# SEMIEMPIRICAL SCF-MO CALCULATIONS ON THE TAUTOMERIC EQUILIBRIUM OF HISTAMINE IN GAS PHASE AND IN AQUEOUS SOLUTION

*CLAUDIO A. OLEA-AZAR[1] AND JULIA E. PARRA-MOUCHET[2]*

[1]Departamento de Química, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile. Santiago, Chile.
[2]Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653 Santiago, Chile.

## ABSTRACT

The potential energy surface of histamine monocation is calculated by MNDO types methodologies and by the Reaction Field model at CNDO/2 level, in order to rationalize the experimental findings about the relative abundance of histamine monocation tautomers in gas phase and in aqueous solution, respectively. The results indicate that the most stable form in gas phase exhibits an intramolecular H-bonding between the imidazolic and the amino N atoms. The corresponding proton transfer potential energy function across the H-bridge calculated in vacuum, consists of an asymmetric double well curve favoring the form in which the proton is mainly bonded to the aromatic N atom. The influence of the solvent polarity on the H-bridge structure consists on an inversion of the minima in the proton transfer curve, together with a lowering of the torsional energy barrier of the side chain respect to the aromatic ring.

Finally, a mechanism involving an intramolecular proton transfer, which explains the tautomeric equilibrium of histamine from gas phase to aqueous solution is proposed. The mechanism is rationalized in terms of charges distribution and HOMOs characterization.

***Key Words***: Quantum chemical, semiempirical, histamine, hydrogen bonding, solvation.

## RESUMEN

La superficie de energía potencial de la histamina protonada es calculada por metodologías tipo MNDO y por el modelo del Campo de Reacción a nivel CNDO/2, con el propósito de racionalizar los datos experimentales acerca de la abundancia relativa de los tautómeros de la histamina monocatión en fase gaseosa y en solución acuosa respectivamente.

Los resultados indican que el confórmero más estable en fase gaseosa debería exhibir un enlace por hidrógeno intramolecular entre el nitrógeno imidazólico y el del grupo amino. La función potencial de transferencia protónica correspondiente, calculada en vacío, consiste en una curva asimétrica de doble pozo, favoreciendo la forma en la cual el protón se encuentra formalmente enlazado al átomo de nitrógeno aromático. La influencia de un medio polar en la estructura del puente de

hidrógeno, consiste en una inversión de los mínimos; además produce una disminución de la barrera de torsión de la cadena lateral respecto del anillo aromático.

Finalmente, se propone un mecanismo que involucra una transferencia protónica intramolecular, para explicar la abundancia relativa de los tautómeros de la histamina protonada desde la fase gaseosa a la fase acuosa. Este es racionalizado en términos de distribución de carga y caracterización de los HOMOs.

***Palabras Claves***: Química cuántica, semiempíricos, histamina, enlace hidrógeno, solvatación.

## INTRODUCTION

Histamine (2-(4-imidazolyl)ethylamine), HA, which plays important roles in biological systems, has been extensively studied in the last decades. Special attention has been devoted to the pharmacological properties of this autacoid, which is mediated by at least three receptors, denoted H1, H2, and H3 [1a-c]. We have been particularly interested in the histamine-H2 molecular interaction models and we have recently reported a molecular model of the H2 histamine receptor and some of its agonists and antagonists[2-4].

In aqueous solution, HA exists as a mixture of all neutral and protonated tautomers (see Fig. 1) and the relative concentration of each species is highly dependent on the pH. For example, at pH values of 5.4 and 8.4, the dication abundance is 71.5% and 0.25%, respectively. At physiological pH of 7.4, more than 96% of all the HA molecules are protonated at the alkyl nitrogen[5-8]. In neutral aqueous solutions HA is mainly a mixture of +HN1H and +HN3H forms. $^{13}C$-NMR studies[9] confirmed by potentiometric pKa determinations[5], showed that in neutral buffer solution, an approximately 80% of the molecules exist as the +HN3H tautomer in equilibrium with the +HN1H form.

