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Tautomerism of neutral and monoprotonated histamine—a comparison of semi-empirical and *ab initio* quantum mechanical predictions for 'essential' and 'scorpio' conformations†

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ABSTRACT: Relative energies were calculated at different semi-empirical (CNDO, INDO, MINDO/3, MNDO, AM1, and PM3) and *ab initio* levels (RHF/STO-3G//STO-3G, RHF/STO-4G//STO-4G, RHF/3-21G//3-21G, RHF/6-31G//6-31G, RHF/6-31G*//6-31G, RHF/6-31G*//6-31G*, RHF/6-31 ++ G**//6-31G*, RHF/6-311 ++ G**/6-31G*, RHF/6-31G**//6-31G**, RHF/31 ++ G**//6-31 ++ G**, MP2/6-31G*//6-31G* and MP2/6-31G**//6-31G**) for so-called 'essential' (*trans*) and 'scorpio' (*gauche*) conformations of the neutral and monoprotonated histamine tautomers. For the monocationic forms, the polarizable continuous model was applied to geometries optimized at the RHF/6-31G* level. The comparison shows that, generally, both types of calculation (semi-empirical and *ab initio*) predict the same tautomeric preference for the conformations of histamine and its monoprotonated cation when not interacting with the environment, i.e. for conditions corresponding to the gas phase. For the monocation, the ring *N*-aza protonated form (ImH^+) is favoured in the gas phase for both conformations (*trans* and *gauche*); this is contrary to water solution, where the chain *N*-amino (AmH^+-T_1) predominates. This difference results mainly from the high polarizability of the imidazole ring in the gas phase which is strongly reduced in solution. Some 'discrepancies' are only observed for neutral histamine, for which the relative energy is close to zero. Good agreement of results predicted by various methods can result from the fact that in histamine the proton is transferred between atoms of the same element (nitrogen). Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: histamine; tautomerism; relative energies; semi-empirical and *ab initio* calculations

INTRODUCTION

Histamine—a biogenic amine, synthesized locally from *L*-histidine by the *L*-histidine decarboxylase (EC 4.1.1.22)—exhibits a very complex physiological activity. As with adrenaline and acetylcholine, it acts at the central nervous system level and in the regulation of sleep.[1] It is also responsible for concentration of the smooth muscle of the gut, intestine and bronchi, as well as for strong depressive action and allergic reactions.[2,3] Other functions are related to blood pressure, heart stimulation, vasodilation, gastric juice secretion, immunological reactions, *etc*.[1,4] All these biological effects are related to interactions of histamine with different types of specific receptor (H_1, H_2, H_3 and H_4).[1,4–8]

Although numerous studies for histamine, its analogues, agonists and antagonists have been realized, and there are more than 50000 references in the National Center for Biotechnology Information (NCBI) database,[9] the relations between the structure and biological activity of histamine are not yet established. The reasons are as follows. Histamine is a very complicated system of different protonated, tautomeric and conformational states (Fig. 1) and thus investigations on its structure are very difficult. Many IR, Raman and NMR spectra have been reported in the literature, but their interpretations have not led to common conclusions.[10–17] Even in the gas phase, high-level *ab initio* calculations performed for ten selected conformations did not reproduce well the experimental results for the neutral molecule.[18,19] Only in the solid state was the structure of histamine species well resolved.[20,21]

Attracted by this dynamic molecule and its interesting biological activity, we have undertaken investigations on its structure in different environments. We started from the gas phase in order to understand better the internal

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†This work is dedicated to Dr John Shorter on the occasion of his 75th birthday.

