta$—C$^\gamma$—C$^\beta$) = −43°, τ(C$_{arom}$—C$_{arom}$—C$^\gamma$—C$^\beta$) = 53°. The τ_3 torsion angle was fixed at 51.8° by analogy with IV.

The three figures present a global energy minimum corresponding to a *gauche* conformation at τ_1 = 60°, τ_2 = −90° for histadyl (Fig. 1) and pheniramine (Fig. 3), and at τ_1 = 180° or −120°, τ_2 = 60° for diphenhydramine (Fig. 2). There are secondary energy minima on these maps associated with extended forms, e.g., at τ_1 = −60°, τ_2 = 180° in Fig. 1 (2 kcal/mole above the global minimum), at τ_1 = −90°, τ_2 = 180° in Fig. 2 (1 kcal/mole above the global minimum), and at τ_1 = 60°, τ_2 = 180° in Fig. 3 (2 kcal/mole above the global minimum). The evaluation of the populations of the *gauche* and *trans* rotamers, following the procedure outlined above, indicates a very strong predominance, of over 90%, of the *gauche* tautomers in the three cases (Figs. 4–6). Examination of the models corresponding to the three *gauche* conformers, however, shows striking differences in their structure, pointing to differences in the origin of their stability. The stable *gauche* conformer of diphenhydramine (Fig. 2) is essentially due to a strong electrostatic interaction between the cationic head and the esteric oxygen, typical of the O—C—C—N$^+$ interaction as established in particular in studies on acetylcholine and related compounds (44–46). In contrast, the *gauche* conformers of histadyl and pheniramine are stabilized by the electrostatic interaction between the cationic head and the nitrogen atom of their

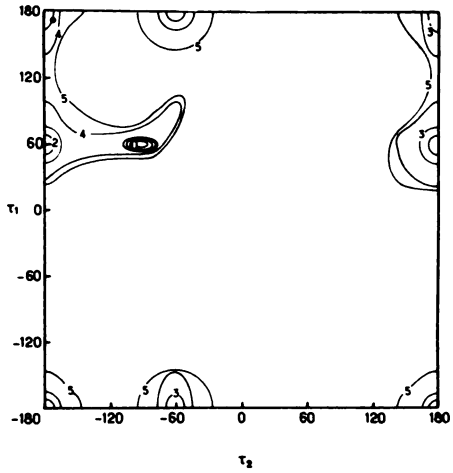


FIG. 3. *Conformational energy map of protonated pheniramine with τ_3 = 51.8° (crystallographic value)*
Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy. ●, X-ray crystallographic conformation of brompheniramine maleate (4).

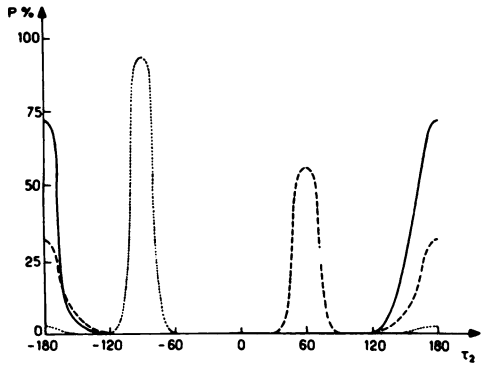


Fig. 4. *Populations (P) of conformers of protonated histadyl*

····, free molecule computed with τ_3 = 41.4°; ——, free molecule computed with τ_3 = 180°; – – –, hydrated molecule.

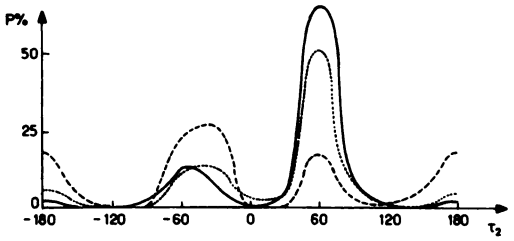


FIG. 5. *Populations (P) of conformers of protonated diphenhydramine*

····, free molecule computed with τ_3 = 51.8°; ——, free molecule computed with τ_3 = 180°; – – –, hydrated molecule.

pyridine ring, this interaction taking the form of weak hydrogen bonding.

In Figs. 1 and 3 are also indicated the X-ray crystallographic conformations of histadyl and pheniramine with respect to τ_1 and τ_2. Both molecules are in an extended conformation in the crystals, corresponding to only local energy minima 2–3 kcal/mole above the global one. In our opinion, this situation must be due to the action of crystal packing forces. A confirmation of this viewpoint, at least for the case of pheniramine, comes from recent circular dichroism studies of this compound in nonpolar solvents (23), i.e., under conditions closer to those corresponding to the free molecule approximation. These studies point to the predominance of the very conformer which our computations predict to be the preferred one: a *gauche* conformer stabilized by an attractive interaction between the protonated aliphatic nitrogen and the aromatic nitrogen of the pyridine ring.

