COMPARATIVE SCF MO STUDIES FOR SOME HISTAMINE ANALOGUES AS AGONISTS OF THE H2 RECEPTOR OF HISTAMINE

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ABSTRACT

This paper presents SCF AM1 and CNDO/2 RF calculations of the potential energy surface of histamine monocation (HA) and the agonists 2-(4-thiazolyl)ethylamine (TIA) and 2-(4-oxazolyl)ethylamine (OXA). The similarity of the conformational and electronic structures between HA, TIA and OXA, suggests that both HA analogues should have agonist character, according to the intramolecular proton transfer model that we have proposed in order to explain the activation of the histamine H2 receptor. In this model both the intramolecular proton transfer and the basicity of the nitrogen atoms in the hydrogen bridge are assumed to trigger the activity of the receptor. In this context, the activity of the species analyzed here should decrease in the order HA, TIA, and OXA.

KEY WORDS: Histamine agonists theoretical calculations

RESUMEN

En el presente trabajo se presentan los resultados SCF AM1 y CNDO/2 RF de la superficie de energía potencial de la histamina protonada (HA) y de los agonistas 2-(4-tiazolil)etilamina (TIA) y 2-(4-oxazolil)etilamina (OXA). La similitud entre las estructuras conformacionales y electrónicas de HA, TIA y OXA, sugiere que ambos análogos de histamina tendrían carácter agonista, en base al modelo de transferencia protónica intramolecular que hemos propuesto para explicar la activación del receptor H2 de la histamina. En este modelo tanto la transferencia protónica intramolecular como la basicidad relativa de los átomos de nitrógeno en el puente de hidrógeno juegan un papel relevante en la activación del receptor H2. En este contexto, la actividad de las especies analizadas debiera decrecer en el orden HA, TIA y OXA.

PALABRAS CLAVES:Histamina agonistas calculos teóricos

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INTRODUCTION

hine plays a major role in a variety of biological systems. For example, it has effects on [1], increases the heart rate[2] and stimulates gastric acid secretion[3]. The actions of HA are family of closely related receptor proteins denoted by H1, H2 and H3, originally defined binding studies[4,5]. We have recently reported a basic tridimensional model of the H2

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INTRODUCTION

Histamine plays a major role in a variety of biological systems. For example, it has effects on smooth muscle[1], increases the heart rate[2] and stimulates gastric acid secretion[3]. The actions of HA are mediated by a family of closely related receptor proteins denoted by H1, H2 and H3, originally defined on the basis of binding studies[4,5]. We have recently reported a basic tridimensional model of the H2 receptor[6].

Over the past decades much attention has been paid to the structural requirements for the various types of histamine receptors. The structural requirements of histamine, as an H2 agonist, are considered to be the protonated side chain nitrogen atom and the ability of the imidazole system to undergo a tautomeric shift. Weinstein *et al.*[7] have postulated a mechanistic model for the activation of H2 receptors which is generally accepted and has served as an important concept for further studies[8-10]. However, there are some doubts regarding the feasibility of the intermolecular proton transfer involved in that mechanism[10].

Eriks *et al.*[11] developed a new model for the H2 histamine receptor activation. This model is able to accommodate and explain the agonistic activities of all known histamine H2 receptor agonists, including nontautomeric ones. According to this model, the affinity of an H2 agonist depends only on the basicity of the heterocyclic ring, in contrast to the proton transfer models[7], with interaction taking place in the extended form of the agonist, whereas the occurrence of the extended forms is determined by interaction with a basic moiety at the receptor surface.