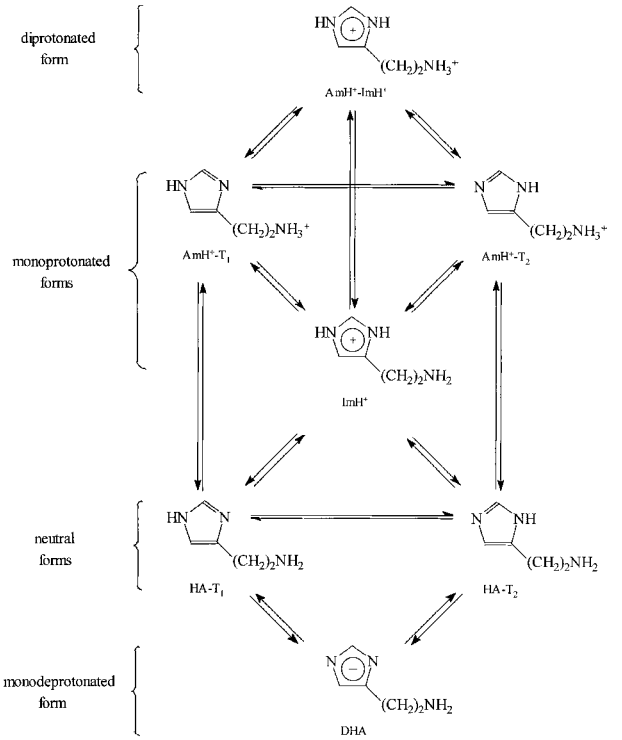

Figure 1. Proton-transfer reactions in the neutral and monoprotonated histamine

effects possible in histamine species and to be able to distinguish external effects possible in solution. In this paper, we concentrate our attention on the prototropic tautomerism possible in the neutral (HA-T_1 and HA-T_2) and monoprotonated forms (AmH^+-T_1, AmH^+-T_2 and ImH^+).

These processes play an important role in the interactions of histamine with specific receptors.[4–7,22,23] Many researchers have studied the tautomeric preferences in histamine by computational methods (developed in the last two decades); however, their results are incomplete.[24] Most of them considered only two (instead of three) of the monoprotonated forms, AmH^+-T_1 and AmH^+-T_2, that are preferred in solution.[22,23,25–29] Recent gas-phase basicity measurements for free histamine indicated that the ImH^+ form cannot be omitted; what is more, it should be considered as favoured in the gas phase.[30,31] For these reasons, calculations for the histamine species given in Fig. 1 need re-examination.

Owing to the flexibility of the alkylamino side chain more than 100 conformations can be considered for one form of histamine.[24,26] Investigations for such a large number of structures need many computational hours. Therefore, a choice of one optimal computational method is very important. In this paper we test semi-empirical and *ab initio* methods on isolated molecules of the neutral and monoprotonated forms of histamine. For calculations, we chose two conformations: one called the 'essential' (*trans*) conformation, identified in the solid state;[20,21] the other called the 'scorpio' (*gauche*) conformation, preferred in the gas phase.[18,19,30] Relative energies between individual tautomers having the same conformations were calculated, and tautomeric preferences in histamine species discussed. We took into account all computational data reported previously for selected conformations. For the histamine monocation, relative energies were also estimated in water solution using the polarizable continuum model (PCM) and the geometries optimized at the RHF/6-31G* level.

METHODS

Relative energies between individual tautomers [$\Delta E = E(T_i) - E(T_j)$] were calculated for the *trans* and *gauche* conformations of the neutral (Fig. 2) and monoprotonated histamine (Fig. 3). Semi-empirical calculations were performed at the complete neglect of differential overlap (CNDO),[32] intermediate neglect of differential overlap (INDO),[32] modified INDO (MINDO/3),[33] modified neglect of diatomic overlap (MNDO),[34] Austin model 1 (AM1),[35] and parametric method 3 levels (PM3)[36] using the HYPERCHEM program.[37] *Ab initio* calculations[38] were performed at the RHF/STO-3G//STO-3G, RHF/STO-4G//STO-4G (with Gaussian expansions of Slater-type

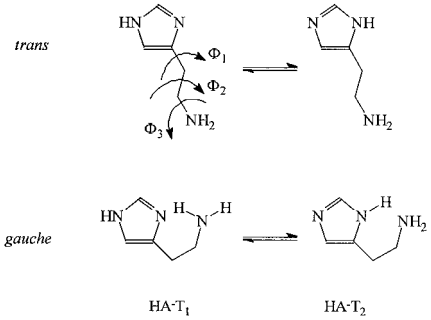

Figure 2. The *trans* and *gauche* conformations for the neutral histamine tautomers

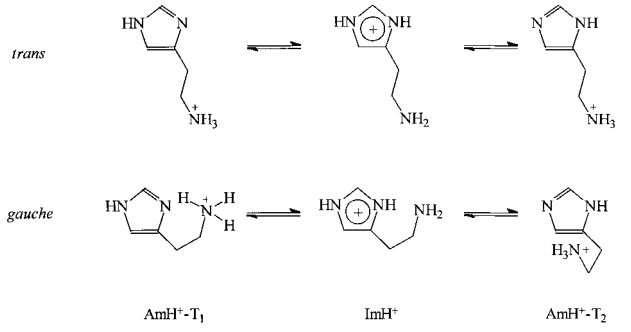

Figure 3. The *trans* and *gauche* conformations for the monoprotonated histamine tautomers