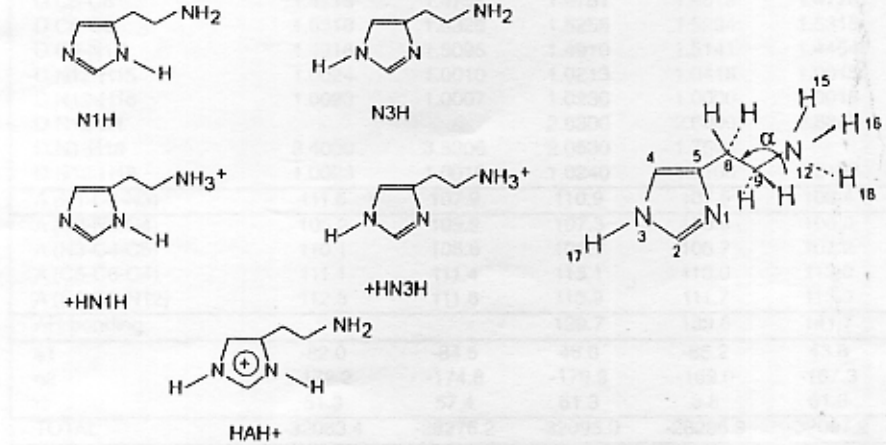


**FIG. 1**. Structural formulas of the histamine and histamine monocation tautomers.

HA hydrochloride crystals consist of intermolecularly hydrogen bonded +HN3H tautomers. The H bridge is formed between N1 and N12 adjacent HA units[10]. Crystalline neutral HA exhibits N1H molecules intramolecularly H-bonded between N12 and N3 atoms[11].

To account for the gas phase system, the potential energy surface of HA monocation has been examined by SCF MO methodologies[12-14]. In particular, Hernández Laguna and collaborators have extensively studied the potential energy surface of these compounds[15a-h], including experimental FT-ICR measurements together with high level *ab initio* calculations[15g]. The results showed that in gas phase ring protonation is favored over side chain protonation.

Nagy and col., have recently reported *ab initio* and Montecarlo-MEP calculations on the tautomers/conformers, T/Cs, relative energy of histamine and (αR, βS)-α,β-dimethylhistamine. Their results indicated that for neutral histamine the most stable conformers were the N1H *syn* and the N3H *syn* this last one being stabilized by intramolecular H-bonding[16]. The results for the relative abundance of protonated HA structures at physiological pH were +HN3H *syn* (64%) in equilibrium with the two extended forms, +HN3H (34%) and +NH1H (2%)[16].

In the present paper we address the same subject incorporating the role played by the intramolecular H-bonding between N1 and N12 (Fig. 1), on the relative energy of protonated HA T/Cs in gas phase and in water. The gas phase description of the protonated HA system is calculated by the AM1 and PM3 methodologies while the solvent effects are examined by the Reaction Field model at CNDO/2 level (CNDO/2-RF). The results obtained are analyzed in terms of charge distribution and on the nature and relative energy of the HOMOs. Finally, a mechanism for the tautomeric equilibrium of HA in aqueous solutions is proposed.

## METHODS AND CALCULATIONS

The electronic structure of the HA T/Cs were studied using two refined parametrization sets of the MNDO hamiltonian[17]: AM1 [18] and PM3[19]; both programs were taken from the MOPAC 6.0 package. Reliable results are expected for protonated HA since the AM1 and the PM3 hamiltonians are parametrized using a much larger number of molecules containing only two or more atoms of the H-C-N-O set than for compounds containing any other element; as shown by a survey of more than 600 compounds performed by J.P. Stewart[20]. It is also relevant the report of J.J. Dannenberg and E.M. Evlet[21], who have shown that the AM1 underestimation of the H-bonding energy is much more prevalent in the cases of neutral rather than charged complexes, where the average underestimation values are of the same order of magnitude of the experimental errors; also, the AM1 model has shown to give reliable geometries of the H-bonded complexes.

The AM1 and PM3 calculations were performed on optimized conformer geometries, obtained by the gradient optimization procedure, invoking the EF and PRECISE options. All the points involved in the calculation of potential energy surfaces were calculated by performing complete geometry optimization under the constraint of plane imidazole ring.

The solvent effects on the electronic structure of the HA monocation T/Cs, were studied by the CNDO/2-RF theoretical scheme, where the solvent polarity is represented by a dielectric constant[22].

In the representation of the solvent, only the effect of the electrostatic field created by a continuum account, rather than a supermolecule approach, because solvation in polar solvents seems to be governed mainly by electrostatic driving forces. In fact, it has been shown that the discrete-continuum model does not yield a better description of the solvation process than the continuum model does for most systems and, in particular for amines[23] which is the case of HA. We have used this model to rationalize the solvent effects on several containing amines systems[24], and to analyze the Weinstein model for histamine-H2 receptor activation[25].

