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Gas-phase lithium cation basicity of histamine and its agonist 2-(β-aminoethyl)-pyridine Experimental (FT-ICR-MS) and theoretical studies (DFT) of chelation effect

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This article is dedicated to the memory of Sharon Lias.

Abstract

The gas-phase lithium cation basicities (LCBs) were obtained for histamine (HA) and its agonist 2-(β-aminoethyl)-pyridine (AEP) from collision-induced dissociation of lithium adducts using Fourier-transform ion cyclotron resonance mass spectrometry (FT-ICR-MS). For measurements, $MeO(CH_2)_2OMe$, $Et_3P{=}O$ and $(Me_2N)_3P{=}O$ (HMPA) were used as the reference compounds. The experimental LCB of AEP was located between those of $Et_3P{=}O$ and $(Me_2N)_3P{=}O$. The experimental LCB of HA was found to be higher than those of AEP and HMPA by more than 2 kcal mol^{-1} clearly indicating that the LCB of HA is higher than any LCB for a neutral base yet measured (crown-ethers excepted). The experimental LCBs of the parent bases (pyridine and imidazole) are lower by more than 10 kcal mol^{-1}. In parallel, DFT calculations {B3LYP/6-31G*//B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G*} were performed for HA, AEP and their lithium adducts. Among the 22 reasonable conformations of the HA-Li$^+$ adduct, only one appears to be significantly more stable than the others. This is also the case for one structure among seven conformations of the AEP-Li$^+$ adduct. These two stable structures have the 'scorpion' conformation, in which the Li$^+$ cation is almost equally chelated by two basic nitrogen atoms, the ring N-aza and the chain N-amino. Other HA-Li$^+$ and AEP-Li$^+$ conformations have noticeably higher energies than the 'scorpion' structures. The difference between the DFT calculated LCBs of HA and AEP (about 4 kcal mol^{-1}) is in agreement with that experimentally obtained (>2 kcal mol^{-1}). The high experimental and theoretical values of LCB for HA and AEP militate in favor of a strong chelation of Li$^+$ by both ligands in the gas-phase. This chelation effect was also evidenced previously for the proton gas-phase basicity.

Keywords: FT-ICR-MS; DFT calculations; Histamine; 2-(β-Aminoethyl)-pyridine; Gas-phase lithium cation basicities

1. Introduction

Histamine (HA), a biogenic amine, exhibits a very complex physiological activity. It is secreted in situations of stress and allergic reactions. Being a chemical mediator, it acts on the central nervous system and in the regulation of sleep [1]. It causes contraction of the smooth muscle of the gut, intestine and bronchi [2,3]. It also influences blood pressure, heart stimulation, vasodilation, gastric juice secretion, immunological reactions, etc. [1,4]. All these biological effects are related to interactions of HA with different specific receptors (H1, H2, H3, H4), which have hydrophilic or hydrophobic, positively or negatively charged binding sites [1,4–8]. 2-(β-Aminoethyl)-pyridine (AEP) is an agonist of the histamine H1 receptor which mediates contractions of smooth muscles [9]. It displays similar physiological effects to HA, binding with high affinity and specificity to the histamine H1 receptor [10,11].

From the chemical point of view, HA is a trifunctional nitrogen compound that possesses one acidic site, the amino NH group in the aromatic ring, and two basic sites, the

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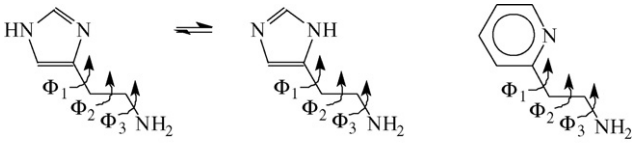
N-aza atom in the ring and the N-amino atom in the aliphatic side chain. AEP is a bifunctional nitrogen ligand that has sites very similar in basicity, the ring N-aza and the chain N-amino. The ethylamino side chains of both compounds may adopt a large number of conformations. They display rotational isomerism around one C–N and two single C–C bonds. In addition, HA exhibits a prototropic tautomerism (HA1 ⇌ HA2) corresponding to a proton-transfer from one to the other nitrogen atom in the imidazole ring, in concert with the migration of π electrons. Hence, HA may take two tautomeric forms, HA1 and HA2, with the ethylamino group at the 4- and 5-position in the imidazole ring, respectively.



HA1 HA2 AEP

In previous papers, our attention was mainly concentrated on the proton-transfer reactions for histamine and its agonist 2-(β-aminoethyl)-pyridine [12–17]. It has been found that similarly to other bidentate nitrogen ligands with a flexible conformation (diamines, aminoamidines, aminoguanidines), HA and AEP exhibit exceptionally high basicity in the gas-phase. The ring N-aza atom is the preferred site of protonation, and the protonated group forms an intramolecular H-bond with the other basic site, the chain N-amino atom in the so-called 'scorpion' conformation. The ring N-aza atom appears to be also the favored site of protonation in non-polar solvents: cyclohexane, benzene and CCl_4. The chain N-amino atom seems to be preferentially protonated in solvents of weak or intermediate polarity: $CHCl_3$, THF and acetone. In aqueous solution, there are no doubts that the chain N-amino atom is the most favorable protonation site. In fact, in the presence of H-bond acceptor solvents, the chain NH_3^+ is better solvated, owing to the three N^+–H sites for H-bonding, as compared to a single one for the protonated N-aza. Moreover, the high polarizability of the pyridine ring induces strong gas-phase basicity of the N-aza site, as compared to what is observed in polar solvents. In water, the polarizability effect is reduced to almost zero, hence the basicity of the N-aza is noticeably reduced. This behavior is consistent with other literature data reported for the proton-transfer reactions for HA in the gas-phase and in water [18–22].