Table 1. Calculated Φ_1 and Φ_2 angles (°) for the *trans* and *gauche* conformations of the neutral histamine forms (Fig. 2)

	trans				*gauche*			
	HA-T_1		HA-T_2		HA-T_1		HA-T_2	
Method	Φ_1	Φ_2	Φ_1	Φ_2	Φ_1	Φ_2	Φ_1	Φ_2
CNDO[a]	−66.4	179.7	62.4	179.8	59.9	−51.8	30.5	−52.8
INDO[a]	−61.5	179.5	58.6	179.9	54.9	−42.6	26.1	−51.5
MINDO/3[a]	−78.8	−177.6	82.7	176.3	91.1	−62.9	100.0	−57.4
MNDO[a]	−88.3	179.8	87.0	177.1	74.7	−74.6	88.9	−67.6
AM1[a]	−66.5	−179.7	58.4	176.3	65.4	−60.3	40.2	−70.9
PM3[a]	−116.7	−178.4	73.9	177.4	99.3	−69.0	58.4	−74.8
STO-3G[b]	58.7	182.2	75.2	183.8	56.3	−66.6	37.9	−61.3
3-21G[c]	60.3	181.7	71.8	179.5	−53.4	68.3	−38.6	66.1
6-31G[d]	58.9	180.2	73.8	181.0	−58.7	69.4	−43.6	67.4
6-31G*[a,e]	66.9	177.5	−72.6	177.7	−63.8	68.1	−46.6	67.7
6-31G**[a,f]	−66.0	177.6	69.4	−179.9	−63.5	68.3	−46.5	67.6
MP2/6-31G[g]	55.1	179.8	72.5	180.0	55.9	68.1	41.7	65.9
MP2/6-31G**[h]	–[i]	–[i]	–[i]	–[i]	−62.2	66.9	43.4	66.2

[a] This work.
[b] Ref. 23.
[c] Ref. 18.
[d] Refs 30 and 47.
[e] Ref. 28.
[f] Ref. 48.
[g] Ref. 47.
[h] Ref. 49.
[i] Not reported.

atomic orbitals), RHF/3-21G//3-21G (with small split valence basis set), RHF/6-31G//6-31G (with extended Gaussian-type basis), RHF/6-31G*//6-31G, RHF/6-31G*//6-31G*, RHF/31G**//6-31G** (split valence basis set with polarization functions), RHF/6-31 ++ G**//6-31G*, RHF/6-311 ++ G**/6-31G*, RHF/6-31G**//6-31G**, RHF/31 ++ G**//6-31 ++ G** (basic set supplemented with diffuse functions), MP2/6-31G*//6-31G* and/or MP2/6-31G**//6-31G** (second-order Möller–Plesset perturbation)[39] using the GAMESS 99 program.[40] For the monocationic forms, the effect of solute–solvent interactions in an aqueous solution was studied using the PCM[41–46] and the geometries optimized at the RHF/6-31G* level.

RESULTS AND DISCUSSION

Semi-empirical and *ab initio* calculations were carried out for two selected conformations (*trans* and *gauche*) of the neutral (Fig. 2) and monoprotonated histamine (Fig. 3). Selected geometrical parameters (Φ_1, corresponding to the dihedral N—C—C—C, and Φ_2 angles given in Fig. 2) obtained after geometry optimization at each level of calculation, together with the literature data[18,23,28–30,47–51] are listed in Tables 1 and 2. Comparison indicates that, generally, the Φ_2 angle varies little when going from the semi-empirical to the *ab initio* methods. It is close to 180° and 60° in the *trans* and *gauche* conformations respectively. Larger changes are observed for the Φ_1 angle, which varies from about ±30 to ±130° in the *trans* conformation, and from ±30 to ±150° in the *gauche* conformation. This variation, however, has no significant influence on the tautomeric preferences in histamine species.