The CNDO/2 and CNDO/2-RF calculations were performed using a software developed by Prof. Renato Contreras using the optimized AM1 and PM3 geometries. The calculations were performed at the dielectric constant values of 1 (gas phase) and 80 (water).

## RESULTS AND DISCUSSION

AM1 calculations were carried out on the tautomers-conformers, T/Cs, of HA monocation. For those structures involved in an intramolecular H-bond, PM3 calculations were also performed. Fig. 1 shows the various tautomers definition. It also shows the atoms numbering of the +HN3H form, including the dihedral angle alpha, α, which was used as a parameter in the conformational analysis of HA tautomers. this numeration holds for all the HA forms. As the figure shows, α is defined as the dihedral angle (C5-C8-C9-N12). The magnitude of α is then, the torsional angle of the side chain around the C8-C9 bond. The center of coordinate (α=0) corresponds to the syn structure.

The first set of calculations were devoted to a partial description of the HA monocation potential energy surface. The torsional potential energy function around α, TPEF, was calculated for all protonated HA T/Cs. It is quite possible that for a given α value more than one conformer can exist, but the geometry optimization process will provide the most stable one for that alpha value; then the TPEF obtained will represent a minimum path of the potential energy surface.

The TPEF for each HA monocation was calculated for α values ranging from 0 to 180 degrees, with increments of 10 degrees; close to the critical points, complete optimization procedure was achieved. Table I displays the significant geometrical parameters of the most

**TABLE** I. AM1 and PM3 molecular geometries and energies of more stable protonated forms to HA.

| | +HN1H AM1 | +HN1H PM3 | +HN3H AM1 | +HN3H PM3 | HAH+ AM1 |
|---|---|---|---|---|---|
| D N1-C2 | 1.3960 | 1.3862 | 1.3848 | 1.3524 | 1.3689 |
| D C2-N3 | 1.3547 | 1.3532 | 1.3977 | 1.3864 | 1.3738 |
| D N3-N4 | 1.3865 | 1.3810 | 1.3906 | 1.4020 | 1.3999 |
| D C4-C5 | 1.4176 | 1.3968 | 1.4101 | 1.3839 | 1.4082 |
| D N-H17 | 0.9879 | 0.9877 | - | - | 0.9963 |
| D N3-H17 | - | - | 0.9893 | 0.9882 | 1.0060 |
| D C5-C8 | 1.4715 | 1.4758 | 1.4751 | 1.4819 | 1.4778 |
| D C8-C9 | 1.5310 | 1.5326 | 1.5255 | 1.5294 | 1.5315 |
| D C9-N12 | 1.4918 | 1.5095 | 1.4910 | 1.5141 | 1.4454 |
| D N12-H15 | 1.0024 | 1.0010 | 1.0213 | 1.0418 | 1.0015 |
| D N12-H16 | 1.0023 | 1.0007 | 1.0230 | 1.0000 | 1.0015 |
| D N12-N1 | - | - | 2.8300 | 2.6300 | 2.8880 |
| D N1-H18 | 3.4000 | 3.5900 | 2.0530 | 1.7500 | - |
| D N12-H18 | 1.0023 | 1.0010 | 1.0240 | 1.0100 | 2.2400 |
| A (N1-C2-N3) | 111.5 | 107.9 | 110.9 | 107.5 | 108.4 |
| A (C2-N3-C4) | 105.9 | 109.9 | 107.3 | 109.6 | 108.8 |
| A (N3-C4-C5) | 110.1 | 108.6 | 106.1 | 105.7 | 107.2 |
| A (C5-C8-C4) | 111.1 | 111.4 | 113.1 | 113.0 | 113.0 |
| A (C8-C9-N12) | 112.3 | 111.8 | 113.9 | 111.7 | 113.0 |
| AH-bonding | | | 129.7 | 139.6 | 141.7 |
| ϕ1 | -82.0 | -84.5 | 46.8 | -85.2 | 43.8 |
| ϕ2 | -172.2 | -174.8 | -179.9 | -169.0 | -167.3 |
| α | 51.3 | 57.4 | 61.3 | 3.8 | 61.8 |
| TOTAL ENERGIES | -32083.4 | -28276.2 | -32095.0 | -28296.9 | -32097.2 |