We have recently proposed a molecular mechanism to explain the activation of the H2 receptor upon HA interaction[12]. To build up this mechanism several quantum mechanical calculations were performed. The reliability of the quantum chemical methodologies were tested against experimental data. The main results obtained are:

- AM1 and PM3 calculations of the HA potential energy surface show that the most stable tautomers/conformers are two protonated N3H forms exhibiting an internal H-bond between the amino N atom and the imidazol N atom. In agreement with both the experimental FT-ICR measurements[14] and high level *ab initio* calculations[13].
- The molecular modeling of the H2 receptor[6] suggests the presence of an electric field in the active site environment. The electric field effects on the HA structure were studied using the Reaction Field, RF, model in the continuum representation at the CNDO/2 level, CNDO/2-RF [15]. The results are in agreement with the experimental data which show that, in aqueous solution, the most abundant species of HA monocation is a non H-bonded species protonated at the amino N atom[16,17]. We have arrived to the same results for the HA hydration[18].
- Consequently, we have calculated the intramolecular proton transfer potential function, PTPF, of HA surrounded by molecular array which simulates the active site of the H2 receptor found from the above mentioned work of molecular mechanics. The electric field at the site was modeled by the RF approach.
- As a result, we have postulated an H2 receptor activation mechanism upon HA, which involves a hydrogen bonding interaction between the extended HA and the carboxylate group of Asp 98. Since HA in gas phase or in nonpolar environments exists mainly as intramolecularly H-bonded conformers, after crossing the transmembranes, HA should reach the active site in this conformation. The intramolecular hydrogen bond would be broken due to the presence of Asp 98 immersed in an electric field, which is mainly created by the ionic fragment in the active site and the electronic distribution of the receptor itself[6].

In summary, according to our mechanism, the activity of the histamine is directly related to the existence of a polarizable intramolecular H-bond. Table I shows the results of the PTPF of HA calculated by the various methods above cited.

TABLE I. Relative energy for critical points of the proton transfer potential function of HA monocation obtained by various methods.

Methods	Ring protonated	Barrier height	Amine chain protonated
PM3 [12]	0.0	12.6	0.3
6-31G**//6-31G** [13]	0.0	9.7	3.7
MP2/6-31G**//MP2/6-31G** [13]	0.0	2.2	0.2
AM1 [12]	0.0	15.2	2.2
CNDO/2 [12]	0.0	4.9	2.5
CNDO/2-RF [12]	3.6	5.5	0.0

The energies are in Kcal/mol.

In order to study the effects of the heterocyclic ring on the intramolecular H-bond as well as on the gauche-trans torsional potential of the ethylamine(/ethylammonium) side chain with respect to the imidazolium(/imidazolyl) group, (about the alpha angle shown in Fig. 1) this work reports AM1 and CNDO/2-RF calculations on 2-(4-thiazolyl)ethylamine monocation, TIA, and 2-(4-oxazolyl)ethylamine monocation, OXA (Figure 1). To account for the gas phase (non polar medium) relative energy of various tautomers/conformers, the potential energy surface of each compound is calculated using the AM1 hamiltonian. The medium polarity effects on the PTPF of both compounds are studied through the CNDO2-RF methodology. Finally, in order to predict the relative agonist activity of OXA and TIA respect to HA, the results obtained are analyzed in terms of the mechanism proposed for the H2 receptor activation upon HA.

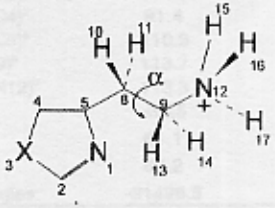

FIG. 1. Internal geometry of HA, TIA and OXA.

X = N, O, S

METHODS

All calculations were performed using the AM1 methodology[10] taken from MOPAC 6.0 package. This methodology has been found to be a useful method for the theoretical modeling of H-bonds in cations[20b]. In addition, for oxazole and thiazole, it has provided bond lengths and bond angles of 6-31G* quality[20b]. The PTPFs, torsional potentials and associated critical points were calculated using analytical gradients of the RHF wavefunction.

The medium polarity effects on the conformational and electronic structure of both species

were studied using the CNDO/2-RF methodology in the continuous solvent representation[18]. This theoretical approach has shown to be reliable in the description of polar solvent effects on acid-base properties; regarding this work, successful results have been obtained for amine containing systems[21]. In particular we have recuperated experimental data concerning the relative abundance of histamine and HA tautomers[18]. The constraints imposed to the CNDO/2 method require that the CNDO/2 energy results follow the same trends as their AM1 counterparts.