Examination of structural data reported for the solid state revealed that histamine easily forms complexes with metal cations [16], e.g., with Cu(I), Cu(II), Ni(II), Cr(III), Co(III), Ca and Pd. Generally, HA plays the role of a bidentate nitrogen ligand in these complexes, where both basic sites, the ring N-aza and the chain N-amino are coordinated to the metal cation. To form these complexes, HA takes the HA1 tautomeric form for the imidazole ring and the *gauche*, called 'scorpion', conformation for the side chain (*gauche*-HA1). However, in one interesting macro-complex of Cu(I), $\{[Cu_2(HA)_3(CO)_2]^{2+}\}$, HA exists in two possible tautomeric forms and in two conformations: *gauche*-HA1, which chelates each of the two Cu(I) cations, and *trans*-HA2, which forms a bridge between the two metal centers [23,24]. This variation in the structures of the HA–metal cation complexes in the solid state encouraged us to undertake an examination of the complex formation in the gas-phase, where molecules are isolated, and where there are no interactions with a solvent or a counter ion. Similar investigations performed for its agonist AEP may reveal similarities or differences between the two analogous ligands in the complexation reaction of the metal cation. In the present mass spectrometry and density functional theory study, we chose Li^+ as a typical cation with bonding properties different from those of the proton, and for which affinity and basicity scales are well developed, for their use as references, and for useful comparison with similar structures. Furthermore, Li^+ is the smallest cation after H^+, rendering possible high-level quantum chemical calculation. For the experimental determination of the gas-phase lithium cation basicities of HA and AEP and for investigating the structure of HA-Li^+ and AEP-Li^+ adducts in the gas-phase, we used Fourier-transform ion cyclotron resonance mass spectrometry (FT-ICR-MS) [25], complemented by density functional theory {DFT(B3LYP) with two 6-31G* and 6-311+G** basis sets} [26–30] for theoretical analysis of the structure and energetic of the systems under study.

2. Experimental and computational details

2.1. Materials

Histamine (HA), 2-(β-aminoethyl)-pyridine (AEP) and the reference bases {$MeO(CH_2)_2OMe$, $Et_3P{=}O$ and $(Me_2N)_3P{=}O$ (hexamethylphosphoramide, HMPA)} for gas-phase LCB measurements were commercially available (Aldrich).

2.2. LCB measurements

Gas-phase lithium cation basicity (LCB) measurements for HA and AEP ligands were performed at the Université de Nice-Sophia Antipolis by using the same Fourier-transform ion cyclotron resonance mass spectrometer (FT-ICR-MS) as for gas-phase basicity (GB) measurements for histamine [12]. The relative LCB values were determined using the kinetic method [31,32] based on the collision-induced dissociation of lithium adducts ($[B_1LiB_2]^+$) formed between a given (B_1) and a reference (B_2) bases [25,33]. The dissociation via the two pathways (Eqs. (1) and (2)) led to two ions ($[B_1Li]^+$ and $[B_2Li]^+$), for which the signal intensity ratio was equal to the ratio of the two unimolecular reactions rates k_1 and k_2. From this ratio, the relative LCBs were estimated using Eq. (3). Knowledge of the LCB for reference base (B_2) gave the possibilities to obtain the LCB for the ligands (B_1).

$$[B_1LiB_2]^+ \xrightarrow{k_1} [B_1Li]^+ + B_2 \quad (1)$$

$$[B_1LiB_2]^+ \xrightarrow{k_2} [B_2Li]^+ + B_1 \quad (2)$$

$$\Delta LCB = LCB(B_1) - LCB(B_2) = RT_{eff} \ln\left(\frac{k_1}{k_2}\right) \quad (3)$$

In this equation, the effective temperature T_{eff} should be determined by calibrating the experimental $\ln(k_1/k_2)$ against known LCBs. Based on previous experiments, we used

$T_{eff} = 398 \pm 23$ K [25]. This temperature should be considered as a calibration parameter and is not related to the actual experimental temperature. Measurements were conducted against three reference bases {$MeO(CH_2)_2OMe$, Et_3PO and HMPA} for AEP and against two reference bases (AEP and HMPA) for HA. All measurements were performed at a 1.6 T uniform magnetic field strength and at a cell temperature of about 300 K, Li^+ being generated by laser desorption-ionization (UV nitrogen laser) from a lithium benzoate target. It will be noted that LCBs for the reference compounds are anchored to data obtained at 373 K [34]. In the early stage of LCB determinations, Li^+ was generated by thermionization, and the Li^+ source heating led to a mean temperature of the ICR cell of about 100 °C. Therefore, we consider that the experimental LCBs obtained for HA and AEP in the current work refer again to a temperature of 100 °C (373 K).