a. Total energies in Kcal/mol; b. Bond lengths in Å; c. ϕ1 = C9-C8-C-C4; d. α = N12-C9-C8-C5
e. ϕ2 = H1-N12-C9-C8

stable forms together with the associated total energy, provided by AM1 calculations. The results indicate that all three protonated HA tautomers show two energy minima, one at an α value of 180 degrees and the most stable form which occurs at an α value around 60 degrees. Also, +HN1H tautomers are more than 10 kcal/mol less stable than both +HN3H and HAH+ tautomers. These results are in agreement with *ab initio* calculations at various levels of accuracy reported by Hernández-Laguna and collaborators (15g, 15h), where the most stable T/C corresponds to the "Scorpio" form. Same results have been reported by Nagy and collaborators[16].

The barrier height to internal rotation around α of +HN3H and HAH+ conformers were 9.2 kcal/mol and 7.3 kcal/mol, respectively; both maxima occur at α values around 150°. This is a relevant result, since the nuclear repulsion energy of the folded forms (α = 60°) is larger than those of the extended conformers (α = 180°), but the total energy of both compounds follows the opposite trend. The existence of an intramolecular H-bonding between N1 and N12 atoms accounts for these results. Moreover, the internuclear distances displayed in Table 1 between the atoms involved in the hydrogen bridge, i.e., N1-H18, N12-H18 and N1-N2 reinforce this hypothesis. This intramolecular H-bonding has been reported for the most stable neutral N3H tautomer[26].

Then, according to the AM1 results, the most stable protonated HA species is the HAH+ conformer intramolecularly H-bonded to the amino group, HybHAH+, which is more stable by 2.3 and 15 kcal/mol that the H-bonded +HN3H, Hyb+HN3H, and +HN1H forms, respectively.

Because the most stable histamine monocation structure exhibits H-bonding between the atoms N1 and N12, PM3 calculations were carried out to improve the H-bonding energetic description. The total energy minima of the PM3 TPEFs and the significant geometrical parameters are shown in Table II. The calculated PM3 energy barriers to internal rotation about α are smaller than those obtained from the AM1 method. The underestimation of H-bonding energy of the AM1 method compared to that of the PM3 model can be noticed by the difference between the energy minima at α = 60°. However, regardless the refined MNDO hamiltonian used, the most stable structure corresponds to a protonated N3H form exhibiting an intramolecular H-bond between N1 and N12 atoms, in agreement with *ab initio* results[15]. In particular, the results of the present paper

Table II Significant PM3 geometrical parameters[a] and total energy[b] for the most stable structure of protonated N3H tautomers.

| Parameter | HAH+ | +HN3H |
|---|---|---|
| C5-C8 | 1.484 | 1.482 |
| C8-C9 | 1.530 | 1.525 |
| C9-N12 | 1.493 | 1.514 |
| N1-H18 | 1.042 | 1.808 |
| N12-H18 | 1.758 | 1.031 |
| N1-N12 | 2.614 | 2.637 |
| C5-C8-C9 | 122.2 | 112.7 |
| C8-C9-N12 | 111.0 | 111.6 |
| C4-C5-C8-C9 | 149.4 | 147.6 |
| C5-C8-C9-N12 | 58.5 | 60.2 |
| C8-C9-C12-H15 | -165.5 | -168.8 |
| Total Energy | -28296.84 | -28296.53 |

[a]Bond distances in Å and bond angles in degrees.
[b]Energies in kcal/mol

are very similar to those for the +HNH3 tautomer reported by O. Tapia *et al.*[15d], where a bent +HN3H tautomer which they called the "Scorpion" form exhibiting H-bonding between N1-N12, was found to be the most stable conformer according to the *ab initio* STO-4G calculations. In that paper, the authors made some remarks about experimental findings, which are described for comparison purposes with the results provided by this work. Based on experimental data for the gas phase basicity of the HA monocation and from the gas phase basicity of related compounds, they estimated a value of -7.5 kcal/mol for the contribution from chelation to the stabilization energy of the protonated folded histamine.