The contribution of this form diminishes in aqueous solution, a problem which we discuss later. Also, when the pyridine nitrogen becomes protonated, the preferred conformation changes to an extended one, owing to the electrostatic repulsion between the two positive centers, a situation very similar to the one occurring in histamine itself and which we have discussed in detail (9).

No X-ray crystal data are available as yet for diphenhydramine.

Because the predominance of the *gauche* conformers seems to be governed by the interaction of the cationic head with electron-rich atoms on the molecular periphery and because this interaction may depend upon the orientation of the cationic head about the C^{α}—N bond, we have recomputed the conformational energy maps of II, III, and IV with τ_3 = 180° (other things kept equal). In this orientation of the cationic head, its proton is continuously directed toward the outside and cannot interact with the esteric oxygen or the pyridine nitrogen.

The results for histadyl (Fig. 7) and pheniramine (Fig. 8) show a profound modification of the conformational energy map. The attractive interactions between the

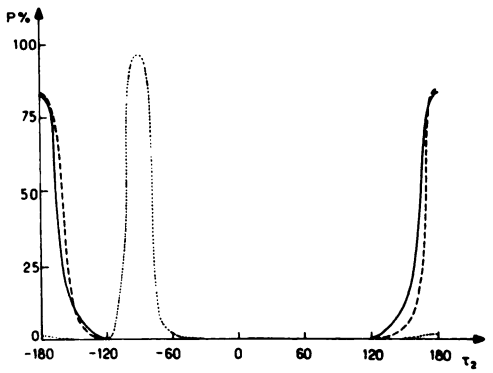


FIG. 6. *Populations (P) of conformers of protonated pheniramine*

···, free molecule computed with τ_3 = 51.8°; ——, free molecule computed with τ_3 = 180°; – – –, hydrated molecule.

cationic head and the pyridine nitrogen are no longer visible, and the most stable conformer should now be an extended one with $\tau_1 = -90°$, $\tau_2 = 180°$ in histadyl and $\tau_1 = 60°$, $\tau_2 = 180°$ in pheniramine. In contrast (Fig. 9), the global energy minimum for diphenhydramine continues to be associated with a *gauche* form, at $\tau_1 = 180°$, $\tau_2 = 60°$, analogous to the one

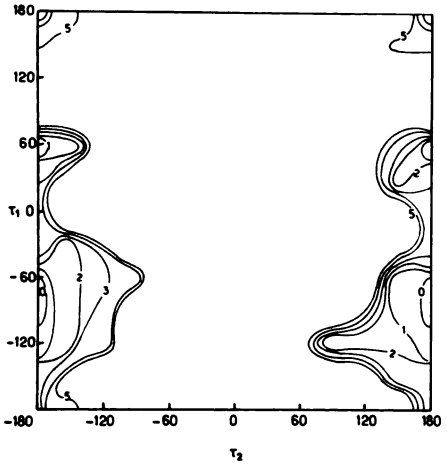


FIG. 7. *Conformational energy map for protonated histadyl with $\tau_3 = 180°$*

Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken zero energy.

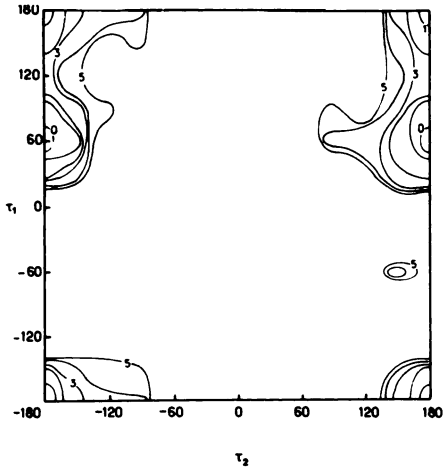


FIG. 8. *Conformational energy map for protonated pheniramine with $\tau_3 = 180°$*

Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy.