2.3. LCB computations

Density functional theory (DFT) calculations were performed at the Interdisciplinary Center for Molecular Modeling (ICM, Warsaw) using the Gaussian 98 program package [35]. To select all possible stable conformations for HA-Li^+ and AEP-Li^+ adducts, the lithium cation (Li^+) was set at the coordinates of the proton in previously described monoprotonated structures of AEP and HA [17]. The initial geometry obtained in this way was fully optimized without symmetry constraint, and vibrational frequencies calculated at the B3LYP/6-31G* level [26–30]. All frequencies were positive, indicating that the DFT optimized structures correspond to the energy minima. For the neutral ligands HA and AEP, the conformations found previously were considered here as found previously [14,16,17,36]. The energies, enthalpies and Gibbs free energies at 298 K were calculated at the B3LYP/6-31G*//B3LYP/6-31G* level, as well as at the B3LYP/6-311+G**//B3LYP/6-31G* level for comparison.

The gas-phase lithium cation basicities [23,34,37], defined as the negative Gibbs free energy {$LCB = -\Delta G(Li^+)$} associated with the B_iLi^+ adduct formation {equilibrium (4)}, were calculated for the most stable structures of ligands (B_i) and adducts (B_iLi^+) at 298 K using Eq. (5). Thermochemical parameters, H and G in kcal mol^{-1} and S in cal mol^{-1} K^{-1} (1 cal = 4.184 J) at 298 K for the Li^+ cation are as follows: −4569.6433, −4579.1237 and 31.798 at the B3LYP/6-31G*//B3LYP/6-31G* level, and −4569.8773, −4579.3584 and 31.798 at the B3LYP/6-311+G**//B3LYP/6-31G* level. We have shown previously [34,37] that the calculated entropies and enthalpies do not change significantly when proceeding from 298 to 373 K. Therefore, the LCB(373 K) values were inferred, using Eq. (6), from the Gibbs free energies at 373 K estimated from enthalpy and entropy data at 298 K: $G(373\,K) = H(298\,K) - 373\,S(298\,K)$ for Li^+, B_i and B_iLi^+. The relative LCBs between HA (B_1) and AEP (B_2) were obtained at 298 and 373 K from Eq. (7). As it can be inferred from data in Table 2, the ΔLCB values are almost independent of the temperature between 298 and 373 K.

$$B_i + Li^+ \rightleftarrows [B_iLi]^+ \quad (4)$$

$$LCB(298\,K) = G(Li^+, 298\,K) + G(B_i, 298\,K) - G(B_iLi^+, 298\,K) \quad (5)$$

$$LCB(373\,K) = G(Li^+, 373\,K) + G(B_i, 373\,K) - G(B_iLi^+, 373\,K) \quad (6)$$

$$\Delta LCB(T_i) = G(B_1, T_i) - G(B_2, T_i) + G(B_2Li^+, T_i) - G(B_1Li^+, T_i) \quad (7)$$

No corrections for basis set superposition error (BSSE) were made. Although, it was earlier postulated that neglecting the BSSE may lead to an overestimation of lithium affinities [38,39], the examination of this hypothesis led to the conclusion that the BSSE correction is small and almost constant at the 6-31G* and 6-311+G** levels {about 0.5 kcal mol^{-1} or less [37,40]). The BSSE has no important influence on the relative LCBs.

3. Results and discussion

3.1. Remarkably high experimental LCBs for HA and AEP

The experimental value of the lithium cation basicity for 2-(β-aminoethyl)-pyridine was obtained from the kinetic method (collision-induced dissociation of lithium adducts) using three reference compounds, $MeO(CH_2)_2OMe$, $Et_3P{=}O$ and $(Me_2N)_3P{=}O$ (HMPA), which are among the strongest organic bases in the current LCB scales for neutral compounds [34,41]. The relative LCBs are shown in Fig. 1. The experimental LCB value for AEP (47.4 kcal mol^{-1}) is between those of $Et_3P{=}O$ and $(Me_2N)_3P{=}O$. The same method was applied to the LCB measurements for histamine. However, only two reference compounds, AEP and HMPA, could be used, because histamine form a stronger chelate with the Li^+ cation than AEP, and its experimental LCB value (>49 kcal mol^{-1}) is higher than those of AEP and HMPA by more than 2 kcal mol^{-1}, positioning HA outside the current LCB scale.