The corresponding theoretical value was estimated as the energy difference between the folded H-bonded form ($\alpha$ = 60°) and the extended structure ($\alpha$ = 180°) of the protonated HA (+HN3H). The STO-4G result obtained was -31.9 kcal/mol; according to the authors, the failure of this result is probably due to the limited characteristics of that basis set (and they proved it in a more recent published paper[15h]). From our calculations, the corresponding AM1 and PM3 results are -7.3 kcal/mol are -6.7 kcal/mol (HAH+), respectively. It can be observed that our calculations correlate fairly well with the experimental data, which shows once again the reliability of these methodologies in the description of HA monocation structure.

In summary, the most interesting feature of the calculated AM1 and PM3 TPEFs is that both tautomers, HAH+ and +HN3H, exhibit the minimum energy at the same torsional angle and the energy difference between those minima is very small, which strongly suggests the occurrence of proton transfer between N1 and N12.

The proton transfer potential function, PTPF, between N1-N12 atoms was calculated by AM1 and PM3 methodologies, Figure 2 shows the results. As before, because of the optimization procedure the calculated PTPFs may be considered to represent the minimum energy path for the proton transfer.

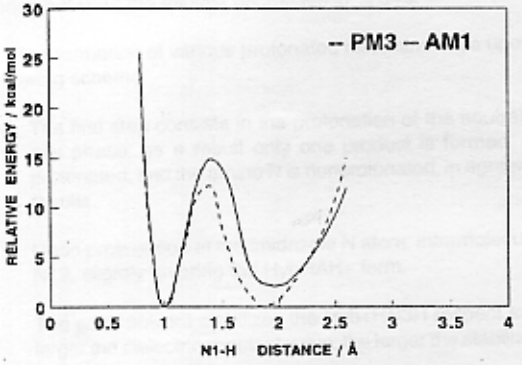


FIG. 2. AM1 and PM3 proton transfer potential function between N1 and N12 (N1...H...N12). AM1 results (solid line) and PM3 results (dashed lines).

Both methodologies show a double well potential curve for the intramolecular proton transfer. One minimum shows the N1-H distance of 0.99 Å, HybHAH+, and the other one shows a N12-H distance of 1.03 Å, Hyb+HN3H. The relative energy of these minima proved to be slightly dependent on the MNDO hamiltonian used. In fact, the double well potential functions illustrated in Fig. 2 show that, according to the AM1 curve, the energy difference between the minima is 2.2 kcal/mol favoring the HybHAH+ form, while the corresponding value obtained from the PM3 results is 0.3 kcal/mol. Also, the two wells are connected through a proton transfer barrier of 15.2 and 12.6 kcal/mol, provided by the AM1 and PM3 calculations, respectively.

A. Hernández-Laguna and collaborators have recently reported the critical points of the N3H monocation T/Cs [15h] from an exhaustive description of the potential energy surface of the protonated N3H conformer provided by *ab initio* 6-31G**//6-31G** and MP2/6-31G**//MP2/6-31G** level calculations. According to the 6-31G**//6-31G** results the most stable T/C is HybHAH+ and the next one is Hyb+HN3H; the energy difference between these two forms is 3.7 kcal/mol, and the proton transfer barrier is 9.7 kcal/mol and 6.0 kcal/mol respect to the first and to the second minimum, respectively. The agreement of the AM1 results with these is apparent. When correlation effects were taken into account by the MP2/6-31G**//MP2/6-31G** basis set[15h], the proton transfer barrier height is 2.2 kcal/mol and the energy difference between the minima is 0.3 kcal/mol, this last value corresponds to that calculated by the PM3 method. The AM1 and PM3 energy barriers to proton transfer, are expected to be less reliable than the stationary points, due to the fact that the parametrization of MNDO hamiltonians is built up from experimental data. For the present purposes, it is important to keep in mind that the AM1 and PM3 energy barriers magnitude to proton transfer represent an upper bound of this parameter.

An important feature displayed by both curves in Fig. 2 is that the PTPF around N1 is narrower than that occurring around N12, indicating that the force constant and the bond energy of the N1-H bond are larger than those corresponding to the N12-H one, in agreement with various theoretical calculations (8, 12, 14, 15 and 16); consequently the first energy minimum (HybHAH+) represents a more covalent bond than that of Hyb+HN3H, which is described by a shallow well, corresponding to an ion pair interaction. This characteristic of the PTPF suggests that the presence of an electric field like those created by polar solvent molecules, ions, other molecules, etc., should stabilize the more ionic form, Hyb+HN3H, in a larger magnitude than the more covalent HybHN1H+ form. Therefore, a polar solvent such as water for example, could produce a change in the shape of the PTPF.