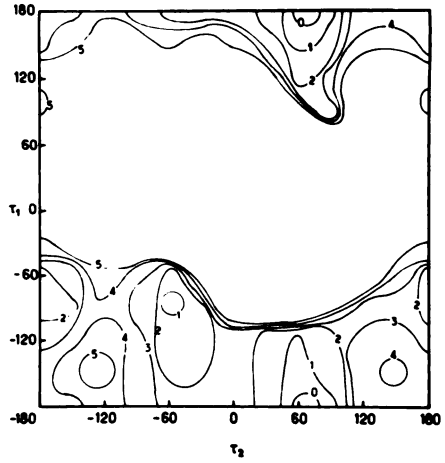


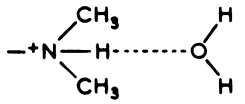
FIG. 9. *Conformational energy map for protonated diphenhydramine with $\tau_3 = 180°$*

Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero

predicted and observed in acetylcholine (45). The strength of the attractive electrostatic association between the cationic head and the esteric oxygen atom of diphenhydramine thus significantly exceeds the attraction between the cationic head and the pyridine nitrogens of histadyl and pheniramine and does not depend on the possibility of hydrogen bonding. [We have already indicated on a number of occasions (9, 45, 47; see also ref. 48) that the positive charge of the cationic head is not localized on the nitrogen atom but is spread essentially on the hydrogen atoms of $-N^+H_3$ and $N^+(CH_3)_3$.]

The computations indicate that the global energy minimum of Fig. 1 is about 3 kcal/mole and that of Fig. 2 about 2 kcal/mole lower than those of Figs. 7 and 8, respectively. On the other hand, the global energy minima of Figs. 3 and 9 are practically degenerated.

We now consider the effect of water on the conformational properties of the antihistamines. Within the "supermolecule" approach, the problem is simplified in this case by the existence of one particularly important hydration site, represented in all the molecules considered here by the N^+—H bond of the cationic head. The fixation of a molecule of water on that site, following the scheme indicated in VII as a



VII

result of model studies *ab initio* on ammonium and alkylammonium with the $N^+ \cdots O$ distance equal to 2.6 A (35), corresponds to the formation of a relatively strong hydrogen bond (−28 kcal/mole)[2] whose existence is likely to have an appreciable perturbative influence on the intramolecular interaction between the cationic head and the remaining parts of the molecules and thus to play an essential role in a possible modification of the ratio of *trans* and *gauche* rotamers.

The extent of the perturbation is illustrated in Figs. 10–12, which represent the conformational energy maps of histadyl, diphenhydramine, and pheniramine, respectively, carrying a molecule of water at their cationic head in the manner indicated in VII, all remaining input data being the same as in Figs. 1–3.

The effect of hydration on the conformational characteristics of the compounds is obviously appreciable. Thus, although the global energy minimum for hydrated histadyl (Fig. 10) still corresponds to a *gauche* form at $\tau_1 = -120°$, $\tau_2 = 60°$, there now appears a broad local energy minimum for the *trans* conformer at $\tau_1 = -60$–$100°$, $\tau_2 = 150$–$180°$, only 1 kcal/mole above the global one. A similar situation is observed for hydrated diphenhydramine (Fig. 11). In hydrated pheniramine the global energy minimum corresponds to a *trans* form at $\tau_1 = 60°$, $\tau_2 = 180°$, with only a small local energy minimum for a *gauche* form at $\tau_1 = 180°$, $\tau_2 = -90°$.

The evolution of the *gauche-trans* equilibrium in the hydrated forms with respect to the free ones is still more evident in Figs. 4–6, from which it may be deduced that, within the approximation adopted, the *gauche/trans* ratio is 72:28 in diphenhydramine, 57:43 in histadyl, and 1:99 in pheniramine. Thus the hydration of the cationic head has a moderate effect on the percentage of the *gauche* form in diphenhydramine, a strong effect in histadyl, and a very strong effect in pheniramine. The attachment of a water molecule therefore is to disrupt the interaction between the cationic head and the pyridine nitrogens in

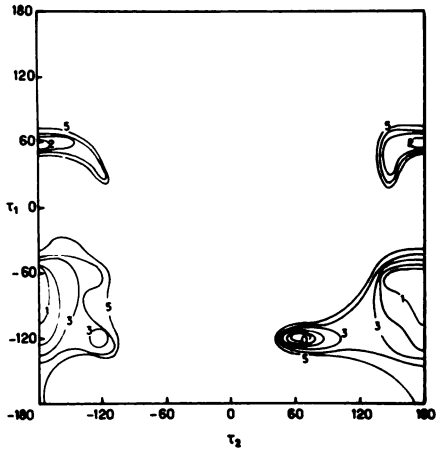


FIG. 10. *Conformational energy map for hydrated protonated histadyl*

Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy.