Relative energies between individual tautomers derived from the total energies of individual tautomers [$\Delta E = E(T_i) - E(T_j)$/kcal mol^{-1}, 1 cal = 4.184 J] calculated at different semi-empirical and *ab initio* levels for the neutral and monoprotonated forms of histamine are summarized in Tables 3 and 4, respectively. For comparison, the literature semi-empirical and *ab initio* results are also given in these tables.[18,19,23,26–30,47–53]

Generally, the semi-empirical and *ab initio* methods predict the same tautomeric preferences in histamine species, particularly for the monocation (Table 4). High-level *ab initio* calculations predict the $\Delta E(1-2)$ values between tautomers AmH^+-T_1 and AmH^+-T_2 close to −12 kcal mol^{-1} and −20 kcal mol^{-1} for the *trans* (mean value -11.9 ± 0.5 kcal mol^{-1}) and *gauche* (mean value -20.5 ± 0.8 kcal mol^{-1}) conformations respectively. The $\Delta E(1-2)$ values obtained by the semi-empirical methods are lower in the negative scale by about 5–10 kcal mol^{-1} than the *ab initio* ones. For the transfer of a proton between the chain *N*-amino (AmH^+-T_1) and the ring *N*-aza protonated forms (ImH^+), all calculated $\Delta E(1-3)$ values are positive for both the *trans* and *gauche* conformations, indicating that the ImH^+ form is favoured in the gas phase. However, the variation of the $\Delta E(1-3)$ values is larger than that of the $\Delta E(1-2)$

Table 2. Calculated Φ_1 and Φ_2 angles (°) for the *trans* and *gauche* conformations of histamine monocations (Fig. 3)

	trans						*gauche*					
	AmH^+-T_1		AmH^+-T_2		ImH^+		AmH^+-T_1		AmH^+-T_2		ImH^+	
Method	Φ_1	Φ_2	Φ_1	Φ_2	Φ_1	Φ_2	Φ_1	Φ_2	Φ_1	Φ_2	Φ_1	Φ_2
CNDO[a]	−43.4	175.4	−92.2[b]	−178.9[b]	−69.9	180.0	29.3	−49.3	−116.5	13.7	29.3	−49.3
INDO[a]	−35.7	174.0	−90.7[b]	−179.1[b]	−67.3	179.7	28.0	−48.8	−93.7	−40.5	28.0	−48.8
MINDO/3[a]	−71.2	178.2	−91.4	−174.4	−89.2	−176.7	47.3	−68.4	−128.9	63.6	101.3	−58.0
MNDO[a]	−38.4	179.0	−98.0	−174.0	−88.6	−177.8	37.0	−62.8	−123.7	55.6	76.0	−61.6
AM1[a]	−32.1	−178.1	−101.9	−172.4	−57.6	−176.8	35.1	−61.6	−146.6	49.3	37.8	−62.2
PM3[a]	−48.2	164.9	−117.8	−169.0	−70.3	−178.1	31.3	−52.6	−151.8	53.6	31.3	−52.6
STO-3G[a,c]	−40.1	169.4	99.5	175.6	−71.6	179.8	30.8	−49.9	−151.0	50.1	31.2	−49.9
STO-4G[a]	−40.5	169.5	−98.3	−176.1	−71.6	180.0	30.6	−49.9	−148.8	48.1	31.2	−50.0
3-21G[a,d]	−41.2	168.7	−80.5	181.7	−73.6	−178.9	37.5	−59.0	−151.4	56.9	36.3	−59.4
6-31G[a,e]	−44.8	168.5	−87.9	182.2	−72.7	179.7	36.8	−59.5	−150.8	56.7	38.1	−61.0
6-31G*[a,f]	−49.9	169.6	−86.7	−177.9	−68.6	−180.0	40.6	−62.9	−151.6	57.0	40.5	−62.2
6-31G**[a,g]	−49.3	170.5	−86.6	182.2	−73.2	175.5	40.2	−62.2	−151.8	56.7	−40.7	62.1
6-31 ++ G**[a]	−49.6	170.3	−86.8	−177.6	−68.8	179.9	40.2	−62.2	−151.8	56.7	39.7	−61.9
MP2/6-31G[h]	40.2	190.8	126.1	176.4	–[j]	–[j]	36.6	59.5	–[j]	–[j]	36.0	59.2
MP2/6-31G**[i]	−46.6	169.1	−95.0	183.0	−74.3	174.8	−38.6	60.0	–[j]	–[j]	−37.3	60.1

[a] This work.
[b] Fixed AM1 geometry.
[c] Ref. 23.
[d] Ref. 29.
[e] Ref. 30.
[f] Ref. 28.
[g] Refs. 48, 50 and 51.
[h] Ref. 47.
[i] Refs. 49–51.
[j] Not reported.