The CNDO/2 and CNDO/2-RF calculations were performed using software developed by Prof. Renato Contreras. The internal geometries used were those provided by the AM1 calculations. Also the relative energy of critical points of PTPFs obtained with Pople standard coordinates[22] shows no difference respect the AM1 geometries.

RESULTS AND DISCUSSION

The first set of calculations were devoted to the description of the torsional potential energy around the alpha angle of TIA and OXA species by the AM1 methodology. Notice that each compound presents two tautomers, depending on the protonated N atom. Figure 1 shows the atoms definition of the TIA and OXA forms, including the dihedral angle α which we have used as the parameter for these calculations on TIA and OXA tautomers. As the figure shows, α is defined as the dihedral angle (C5-C8-C9-N12).

These AM1 calculations were carried out as a function of the α value, which was varied from 0 to 180 degrees in 10 degree increments and seeking the most stable structure by complete geometry optimization through a gradient technique for each value. Close to the energy minima and maxima, the α increments were narrowed and followed by complete geometry optimization including α, i.e. no geometrical restrictions were imposed on the calculations. Figures 2 and 3 display the

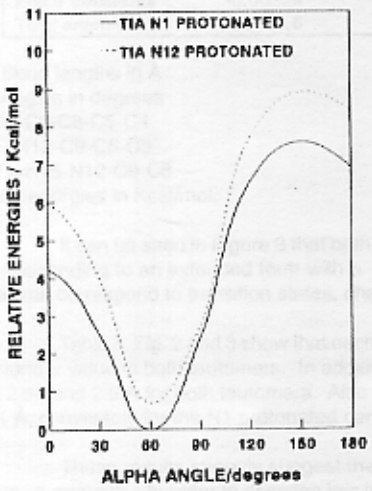

FIG. 2. Torsional potential function of protonated TIA tautomers vs α angle.

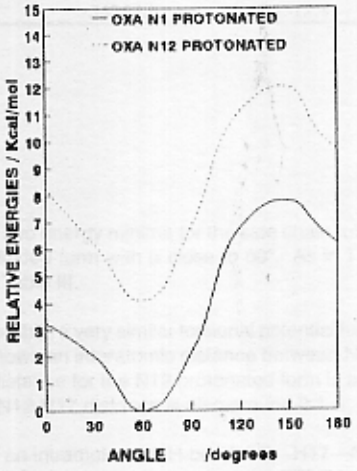

FIG. 3. Torsional potential function of protonated OXA tautomers vs α angle.

relative electronic energies as functions of α for TIA and OXA, respectively, while Table II shows the relevant internal coordinates and the total energy of most stable conformer, where the atom numbering is referred to Fig. 1. Besides the α angle showed in the figure, this Table includes two dihedral angles φ1 and φ2 defined by angle (C9-C8-C5-C4) and angle (H15-N12-C9-C8), respectively. In these tables D and A stand for interatomic distance and bond angle, respectively; while the Greek characters represent dihedral angles.

TABLE II. Internal rotation about α. AM1 molecular geometry and potential energy of more stable protonated forms of TIA and OXA.