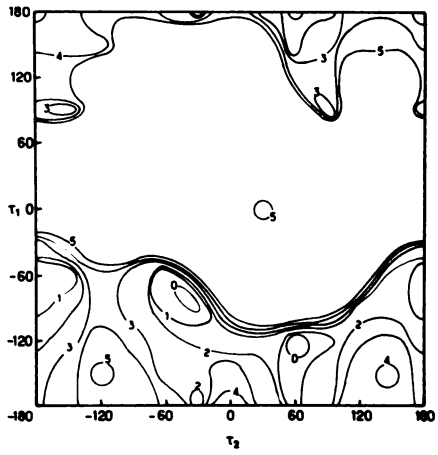


FIG. 11. *Conformational energy map for hydrated protonated diphenhydramine*

Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy.

[2] This value is obtained when the computations *ab initio* are performed with an STO 3G basis set. It is reduced to 20 kcal/mole with the more extended 4-31G basis set, which is closer to the experimental result of Payzaut *et al.* (49).

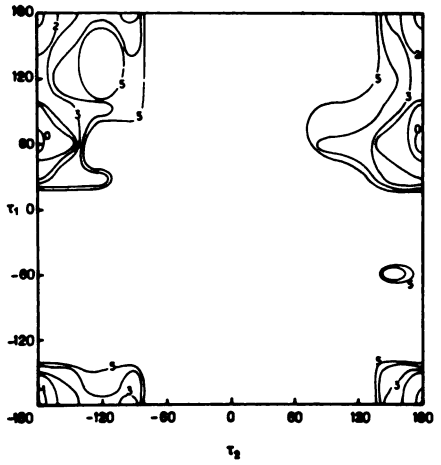


FIG. 12. *Conformational energy map for hydrated protonated pheniramine*

Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy.

histadyl and pheniramine. The extent of the *gauche* form in the equilibrium mixture now seems to be governed by the electronegativity of the main chain X atom with which the hydrated cationic head may interact: it decreases when X changes from O to N to C.

The practically complete disappearance of the *gauche* form in the case of hydrated pheniramine represents such an extreme effect that it seemed suitable to elaborate on the computations in this particular case. Thus the conformational energy maps of Figs. 10–12 have been constructed with the water molecule fixed rigidly in the position of structure VII. This condition is convenient for first-approximation computations, but it is obvious that in reality a certain amount of flexibility will be allowed to the mode of attachment of this water molecule as a function of conformational changes in τ_1 and τ_2. This phenomenon was studied in detail, with variations also allowed in τ_3 (X-ray value, 51°8) and $\tau_0 = \tau$ (N_{pyr}—C^{δ}—C^{γ}—C^{β}), which determines the orientation of the pyridyl ring with respect to the chain (X-ray value, 33°1). The whole range of τ_3 from 0° to 180° was investigated first, in 30° increments, and it was found that the probability of the *trans* conformation remains at about 99% for all values of this angle with the exception of $\tau_3 = 0°$, for which there appears a probability of about 20% for the *gauche* form at $\tau_1 = 120°$, $\tau_2 = -60°$. Figure 13 represents the map obtained for $\tau_3 = 0°$. Its global energy minimum is about 1 kcal/mole above that of Fig. 12. The rotation of the water molecule about the N—H···O axis has no significant influence on the situation. Next τ_3 was varied in 10° increments from 0° to 60°. Again a probability of about 20% for a *gauche* conformation appears for $\tau_0 = 20°$ and $\tau_1 = 120°$, $\tau_2 = -60°$, $\tau_3 = 0°$. The global energy minimum of the associated conformational energy maps is also only about 1 kcal/mole above the global minimum of Fig. 12. It may thus be estimated that the introduction of flexibility somewhat increases the probability of the presence of a *gauche* form in the aqueous solution of pheniramine. These refined computations may thus be considered to modify slightly but not drastically, the results obtained within the rigid frame approximation. Doubtless a similar increase in the proportion of the *gauche* form may be estimated using a similar refinement for the other flexible antihistaminics.