Table 3. Relative energies (kcal mol^{-1}) between histamine neutral tautomers (Fig. 2)

	trans		*gauche*	
Method	ΔE[a]	Ref.	ΔE[a]	Ref.
CNDO	2.1	–[b]	2.0	–[b]
INDO	0.8, 1.9	26, –[b]	1.8	26, –[b]
MINDO/3	0.3	–[b]	1.4	–[b]
MNDO	−0.4	–[b]	0.1	–[b]
AM1	0.5	–[b]	−0.4	–[b]
PM3	0.5	–[b]	−0.2	–[b]
STO-3G//STO-3G	0.6, 1.0	23, 27	2.7	–[b]
LP-3G//STO-3G	1.8	23	–[c]	–[c]
3-21G//3-21G	−0.6	18, 28	3.5	18, 28
6-31G//6-31G	−1.1, −0.7	18, 47	2.5	18, 30, 47
6-31G*//6-31G*	−0.3	28	2.3	28
6-31G**//6-31G**	−0.8	–[b]	2.2	48
6-311 ++ G**//6-31G*	−0.5	28	2.0	28
6-31 ++ G**//6-31 ++ G**	−0.5	47	2.2	47
MP2/6-31G*//6-31G*	−0.9	28	2.6	28
MP2/6-31G**//6-31G**	−0.6	–[b]	2.4	49
MP2/6-311 ++ G**//6-31G*	−0.9	28	2.5	28
MP4SDQ/6-31G*//6-31G*	−0.8	28	2.4	28
QCID/6-31G*//6-31G*	−0.8	28	2.4	28
MP2/6-31G//MP2/6-31G	−1.1	47	2.6	47
MP2/6-31G**//MP2/6-31G**	–[c]	–[c]	2.5	49
MP2/6-311 ++ G**//MP2/6-31G**	−1.3	19	2.6	19

[a] $\Delta E = E(HA\text{-}T_1) - E(HA\text{-}T_2)$ calculated according to data from references given.
[b] This work.
[c] Not determined and not reported.

Table 4. Relative energies (kcal mol^{-1}) between histamine monocations (Fig. 3)

	trans				*gauche*			
Method	$\Delta E(1-2)$[a]	Ref.	$\Delta E(1-3)$[b]	Ref.	$\Delta E(1-2)$[a]	Ref.	$\Delta E(1-3)$[b]	Ref.
CNDO	−5.8, −4.9	25, –[c]	27.8	–[c]	−12.1	–[c]	0.0	–[c]
INDO	−5.4, −5.6	26, –[c]	29.6	–[c]	−31.2	–[c]	0.0	–[c]
MINDO/3	−3.5	–[c]	20.9	–[c]	−5.0	–[c]	20.8	–[c]
MNDO	−8.5	–[c]	5.9	–[c]	−13.4	–[c]	6.1	–[c]
AM1	−8.1	29, –[c]	4.5	–[c]	−12.7	–[c]	2.3	–[c]
PM3	−7.9	–[c]	4.1	–[c]	−16.0	–[c]	0.0	–[c]
STO-3G//STO-3G	−12.1, −10.4, −14.9	27, 23, 52	7.6	–[c]	−37.8	–[c]	0.0	–[c]
STO-4G//STO-4G	−10.3	–[c]	7.4	53, –[c]	−38.5	–[c]	0.0	–[c]
LP-3G//STO-3G	−9.8	23	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]
3-21G//3-21G	−12.8	28, 29	6.1	–[c]	−26.8	28, –[c]	2.5	–[c]
6-31G//6-31G	−13.3, −13.2	30, 47	10.4	30	−24.6	–[c]	5.8	30, 47
6-31G*//6-31G	−11.5	29	2.6	–[c]	−19.3	–[c]	3.2	–[c]
6-31G*//6-31G*	−11.5	28	3.6	–[c]	−19.7	28	3.2	–[c]
6-31G**//6-31G**	−11.6	48, 50	6.1	51	−19.9	–[c]	3.7	48, 51
6-311 ++ G**//6-31G*	−11.7	28	3.9	–[c]	−19.4	28	2.9	–[c]
6-31 ++ G**//6-31 ++ G**	−11.8	47, –[c]	4.6	–[c]	−19.9	–[c]	3.2	47, –[c]
MP2/6-31G*//6-31G*	−12.0	28	3.6	–[c]	−21.5	28	3.2	–[c]
MP2/6-31G**//6-31G**	−12.0	49, 50	2.6	49, 51	−19.9	–[c]	0.2	51
MP2/6-311 ++ G**//6-31G*	−11.9	28	–[d]	–[d]	−20.4	28	–[d]	–[d]
MP4SDQ/6-31G*//6-31G*	−11.9	28	–[d]	–[d]	−21.1	28	–[d]	–[d]
QCID/6-31G*//6-31G*	−11.8	28	–[d]	–[d]	−21.0	28	–[d]	–[d]
MP2/6-31G//MP2/6-31G	−13.6	47	–[d]	–[d]	–[d]	–[d]	0.5	47
MP2/6-31G**//MP2/6-31G**	−12.0	49, 50	2.7	49, 51	–[d]	–[d]	0.2	51