	TIA N12 protonated AM1	TIA N1 protonated AM1	OXA N12 protonated AM1	OXA N1 protonated AM1
DN1-C2[a]	1.396	1.387	1.399	1.421
DC2-X3[a]	1.692	1.671	1.398	1.366
DX3-C4[a]	1-.658	1.655	1.390	1.407
DC4-C5[a]	1.396	1.398	1.396	1.387
DC5.N1[a]	1.397	1.378	1.386	1.389
DN1-H17[a]	2.083	0.998	2.205	1.014
DC5-C8[a]	1.485	1.486	1.475	1.478
DC8-C9[a]	1.524	1.537	1.524	1.532
DC9-N12[a]	1.490	1.443	1.492	1.446
DN12-H15[a]	1.021	1.001	1.024	1.001
DN12-H16[a]	1.023	1.001	1.022	1.001
DN12-N1[a]	2.837	2.990	2.876	2.835
DN12H17[a]	1.038	2.010	1.033	2.149
X = S, O				
A(N1-C2-X3)[b]	114.2	112.3	108.5	105.8
A(C2-X3-C4)[b]	91.4	92.4	105.9	107.6
A(X3-C4-C5)[b]	110.3	112.3	107.5	108.1
A(C-C8-C9)[b]	113.7	115.3	117.1	115.2
A(C8-C9-N12)[b]	113.3	113.3	113.2	113.1
φ1[b]	-34.5	155.4	36.6	-31.6
φ2[b]	61.1	81.6	-49.1	-71.5
α[b]	63.2	65.4	63.9	60.1
Total energies	-31496.8	-31497.5	-34378.4	-34380.3

a. Bond lengths in Å
b. Angles in degrees
φ1 = C9-C8-C5-C4
α = N12-C9-C8-C5
φ2 = H15-N12-C9-C8
Total energies in Kcal/mol.

Due to the fact that protonation at the heterocyclic N atom of TIA and OXA species were 20 and 35 Kcal/mol more stable respect to the protonation in the sulfur and oxygen heterocyclic atoms, only tautomers protonated at N1 and N12 were considered. Figure 2 shows that both TIA tautomers exhibit similar curves, exhibiting two energy minima, one at an α value of 180° and the most stable form at an α value around 60°. The maximum energy values correspond to transition states of the potential energy surface. Table II shows the significant geometry and total potential energy of the most stable OXA and TIA forms, and Table III shows the significant geometry, the potential energy and force constants of transition states. Similar potential energy surfaces have been reported by Hernández-Laguna *et al.* for histamine monocation[13].

TABLE III. Internal rotation about α. AM1 molecular geometry, potential energy and force constants of transition states for protonated forms of TIA and OXA.

	TIA N12 protonated AM1	TIA N1 protonated AM1	OXA N12 protonated AM1	OXA N1 protonated AM1
DN1-C2[a]	1.395	1.398	1.416	1.424
DC2-X3[a]	1.701	1.648	1.404	1.363
DX3-C4[a]	1.661	1.656	1.388	1.408
DC4-C5[a]	1.395	1.398	1.392	1.386
DC5.N1[a]	1.396	1.375	1.380	1.390
DN1-H17[a]	4.003	1.002	3.920	1.012
DC5-C8[a]	1.484	1.484	1.475	1.477
DC8-C9[a]	1.530	1.539	1.530	1.539
DC9-N12[a]	1.495	1.438	1.494	1.438
DN12-H15[a]	1.024	0.999	1.024	0.999
DN12-H16[a]	1.026	1.003	1.026	0.999
DN12-N1[a]	4.143	4.215	4.170	4.340
DN12H17[a]	1.024	3.921	1.002	4.12
X = S, O				
A(N1-C2-X3)[b]	110.4	112.2	107.5	114.7
A(C2-X3-C4)[b]	91.1	92.4	105.6	105.7
A(X3-C4-C5)[b]	114.3	110.5	108.3	108.4
A(C-C8-C9)[b]	110.7	111.7	110.4	111.5
A(C8-C9-N12)[b]	112.6	111.6	112.6	111.4
φ1[b]	-57.3	-68.9	-57.9	-14.9
φ2[b]	58.3	65.4	58.1	66.8
α[b]	146.4	148.4	147.1	149.0
Force constants[c]	-0.00325	-0.00221	-0.00295	-0.00222
Total energies	-31488.6	-31490.1	-34369.9	-34372.4

a. Bond lengths in Å
b. Angles in degrees
φ1 = C9-C8-C5-C4
α = N12-C9-C8-C5
φ2 = H15-N12-C9-C8
Total energies in Kcal/mol.