We may now compare the theoretical results with the available experimental data for these and related compounds. Although rather scarce, these data never-

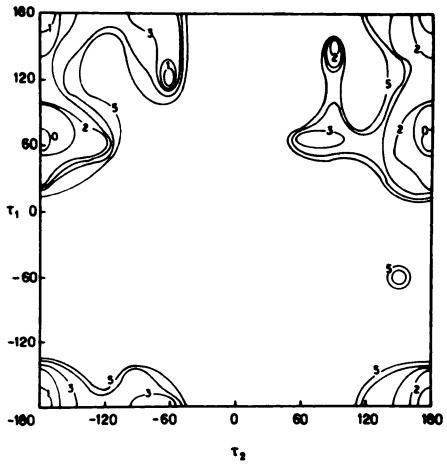
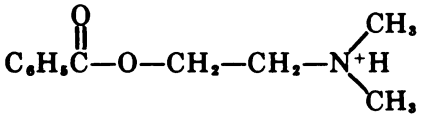


FIG. 13. *Conformational energy map for hydrated protonated pheniramine with $\tau_3 = 0°$*

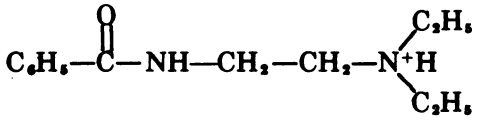
Isoenergy curves in kilocalories per mole with respect to the global energy minimum, taken as zero energy.

theless seem in general agreement with our computations. As concerns the antihistamines themselves, two studies are available. One by Ham (22), using NMR spectroscopy, showed that while diphenhydramine exists predominantly in water in the *gauche* form, cationic ethylenediamine derivatives (pyrilamine, tripelennamine, and methapyrilene) exist rather as approximately equivalent mixtures of *gauche* and *trans* conformers. The second study, by Testa (23), using circular dichroism measurements, refers to pheniramine and confirms the predominance of the *gauche* form in inert solvents (see above) but of the *trans* form in water. A related NMR study by Testa (23) on norpheniramine indicates a nearly equivalent mixture of *trans* and *gauche* conformers in solution. As the methyl groups are expected to increase the proportion of the *trans* form, this result also permits one to estimate that the *trans* form would predominate in solution for pheniramine. Altogether this group of data confirms our finding that in solution the proportion of the *gauche* form should increase with the electronegativity of the X atom of the X—C—C—N^+ chain of antihistamines.

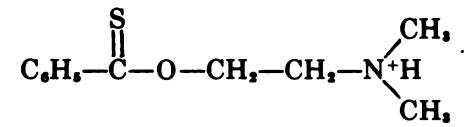
A number of experimental data on solution studies on related compounds, in particular in the series of acetylcholine derivatives and quaternary ammonium ions, further confirm this proposal. Thus it was shown by Mautner *et al.* (25) that while



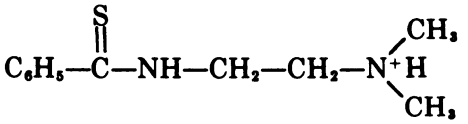
exists 100% in the *gauche* form,



exists only 74% in that form. Likewise, the proportion is 96% for



and 71% for



the similar decrease in both cases indicating that it is not due to the presence of the C_2H_5 groups at the cationic head of the second compound of the series. Partington *et al.* (24) have shown that while acetylcholine exists 100% in the *gauche* form in solution, and choline methyl ether [CH_3—O—CH_2—CH_2—$N^+(CH_3)_3$] 88%, phenylethyltrimethylammonium [C_6H_5—CH_2—CH_2—$N^+(CH_3)_3$] and cyclohexylethyltrimethylammonium [C_6H_{11}—CH_2—CH_2—$N^+(CH_3)_3$] exist only 17% and 22%, respectively, in that form. In these experiments β-aminoethyltrimethylammonium [NH_2—CH_2—CH_2—$N^+(CH_3)_3$] exhibits the very small *gauche* proportion of 13%. Finally, Terui *et al.* (27) indicated a proportion of 92% of the *gauche* form for HO—CH_2—CH_2—$N^+(CH_3)_3$ in solution but of only 15.7% and 12.3%, respectively, for CH_3—CH_2—CH_2—$N^+(CH_3)_3$ and C_6H_5—CH_2—CH_2—$N^+(CH_3)_3$.

CONCLUSION

The theoretical and experimental data described in this paper converge toward a clear-cut indication that, in contradiction to X-ray crystallographic data, antihistamines in solution, like histamine itself, are present in a mixture of *gauche* and *trans* conformers. The relative proportion of these species varies as a function of the chemical nature of the compound. According to our proposal, the proportion of the *trans* conformer in the equilibrium mixture of the flexible antihistamines of the X—C—C—N type should run inversely to the electronegativity of X: large for X = C, moderate for X = N, and small for X = O. Both computations (9) and experimental data (17, 18) reveal a slight predominance of the *trans* conformer in histamine. From that point of view it is the antihistaminic ethylenediamine derivatives which most closely resemble histamine itself. The availability in the biophase of a multiplicity of conformers must, however, be borne

in mind in the elaboration of theories on antihistaminic activity of drugs.

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