[a] $\Delta E(1-2) = E(\mathrm{AmH^+\text{-}T_1}) - E(\mathrm{AmH^+\text{-}T_2})$ calculated according to data from references given.
[b] $\Delta E(1-3) = E(\mathrm{AmH^+\text{-}T_1}) - E(\mathrm{ImH^+})$ calculated according to data from references given.
[c] This work.
[d] Not determined and not reported.

observed for the transfer of a proton between the T_1 and T_2 tautomers of the chain *N*-amino protonated histamine (AmH^+). For example, the differences between the ΔE values calculated at the RHF/6-31G**//6-31G** and MP2/6-31G**//MP2/6-31G** levels are close to 3.5 kcal mol^{-1} for both conformations. Some semi-empirical methods (CNDO, INDO, and MINDO/3) predict the ΔE values for *trans* conformation larger by 18 kcal mol^{-1} than the MP2 ones. These differences in $\Delta E(1-3)$ observed for both the *trans* and *gauche* conformations cannot be attributed to intramolecular interactions possible in the gas phase for isolated molecules, because intramolecular hydrogen-bonds between the protonated and free basic functional groups can take place only in the *gauche* conformations. They are not possible in the *trans* conformations. Therefore, these differences in $\Delta E(1-3)$ can be explained by different charge distributions in the differently protonated species, the chain *N*-amino ($\mathrm{AmH^+\text{-}T_1}$) and the ring *N*-aza protonated histamine ($\mathrm{ImH^+}$) calculated at different semi-empirical and *ab initio* levels. There is no experimental evidence on the gas-phase conformation of the histamine monocation. However, the exceptionally high gas-phase basicity measured for free histamine[30,31] can only be explained by the chelation effect of the proton by two basic nitrogen atoms (the ring *N*-aza and the chain *N*-amino), among which the *N*-aza is favoured.[30,53–55] This is possible in the *gauche* conformation of the monocation. Such types of conformation and chelation effect were also observed for some metal–histamine systems in the solid state.[24,56–58] Another explanation of the variation of the $\Delta E(1-3)$ may be the differences in thermal corrections at 298.15 K. The thermal corrections to the enthalpy calculated at the RHF/6-31G*//6-31G* level (Table 5) are close to zero (smaller than 0.1 kcal mol^{-1}) for the proton-transfer process between the $\mathrm{AmH^+\text{-}T_1}$ and $\mathrm{AmH^+\text{-}T_2}$, whereas for the proton transfer between the $\mathrm{AmH^+\text{-}T_1}$ and $\mathrm{ImH^+}$ they are considerably larger (1.1 kcal mol^{-1} for the *trans* and 0.7 kcal mol^{-1} for the *gauche* conformation).