The above considerations, in addition to the experimental data about the relative abundance of protonated conformers of HA in aqueous solutions, clearly show the need to study the solvent effects on the protonated N3H PTPFs.

The influence of the solvent polarity on the PTPF of these T/Cs was studied by the Reaction field model, in the continuum solvent representation at CNDO/2 level, CNDO/2-RF.

In order to test the reliability of the CNDO/2 methodology, the PTPF function was calculated in the isolated system and compared with the AM1 and PM3 curves. Fig. 3 shows that the CNDO/2 PTPF, in the absence of a polar medium exhibits the two protonated forms in equilibrium, favoring he HybHAH+; the curve follows the same trends as the AM1 one, which represented the constraints imposed to the CNDO/2 calculations to test its reliability in the description of the proton transfer process in he N3H monocation.

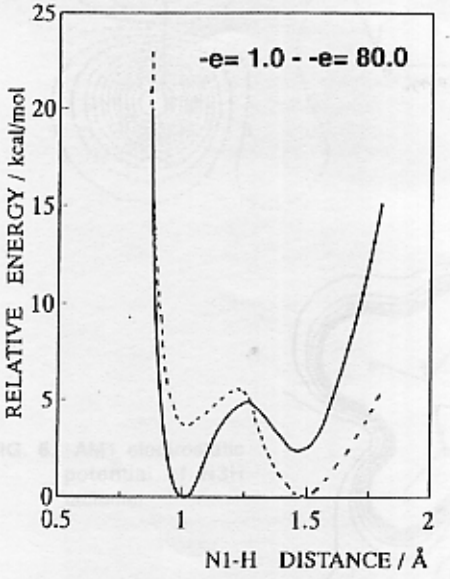


**FIG. 3.** CNDO/2-RF proton transfer potential function between N1 and N12 (N1...N...N12). Dielectric constant value of 1.0 (solid line) and dielectric constant value of 80 (dashed line).

To study the solvent polarity effects on the PTPF, this function was calculated at several dielectric constant values; the results obtained showed that for dielectric constant values larger than 30, the PTPF remained almost unchanged, as it is usual in the RF calculations.

The CNDO/2-RF PTPF calculated for a bulk dielectric constant of 80 exhibits two minima, which occur at the interatomic distances N1-H18 of 1.0 Å and 1.5 Å, respectively. At this point, the N12-H18 distance was 1.1 Å and it corresponds to the Hyb+HN3H form, being 3.6 kcal/mol more

stable than the HybHAH+ species. A barrier height to proton transfer of 5.5 kcal/mol, with respect of this minimum energy point. The energy difference between the minima is in good agreement with the experimental value of 3.97 kcal/mol of Gibbs free energy at 298°K, reported by Nószal and Rabestein respect to the favoring site of protonation at the imidazolic N1 respect to the protonation at the amino N12 obtained from the ratio of protonation microconstants in $D_2O$[27].

As Figure 3 shows the presence of the electric field created by a polar solvent on the T/Cs produces an inversion of the minimum relative energy and a lowering in the proton transfer barrier height. In addition, the intramolecular H-bonding is maintained.

Even though Rashin *et al.*[28], from theoretical calculations have proposed that HA remains H-bonded in aqueous solutions, most of the experimental results[4-6] assume that +HN3H is the most stable form, regardless its conformation. Besides the interaction with water molecules, it could be argued that the increase in the degrees of freedom of the extended +HN3H form respect to the corresponding intramolecularly H-bonded species could be responsible for the free energy decrease associated to this form. By the other hand, the solvent polarity could produce a barrier height decrease of TPEF about α. To get a better insight in this respect the solvent effects on the torsional energy about α were calculated. The results showed a torsional energy barrier decrease from 15.2 kcal/mol (isolated system) to 9.0 kcal/mol which corresponds to 59 % of this magnitude. In turn, the energy difference between the minima decreases in % 54.2%.

The formation of various protonated histamine T/Cs upon solvation can be described through the following scheme:

- The first step consists in the protonation of the neutral tautomer at the imidazole N atom in gas phase; as a result only one product is formed, i.e., the two imidazole N atoms are protonated, and the amino N is nonprotonated, in agreement with experimental and theoretical results.