It can be seen in Figure 3 that both OXA present two energy minima for the side chain rotation, corresponding to an extended form with α = 18°, and a folded form with α close to 60°. As in TIA the maxima correspond to transition states, characterized in Table III.

Table II, Fig. 2 and 3 show that each compound exhibits a very similar torsional potential function around α value in both tautomers. In addition, Table II shows an interatomic distance between N1 and N12 around 2.9 Å for both tautomers. Also the N1-H17 distance for the N12 protonated form is around 2.1 Å; conversely for the N1 protonated compounds the N12-H17 distance is also around 2.1 Å.

These results strongly suggest the existence of an intramolecular H-bond, N5—H17—N12 in both compounds. In order to describe this internal H-bonding in a non polar medium the PTPF for each compound was calculated by the AM1 method; Figure 4 shows the results for TIA and OXA species; also, for comparison purposes, the corresponding PTPF of HA has been included. Each

one of these curves was calculated by complete geometry optimization of the tautomers at each point of the proton position across the H-bridge. As before, the internal geometry was completely relaxed as the proton moved from one minimum to the other, so that the calculated PTPFs may be considered to represent a minimal energy path for the proton transfer process of the gas phase or in a dilute solution in a non-polar solvent.

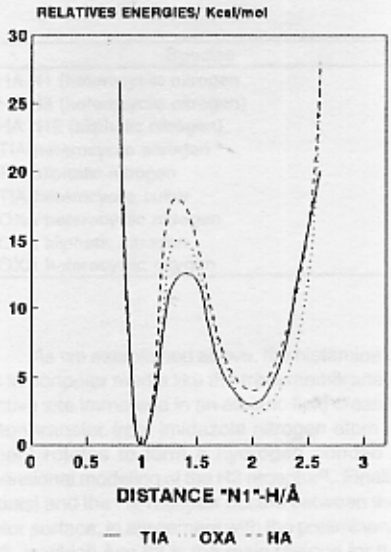

FIG. 4. Proton transfer potential function of protonated TIA, HA and OXA.

The two minima are connected by a transition state with force constant of -1.236 millidynes/Å, -0.853 millidynes/Å and 0.493 millidynes/Å for OXA, TIA and HA respectively. It can be seen that the PTPF of TIA and OXA are very similar to that of HA. However, the calculated barrier height values are presumably overestimated since, as expected, the high level *ab initio* calculations for HA monocations showed to be much more smaller than our AM1 results.

A feature displayed by all curves is that the PTPF around N1 is narrower than that occurring around N12, indicating that N1-H represents a more covalent bond than N12-H which is described by a shallow well, corresponding to a more electrostatic interaction. This characteristic suggests that the presence of an electric field such as that created by a polar solvent, ions, other molecules, etc., should stabilize the more ionic form to a greater extent than the covalent N1-H form.

The polar medium effects on PTPF of HA examined by CNDO/2-RF model, showed an inversion of the energy minima respect to the gas phase results together with a lowering of the torsional barrier described by the α angle, allowing the formation of the extended HA conformer[10]. This structure was found to interact with the H2 receptor active site obtained by molecular mechanic calculation reported earlier[6].

Consequently, the PTPF of OXA and TIA, in the presence of an electric field characterized by a dielectric constant value in the RF model, were calculated by CNDO/2-RF methodology.

Figure 5 shows the TIA PTPF for the isolated system and for the system immersed in a polarizable medium represented by a dielectric constant of 80. It can be noticed that the CNDO/2 PTPF in vacuum follows the same trends as the AM1 curve in Figure 4. The presence of the electric field created by the polar medium on the TIA monocation produces an inversion of the relative energies of both minima, as it was found for HA [18]. A similar behavior was found for the OXA PTPF, which exhibits a difference between the minima of 1.10 Kcal/mol and the barrier height 3.0 Kcal/mol larger than TIA.