It is interesting to mention that the position of tautomeric equilibria in the histamine monocation depend strongly on the environment. To study the effect of solute–solvent interactions in an aqueous solution (conditions close to physiological ones) we chose the PCM.[41–46] For estimation of the relative stability of tautomers (ΔE), the geometries optimized at the RHF/6-31G* level were used. Contrary to the gas phase, the PCM predicts the $\mathrm{AmH^+\text{-}T_1}$ form as favoured in aqueous solution (Table 5). This is in good agreement with estimations based on the acidity–basicity method.[24] According to recent FT-IR and Raman experiments of Collado *et al.*[17] the *trans* conformation has been proposed for the $\mathrm{AmH^+\text{-}T_1}$ in water solution. However, both

Table 5. Relative energies (kcal mol^{-1}) between histamine monocations in the gas phase and aqueous solution (Fig. 3)

Method	Phase	Property	Conformation	
			trans	*gauche*
RHF/6-31G*//6-31G*	Gas[a]	$\Delta E(1-2)$[b]	−11.5	−19.7
		$\Delta H_c(1-2)$[b,c]	0.1	0.0
		$T\Delta S_c(1-2)$[b,d]	−0.5	−0.6
		$\Delta G(1-2)$[b]	−10.9	−19.0
		$\Delta E(1-3)$[e]	3.6	3.2
		$\Delta H_c(1-3)$[c,e]	1.1	0.7
		$T\Delta S_c(1-3)$[d,e]	0.2	0.0
		$\Delta G(1-3)$[e]	4.5	3.8
PCM (6-31G*)	Water[f]	$\Delta E(1-2)$[b]	−1.3	−5.2
		$\Delta E(1-3)$[e]	−2.0	−1.6
Acidity–basicity[g]	Water	$\Delta G(1-2)$[h]	−1.0	
		$\Delta G(1-3)$[i]	−3.6	

[a] Dipole moments (debye) for the AmH^+-T_1-*trans*, AmH^+-T_2-*trans*, ImH^+-*trans*, AmH^+-T_1-*gauche*, AmH^+-T_2-*gauche* and ImH^+-*gauche* are respectively: 9.79, 15.62, 7.16, 4.70, 10.70, 3.20.
[b] $\Delta Q(1-2) = Q(AmH^+\text{-}T_1) - Q(AmH^+\text{-}T_2)$, where Q is the corresponding physicochemical property: E, total energy; H, enthalpy; S, entropy; G, Gibbs free energy.
[c] H_C is a thermal correction to the enthaply at 298.15 K.
[d] S_C is a thermal correction to the entropy at 298.15 K.
[e] $\Delta Q(1-3) = Q(AmH^+\text{-}T_1) - Q(ImH^+)$; Q is as in footnote (b).
[f] Dipole moments (debye) for the AmH^+-T_1-*trans*, AmH^+-T_2-*trans*, ImH^+-*trans*, AmH^+-T_1-*gauche*, AmH^+-T_2-*gauche* and ImH^+-*gauche* are respectively: 11.11, 18.40, 8.39, 5.48, 12.72, 3.89.
[g] Ref. 24.
[h] $\Delta G(1-2) = 1.3643 pK_T(1-2)$.
[i] $\Delta G(1-3) = 1.3643 pK_T(1-3)$.

conformations (*trans* and *gauche*) have been observed in NMR spectra.[10–16] The PCM predicts a lower energy for the *gauche* than the *trans* conformation of the AmH^+-T_1 by *ca* 3 kcal mol^{-1}. The preference of the AmH^+-T_1 may result from the fact that, in water solution, the polarizability of the imidazole ring is strongly reduced, and the ring *N*-aza group is less basic than the chain *N*-amino.[54] A higher stability of the AmH^+-T_1 than AmH^+-T_2 in water solution is also in good agreement with a general rule found for 4(5)-substituted imidazoles, i.e. that the stronger electron-accepting substituent (such as $CH_2CH_2NH_3^+$) is near the *N*-aza group in the ring, i.e. in the 4-position in the preferred tautomer.

Weinstein *et al.*[22] showed additionally that the relative stability of the AmH^+-T_1 and AmH^+-T_2 mixture depends on some kind of interaction of the monocation with a negatively charged group (e.g. OH^-) that may be present in an active site of the receptor. Neutralization of the positively charged aminoalkyl side chain by the OH^- leads to a change in the tautomeric preference in the mixture, and in this case the T_2 tautomer is favoured as in the case for the neutral histamine.[20,24] The rapidity of the proton-transfer reactions, and the high flexibility and plurality of histamine forms, together with the variability of histamine receptors (H1, H2, H3 and H4), make it difficult to select and interpret its principal behaviour in living organisms. However, more complex studies in the presence of dipolar or hydrogen-bonding solvents or groups and anionic species may shed new light on the problem of histamine action. This question will be the subject of our future investigations.