For comparison, monofunctional nitrogen bases containing the chain N-amino or the ring N-aza basic site have lower lithium cation basicities than the bidentate nitrogen ligands AEP and HA by 10–20 kcal mol^{-1}, e.g., the experimental LCB values for

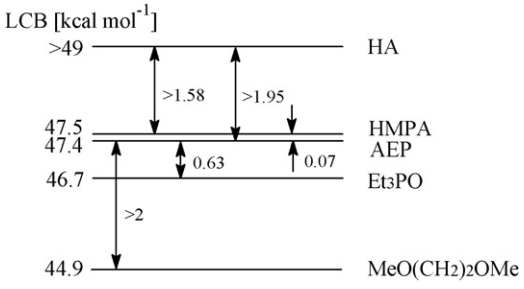


Fig. 1. Relative lithium cation basicities (LCBs in kcal mol^{-1}) measured by FT-ICR-MS for histamine (HA) and 2-(β-aminoethyl)-pyridine (AEP); (HMPA: $(Me_2N)_3P{=}O$).

methylamine, pyridine and imidazole are equal to 31.3, 35.0 and 38.1 kcal mol^{-1}, respectively [34]. The order of their LCB values indicates that the lithium cation interacts more strongly with the ring N-aza than with the chain N-amino site. Moreover, the LCB of imidazole is higher than that of pyridine by almost the same value (ΔLCB = 3.1 kcal mol^{-1}) as is observed here for HA (ethylamino derivative of imidazole) and AEP (ethylamino derivative of pyridine). Three methyl groups substituted at the 2-, 4- and 5-positions in the imidazole ring and acting mainly by their polarizability effect on the N-aza basic site make its experimental LCB (42.6 kcal mol^{-1}) 4.5 kcal mol^{-1} higher than that of unsubstituted imidazole [34]. On the other hand, the Me_2N group at the 4-position in the pyridine ring, acting by its polarizability, field/inductive and resonance effects on the N-aza basic site, increases the experimental LCB of pyridine by 7 kcal mol^{-1} (LCB = 42.0 kcal mol^{-1} for 4-(dimethylamino)pyridine) [34]. It is well known that separation of this group by the methylene group(s) reduces its strong electron donating resonance effect [42] and in consequence the ethylamino group does not increase the LCB of the N-aza site as strongly as the amino group. Analyses of substituent effects in the binding of alkali metal ions to pyridines studied by threshold collision-induced dissociation and ab initio theory lead to LCB(298 K) values in the range from 40.2 ± 1.8 kcal mol^{-1} for methylpyridines to 50.6 ± 5.2 kcal mol^{-1} for aminopyridines [43].

The experimental LCB values of AEP and HA are larger than those of their parent compounds, pyridine and imidazole, by 12.4 and >11 kcal mol^{-1}, respectively. These strong increase of LCBs

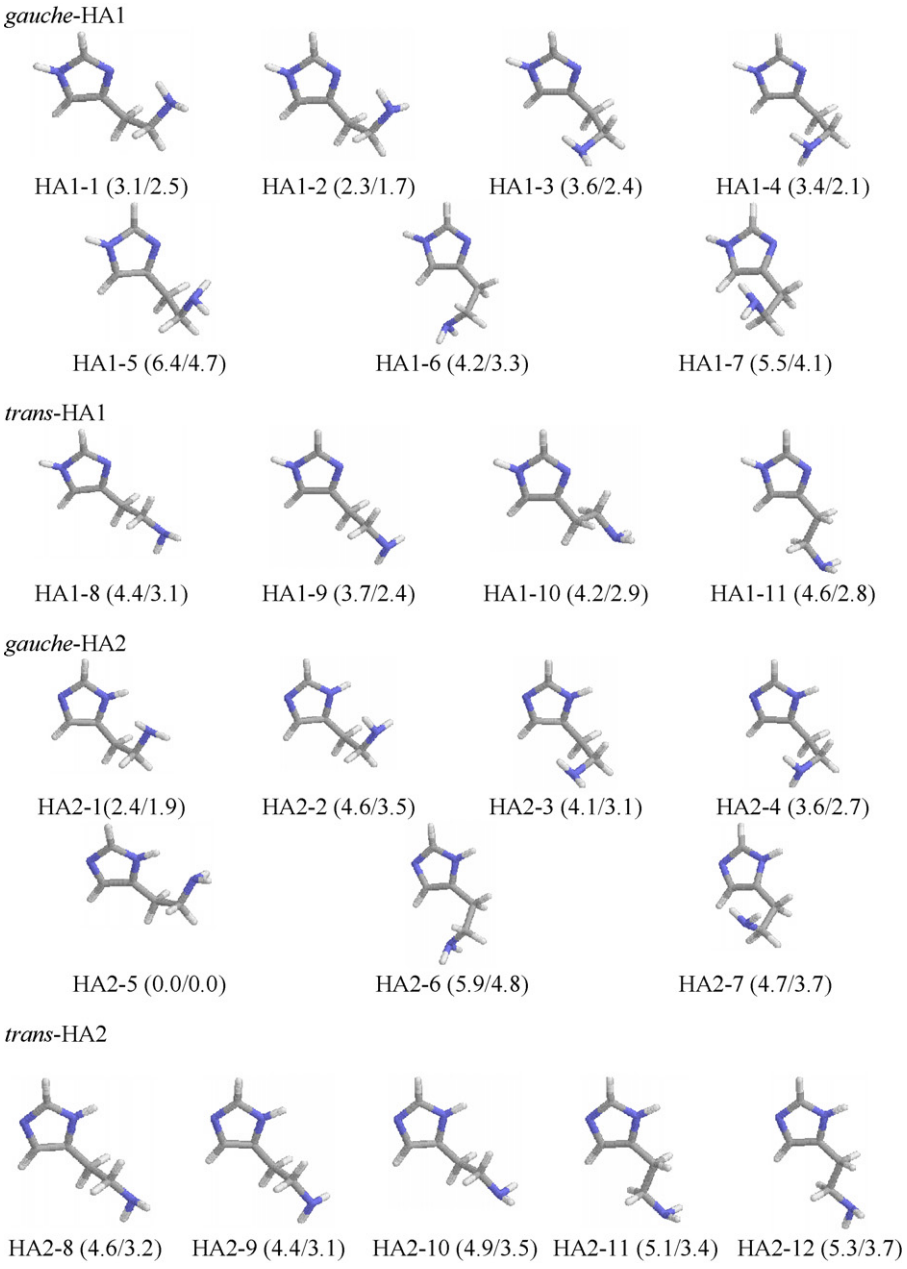
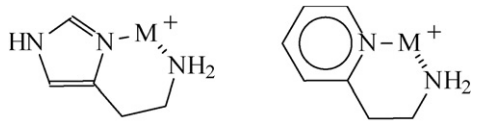