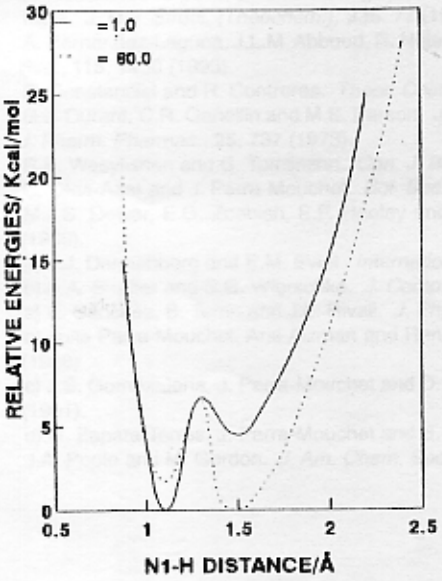

FIG. 5. Influence of a polar medium in the proton transfer potential function of TIA.

Finally, the solvent effects on the torsional energy about α were calculated. The results showed that in the presence of a polarizable medium characterized by ε = 80, the torsional barrier decreases to 2.2 Kcal/mol and 4.5 Kcal/mol for TIA and OXA, respectively.

We have proposed a mechanism for the H2 receptor activation upon HA interactions that involves an intramolecular proton transfer between the two N atoms of HA, in which the basicity of the N atoms may play an important role to explain the difference in agonist character[19]. According to this mechanism, it can be predicted that TIA and OXA should be HA agonist with OXA weaker than TIA. Also the H2 receptor activation depends mainly on the proton transfer from the heterocyclic N atom to the amino N atom. Since the first step consists on the protonation of the heterocyclic N atom, the AM1 proton affinity to this atom in OXA, TIA and HA were estimated as the difference between the protonated H-bonded form and the corresponding neutral tautomer. Table

IV shows the AM1 relative difference of proton affinities for each compound. In all species the heterocyclic ring nitrogen atom is the most basic one; however, a decrease of this parameter is observed from HA to TIA and OXA. These results agree with the hypothesis that the affinity of H2 agonists depends on the basicity of the heterocyclic nitrogen atoms, in good agreement with our mechanism[12] and with experimental data, which correlate the pKa with the activity of some agonists of HA[11].

TABLE IV. Estimated proton affinities in Kcal/mol of HA TIA and OXA species obtained by AM1 calculations.

Species	Proton affinities
HA N1 (heterocyclic nitrogen	176.4
HA N3 (heterocyclic nitrogen)	176.2
HA N12 (aliphatic nitrogen)	173.7
TIA heterocyclic nitrogen	170.1
TIA aliphatic nitrogen	164.8
TIA heterocyclic sulfur	133.6
OXA heterocyclic nitrogen	166.3
OXA aliphatic nitrogen	162.2
OXA heterocyclic oxygen	147.0

As we established above, the histamine compound exists as intramolecularly hydrogen bonded forms in nonpolar media like the transmembranes of the H2 receptor. In the presence of the residues at the active site immersed in an electric field created by these residues and by the rest of the H2 receptor, a proton transfer from imidazole nitrogen atom to the amino nitrogen atom occurs. Then, the amino fragment rotates to form a hydrogen bonded complex with the Asp 98 residues found from the tridimensional modeling of the H2 receptor[6]. Finally, this interaction activates this receptor. The interaction of agonist and the H2 receptor occurs between the extended agonist molecule and a basic moiety at the receptor surface, in agreement with the preliminary tridimensional model of the H2 HA receptor developed by us[6], in which Asp 98 is the main residue for the recognition of HA.

The results obtained for TIA show that this compound behaves like histamine, but because of the lowering on the basicity of the heterocyclic nitrogen of TIA respect to HA, the agonist character of TIA should be smaller than that of HA. In turn, OXA should have smaller agonist character than that of TIA since it presents the largest barrier height to proton transfer and the smallest proton affinities.

ACKNOWLEDGEMENTS

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