- Upon protonation at the imidazole N atom, intramolecular H-bond is formed between N1 and N12, slightly favoring the HybHAH+ form.

- The polar solvent stabilizes the Hyb+HN3H respect to the HybHAH structure; such that the larger the dielectric constant value, the larger the stabilization energy of the Hyb+HN3H respect to the other species.

- The electrostatic solvent effects on the internal rotation around α, stabilize the non H-bonded, +HN3H form respect to the Hyb+HN3H one and it lowers the energy barrier to internal rotation around α.

According to the results obtained, the relative abundance of various T/Cs of HA in aqueous solution can be explained by a molecular mechanism shown in Figure 4.

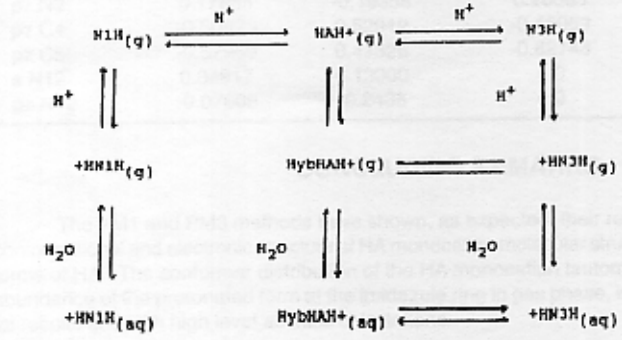


**FIG. 4.** Scheme of the mechanism for the tautomeric equilibrium of histamine in aqueous solution.

To rationalize the proposed mechanism the charge distribution and relative energy of the HOMOs were used. Contour plots of charge density, electrostatic potentials and frontier molecular orbitals were calculated.

The Mulliken net charges and the atomic orbital coefficients provided by AM1 and PM3 methods gave the same qualitative results than those provided by *ab initio* STO-631G. Consequently, the AM1 method was used in these calculations. A molecular explanation of each step of the proposed mechanism was intended.

- Protonation at the imidazole N atom; the most stable structure of the neutral N1H and N3H were calculated and the HOMOs were obtained. Both tautomers showed the HOMO delocalized on the pi system, while the HOMO-1 was mainly localized at N12 representing the electron lone pair on this atom, as shown in Fig. 5. The electrostatic potential contour plot was also calculated for the same molecular system and it is shown in Fig. 6. It is

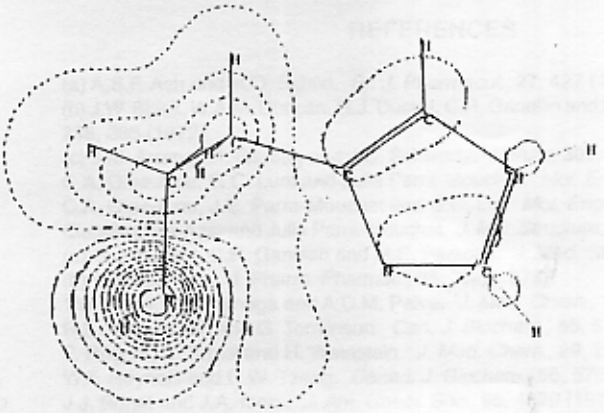

**FIG. 5.** AM1 (HOMO - 1)$^2$ of N3H tautomer.

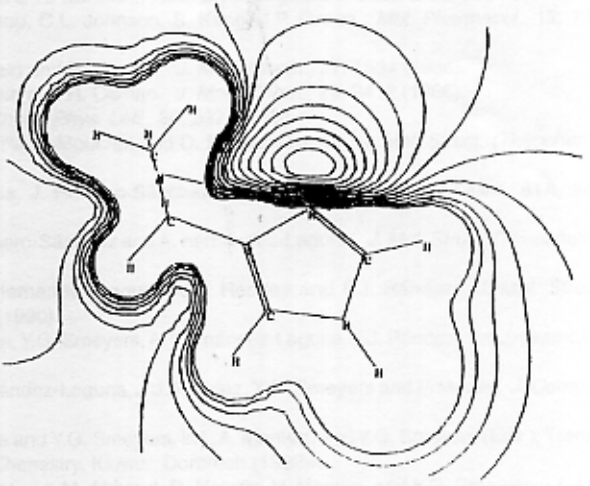

**FIG. 6.** AM1 electrostatic potential of N3H tautomer.

evident that the large negative electrostatic potential at N1 together with the lack of availability of the electron lone pair on N12, are indicative that protonation is highly probable to occur at N1.