Fig. 2. Selected structures of the HA1 and HA2 histamine tautomers computed at the DFT(B3LYP)/6-31G* level (relative electronic energies/relative Gibbs free energies at 298 K in kcal mol^{-1} are given in parenthesis).



HA1-M$^+$ AEP-M$^+$

Scheme 1. (M = H or Li).

for bidentate ligands cannot be explained solely by substituent effects (polarizability and field/inductive) of the ethylamino group, because these effects should be smaller than 5 kcal mol^{-1}. The very high LCB for AEP and HA is attributed to the chelation effect of the lithium cation by two nitrogen basic sites, the ring N-aza and the chain N-amino, similarly as it has been previously reported for the proton [12,14–18,20]. In the chelated structures, both ligands may take the *gauche* ('scorpion') conformation of the ethylamino side chain, and histamine may additionally take the HA1 tautomeric form, similarly as it has been observed for a majority of metal cation complexes of histamine in the solid state [16]. The 'scorpion' conformation has been also found for the monoprotonated forms of both ligands in the gas-phase, where the chain N-aza binds the proton and the chain N-amino forms the hydrogen bond [17], as shown in Scheme 1, when M = H. Higher LCB values for pyridine and imidazole than for methylamine suggest that the lithium cation also interacts more strongly with the ring N-aza than with the chain N-amino site in both ligands, HA and AEP (as for the proton), as shown in Scheme 1, when M = Li.

3.2. Possible conformations of isolated ligands HA and AEP

Because of flexibility of the ethylamino side chain, more than 100 conformations were considered for isolated histamine and 2-(β-aminoethyl)-pyridine. Similarly as in our previous calculations performed for the proton-transfer reactions [17], 23 stable conformations were found for HA at the DFT/(B3LYP)/6-31G* level (Fig. 2). Fourteen of them are *gauche*: seven for one tautomer (HA1-1–HA1-7) and seven for the other one (HA2-1–HA2-7), and nine of them are *trans*: four for one tautomer (HA1-8–HA1-11) and five for the other one (HA2-8–HA2-12). Among them, the *gauche* structures HA2-5 and HA1-2 are the most stable ones for individual tautomers. The HA2-5 structure has the lowest electronic (E_{elec}) and Gibbs free energy (G) value. It is also the most polar structure (calculated dipole moment, $\mu_D = 5.77$ D) (1 D = 3.33564 × 10^{-30} Cm). The HA1-2 structure has larger G value by 1.7 kcal mol^{-1}, and it is less polar ($\mu_D = 4.63$ D) than the HA2-5 structure. The G values for other conformations of the HA1 and HA2 tautomers are larger by 2–5 kcal mol^{-1}. Their μ_D values vary from 2.31 (HA1-5) to 4.91 D (HA2-6).

In the case of histamine agonist AEP [36], nine stable conformations (AEP1–AEP9) were found (Fig. 3). Five of them are *gauche* (AEP1–AEP5) and four are *trans* (AEP6–AEP9). The AEP2 structure is the most stable one. It has the lowest electronic and Gibbs free energy value. It is also the most polar structure ($\mu_D = 2.87$ D). The G values for other structures of AEP dif-