Particular 'discrepancies' in calculated relative energies are observed for the neutral histamine in the *trans* conformation (Table 3). The semi-empirical (except MNDO), RHF/STO-3G//STO-3G and RHF/LP-3G//STO-3G methods predict the T_2 tautomer as favoured in the gas phase (positive ΔE values); this is contrary to the MNDO and other *ab initio* methods, which indicate that the T_1 tautomer predominates in the tautomeric mixture (negative ΔE values). These differences may result from the fact that the relative energy between individual tautomers T_1 and T_2 in the *trans* conformation is close to zero, and thus differences in calculation errors and zero-point energies (ZPEs) [which usually are close to zero for simple 4(5)-substituted imidazoles[59] and can be neglected[60] for $|\Delta E| \gg 0$] may influence the relative energies calculated at different levels in the case of *trans* neutral histamine. Godfrey and Brown[19] showed that for some conformations the differences between the ZPEs of individual tautomers can differ even by 0.5–1 kcal mol^{-1}. However, for the *trans* conformation considered here, the difference between the ZPEs of the neutral T_1 and T_2 tautomers calculated at the MP2/6-311 ++ G**//MP2/6-31G** level[19] is not higher than 0.05 kcal mol^{-1}. In this case, calculation errors should not be very large because the proton is transferred between atoms of the same element, from the amino to the imino nitrogen atom in the imidazole ring for the

same conformation of the aminoethyl group. Therefore, the variability of the calculated ΔE is not very large (mean value -0.05 ± 1 kcal mol^{-1}). High-level *ab initio* calculations predict almost the same ΔE value as those with small (3-21G) and extended Gaussian-type basis sets (6-31 G) without polarization and diffuse functions.

For the most stable *gauche* conformation of the neutral histamine, which can be stabilized by intramolecular hydrogen bonds between the functional ring and chain groups (Fig. 2), the calculated ΔE values vary from -0.4 to 3.5 kcal mol^{-1} (Table 3). High-level *ab initio* calculations and some semi-empirical approximations (CNDO, INDO, MINDO/3) predict the same T_2 tautomer as favoured in the gas phase (positive ΔE values of almost the same order of magnitude; *ab initio* mean value 2.4 ± 0.2 kcal mol^{-1}) as has been estimated[18,19] on the basis of the rotational spectrum recorded for free histamine ($\Delta G = 0.7$ kcal mol^{-1} between the 3G-Vc and 1G-IVa, derived from their mole fractions in the jet after expansion from 130 °C).

In systems where the proton is transferred between atoms of different elements, like in 2-hydroxypyridine between the oxygen and nitrogen atoms ($\Delta G \approx 0.5$ kcal mol^{-1}),[61] the variation of the results predicted by semi-empirical and *ab initio* methods is considerably larger.[62–67] Only the results obtained at the AM1, MP4(SDTQ) and QCISD levels reproduce well the experimental ones.[62,64–66] Many *ab initio* methods (high-level RHF and even MP2) give contradictory results.[62–67] This may be explained by the fact that calculation errors and ZPEs may not cancel out in the calculated ΔE. Some kind of illustration of differences in computational errors may be the comparison of calculated and experimental proton affinities for nitrogen and oxygen bases summarized by Smith and Radom.[68,69] The differences between the computed and experimental results depend on the level of calculations and are positive or negative for various sites.

CONCLUSIONS

Generally, semi-empirical and *ab initio* methods predict the same tautomeric preferences in the gas phase: the T_2 tautomer for the most stable *gauche* conformations in the neutral histamine mixture, and the ImH^+ form for both conformations (*trans* and *gauche*) in the monocationic mixture. High-level *ab initio* calculations predict almost the same relative energy between tautomeric forms as those with small (3-21G) and extended Gaussian-type basis sets (6-31G) without polarization and diffuse functions. Good agreement of computational results may be explained by the fact that the proton is transferred between atoms of the same element, from the amino to the imino nitrogen atom. For the *trans* conformations of the neutral forms, semi-empirical and *ab initio* methods predict exceptionally different positions of the tautomeric equilibrium. This may be explained by the fact that the ΔE is close to zero and thus the ZPEs and calculation errors may not cancel out in the calculated ΔE.

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