- Intramolecular H-bond formation: upon protonation at N1 i.e., the formation of HAH+ structure, the AM1 charge on N12 increases from -0.462 (N3H), -0.480 (N1H) to -0.561 (HAH+) a.u., concomitantly the MO representing the electron lone pair at N12 becomes the HOMO of he HAH+ conformer, indicating that protonation of N3H at N1 triggers the increase of N12 proton affinity of the +HN3H conformer. This process is achieved by increasing the negative charge on N12 and destabilizing the MO which represents the electron lone pair on N12, now the HOMO of the protonated structure.

- Solvent polarity effect on proton transfer process: In order to analyze the effect of solvent polarity on the electronic distribution of the +HAH form, the Mulliken net charge on N12 was recorded.

When going from $\varepsilon = 1.0$ to $\varepsilon = 80.0$ the net charge on N12 changes from -0.07 a.u. to -0.3081 a.u., respectively. The increase of the negative charge on N12 together with the increase in the solvent polarity, illustrate the classic response of the system, i.e., the more polar the solvent the more stable becomes the +HN3H conformer.

The non classic molecular response to an increase of solvent polarity is the destabilization of the MO representing the electron lone pair on N12. Since this MO corresponds to the HOMO of HybHAH+ and HAH+, the increase of the electric field created by the polar solvent enhanced the destabilization of the HOMO i.e., that of the electron lone pair on N12. Then, as polarity increases the proton affinity of the less polar solute also increases and therefore it becomes more reactive to protonation. Table III shows the HOMO eigen values for HybHAH+ and non H-bonded HAH+ conformers. An important feature shown in the Table is the illustration that even though, the solvent effects are mainly of electrostatic nature, the molecular response to the electric field implies a change of the electronic structure. Another important feature of the solvent polarity effect on the tautomeric equilibrium of the histamine in aqueous solution, is a cooperative phenomenon produced by the formation of the nonbonded +HN3H conformer, which increases the solution polarity, since its dipole moment is larger than that of Hyb+HN3H. As the solution polarity increases, the +HN3H concentration increases, which in turn, increases the solution polarity.

**TABLE III.** Homo energies and some relevant coefficients for neutral and protonated forms obtained by AM1 method.

| | N1H | N3H | +HN1H | +HN3H | HAH+ |
|---|---|---|---|---|---|
| ENERGIES | -9.003517 | -8.8771 | -12.86704 | -12.65153 | -13.65574 |
| pz N1 | 0.10926 | -0.00598 | 0.14912 | 0.11872 | 0.00688 |
| pz C2 | 0.51405 | -0.42753 | 0.52710 | 0.49163 | -0.11272 |
| pz N3 | 0.17885 | -0.19358 | 0.28855 | 0.19186 | -0.00435 |
| pz C4 | -0.50823 | 0.52919 | -0.46059 | -0.56730 | 0.15162 |
| pz C5 | -0.57969 | 0.47326 | -0.62148 | -0.56302 | 0.12140 |
| s N12 | 0.04917 | 0.13000 | = 0 | = 0 | -0.24525 |
| pz N12 | -0.07609 | -0.2436 | = 0 | = 0 | -0.73577 |

## CONCLUDING REMARKS

The AM1 and PM3 methods have shown, as expected, their reliability in the description of the conformational and electronic structure of HA monocation molecular structure in gas phase of protonated forms of HA. The conformer distribution of the HA monocation tautomers, specially the large relative abundance of the protonated form at the imidazole ring in gas phase, is in agreement with experimental results and with high level *ab initio* calculations.

The results obtained reinforce the idea that solvation process is mainly of electrostatic nature, since the Reaction Field model recuperates the experimental data of relative abundance of protonated HA in aqueous solution; however, the molecular responses of HybHAH+ to the solvent polarity is relevant for the interpretation of the increase of the +HN3H form abundance relative to the +HAH tautomer in aqueous solution.

We have recently reported a 3D model of H2 receptor of Histamine. Docking studies of the +HN3H folded conformation in our model show that an intramolecular hydrogen bond between N1 and N12 is broken, and the histamine adopts the a conformation similar +HN3H form to interact optimally with the H2 receptor[2]. The same results were obtained for the antagonist of histamine at the H2 receptor[3,4].

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