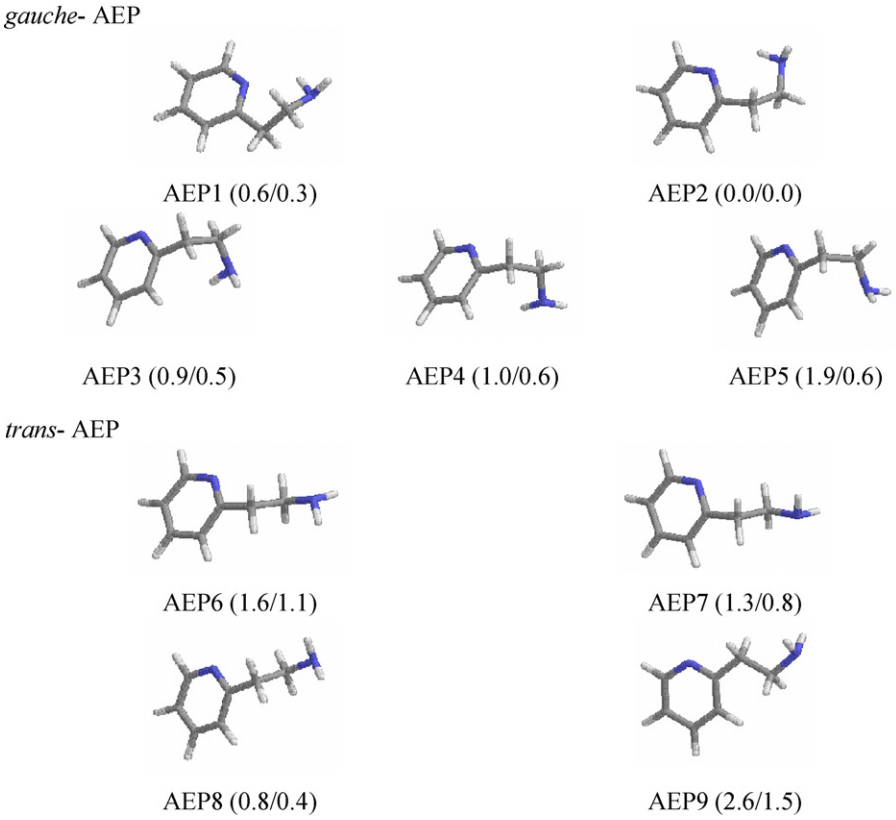


Fig. 3. Selected structures of 2-(β-aminoethyl)-pyridine (AEP) computed at the DFT(B3LYP)/6-31G* level (relative electronic energies/relative Gibbs free energies at 298 K in kcal mol^{-1} are given in parenthesis).

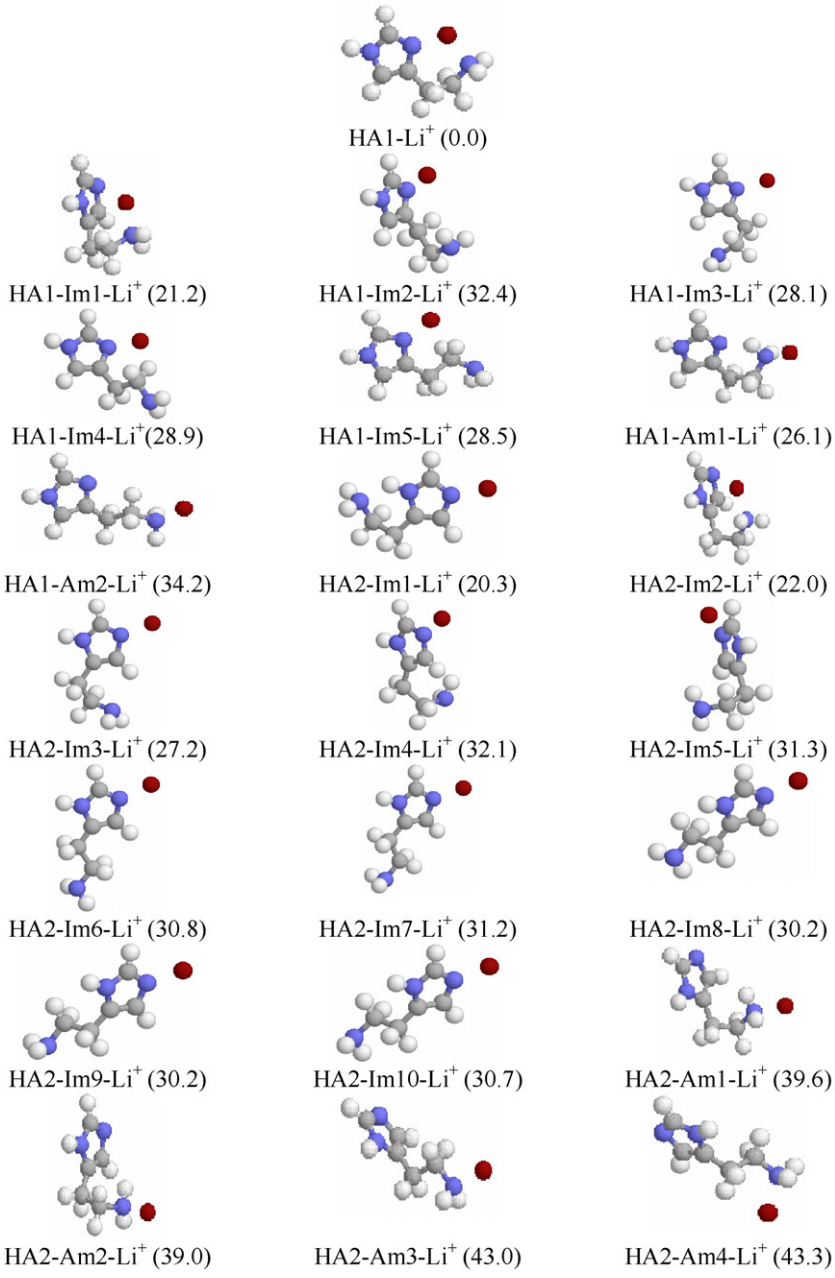


Fig. 4. Selected structures of Li^+ adduct of histamine (HA) computed at the DFT(B3LYP)/6-31G* level (relative electronic energies in kcal mol^{-1} are given in parenthesis).

fer by less than 1.5 kcal mol^{-1}. Their μ_D values vary from 1.20 (AEP9) to 2.80 D (AEP3).

3.3. Possible conformations of isolated HA-Li^+ and AEP-Li^+ adducts

Since two basic sites are present in HA and AEP, the ring N-aza and the chain N-amino, the lithium cation (Li^+) may be linked with one of the two basic sites or may be chelated by both basic sites. For this reason, three types of adducts were taken into account: (i) HA-Im-Li^+ and AEP-Im-Li^+ with the Li^+ cation near the ring N-aza, (ii) HA-Am-Li^+ and AEP-Am-Li^+ with the Li^+ cation near the chain N-amino, and (iii) HA-Li^+ and AEP-Li^+ with the Li^+ cation chelated by the two nitrogens, the ring N-aza and the chain N-amino. In addition, rotational isomerism for the ethylamino side chain in both ligands and prototropic tautomerism of the imidazole ring in histamine (HA1 and HA2 tautomers) were considered for each type of adducts. To reduce the cost of calculations, the initial structures for adducts have been obtained by a replacement of the proton by the lithium cation Li^+ in the previously observed monocationic structures of HA and AEP [12–17]. In this way, 22 thermodynamically stable structures were obtained for the lithium cation-histamine adduct (Fig. 4). Fifteen of them have the lithium cation linked with the ring N-aza: five for one tau-

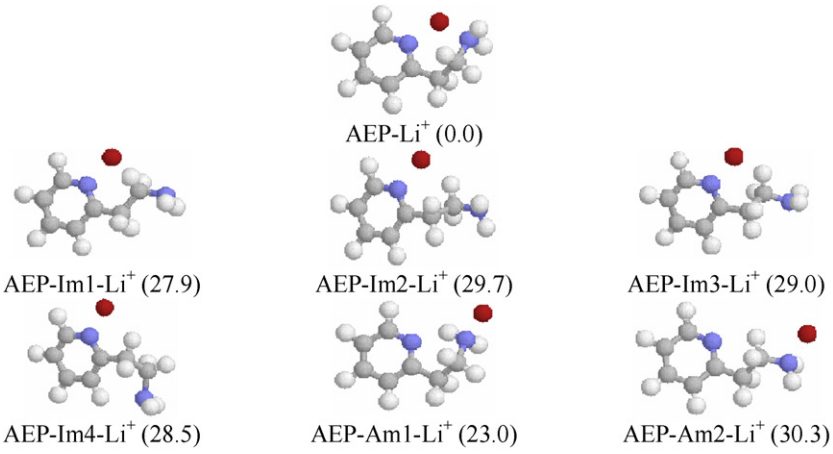


Fig. 5. Selected structures of the Li^+ adduct of 2-(β-aminoethyl)-pyridine (AEP) computed at the DFT(B3LYP)/6-31G* level (relative electronic energies in kcal mol^{-1} are given in parenthesis).

tomer (HA1-Im1-Li^+–HA1-Im5-Li^+) and ten for the other one (HA2-Im1-Li^+–HA2-Im10-Li^+). Six additional structures have the lithium cation linked with the chain N-amino: two for one tautomer (HA1-Am1-Li^+ and HA1-Am2-Li^+) and four for the other one (HA2-Am1-Li^+–HA2-Am4-Li^+). Only in one structure of the HA1 tautomer (HA1-Li^+), is the lithium cation chelated by two basic nitrogen atoms (HA1-Li^+). This structure presents the 'scorpion' conformation for the ethylamino group, similarly to the most stable monoprotonated form of histamine in the gas-phase [14–17], and this structure is the most stable one. It has the lowest electronic and Gibbs free energy value. The *G* values for other structures are larger than that for the most stable one by more than 15 kcal mol^{-1}.

In the case of the lithium cation-2-(β-aminoethyl)-pyridine adduct, seven thermodynamically stable structures were found (Fig. 5). In only one structure, which takes the 'scorpion' conformation of the side chain, similarly as in the case of the most stable monoprotonated form of AEP [17], both basic sites, the ring N-aza and the chain N-amino, chelate the Li^+ cation (AEP-Li^+). In four structures (AEP-Im1-Li^+–AEP-Im4-Li^+), the Li^+ cation interacts with the ring N-aza. In two other structures (AEP-Am1-Li^+ and AEP-Am2-Li^+), the Li^+ cation interacts with the chain N-amino. The AEP-Li^+ structure is the most stable one. It has the lowest electronic and Gibbs free energy value. The *G* values calculated for other structures are larger than that of the most stable one by more than 20 kcal mol^{-1}.

3.4. Selected structural and thermodynamic parameters of the most stable structures for HA, AEP, HA-Li^+ and AEP-Li^+

The most stable structures selected at the DFT(B3LYP)/6-31G* level for the two neutral tautomers of histamine, HA2-5 and HA1-2, are stabilized by intramolecular hydrogen bonds between the ring NH group and the chain N-amino, and between the chain NH_2 group and the ring N-aza, respectively (Fig. 2). The distance between the hydrogen of the ring NH group and the chain N-amino in the HA2-5 structure is equal to 2.16 Å (1 Å = 0.1 nm) and those between the hydrogens of the chain NH_2 group and the ring N-aza in the HA1-2 structure are equal to 2.32 and 3.43 Å. The most stable structure of neutral 2-(β-aminoethyl)-pyridine (AEP2) is also stabilized by the intramolecular hydrogen bond between the chain NH_2 group and the ring N-aza, similarly as for the HA1-2 structure. The distances between the amino hydrogens and the ring N-aza are also similar and equal to 2.34 and 3.43 Å.

For the most stable structures selected at the same level of theory for the Li^+-histamine (HA1-Li^+) and Li^+-2-(β-aminoethyl)-pyridine (AEP-Li^+) adducts, the lithium cation is chelated by two basic sites, the ring N-aza and the chain N-amino. The distances between the lithium cation and the N-aza and N-amino atoms in HA1-Li^+ are, respectively, equal to 1.93 and 2.00 Å. Similar distances between the lithium cation and the N-aza and N-amino atoms in AEP-Li^+ are obtained. They are equal to 1.95 and 1.98 Å, respectively. This suggests that the ring N-aza basic site interacts with the lithium cation only slightly stronger than with the chain N-amino.

All the most stable structures for the neutral bidentate ligands HA and AEP, and their lithium cation adducts have the 'scorpion' conformation for the ethylamino group. Absolute values of the dihedral Φ_1, Φ_2 and Φ_3 angles are between 40–65, 65–80 and 50–75° at the DFT(B3LYP)/6-31G* level, respectively (Table 1). They slightly vary during chelation by the lithium cation from 59.0, 66.5, 50.3 to 50.3, 75.2, 70.8 for the HA1 tautomer and from 64.7, 69.3, 64.1 to 51.6, 80.5, 71.8° for AEP, respectively. The aromatic character of the imidazole ring in HA and of the pyridine ring in AEP does not significantly change during chelation, as shown be the variations of the Harmonic Oscillator Model of Aromaticity (HOMA) index. This geometry-based aromaticity measure [44] was defined on the basis of bond alternation and bond elongation, to describe quantitatively π-electron delocalization: $\mathrm{HOMA} = 1 - \alpha/n\sum(R_{opt} - R_i)^2$, where *n* is the number of bonds taken into account, α a normalization constant (fixed to give HOMA = 0 for the non-delocalized system and HOMA = 1 for the system with all bonds equal to the optimal value), R_{opt} the optimum bond length (assumed to be realized when full delocalization of π-electrons takes place)

Table 1
Selected structural informations (Φ_1 angles (°)), HOMA index[a], and thermochemical quantities, H, G (in kcal mol^{-1}), and S (in cal mol^{-1} K^{-1}) for the most stable structures of the neutral ligands HA and AEP and their adducts with Li^+ at 298 K

Quantity	HA2-5	HA1-2	HA1-Li^+	AEP2	AEP-Li^+
DFT(B3LYP)/6-31G*//DFT(B3LYP)/6-31G*					
Φ_1	42.6	59.0	−50.3	−64.7	51.6
Φ_2	−64.8	−66.5	75.2	69.3	−80.5
Φ_3	−70.5	50.3	70.8	64.1	−71.8
Φ_4	173.5	−63.2	−176.3	−49.4	174.8
HOMA	0.87	0.85	0.86	0.97	0.96
H	−225929.4327	−225927.2904	−230581.9682	−239764.5824	−244413.5718
G	−225954.5657	−225952.9242	−230608.3035	−239791.3438	−244441.0963
S	84.297	85.976	88.329	89.758	92.318
DFT(B3LYP)/6-311+G**//DFT(B3LYP)/6-31G*					
H	−225999.7232	−225997.7340	−230646.5157	−239834.2674	−244477.9895
G	−226024.6461	−226023.1124	−230672.5994	−239860.7471	−244505.1839
S	83.592	85.120	87.485	88.813	91.210

[a] Harmonic oscillator measure of aromaticity [44].

Table 2
Theoretical LCBs (in kcal mol^{-1}) at 298 and 373 K estimated for HA and AEP at the DFT(B3LYP)/6-31G*//DFT(B3LYP)/6-31G* and DFT(B3LYP)/6-311+G**//DFT(B3LYP)/6-31G* levels

Level	T (K)	HA2-5	HA1-2	AEP2
DFT(B3LYP)/6-31G*//DFT(B3LYP)/6-31G*	298, 373	74.6, 72.5	76.3, 74.0	70.6, 68.4
DFT(B3LYP)/6-311+G**//DFT(B3LYP)/6-31G*	298, 373	68.6, 66.5	70.1, 67.9	65.1, 62.9

and R_i are the running bond lengths in the fragment. The HOMA index calculated for the geometries optimized at the DFT(B3LYP)/6-31G* level (Table 1) vary from 0.85 to 0.86 for the HA1 tautomer and from 0.97 to 0.96 for AEP, when going from the neutral forms to the lithium cation adducts. For histamine, there is an excellent agreement with the mean HOMA value (0.85 ± 0.05) found for the experimentally determined structures of histamine derivatives in the solid state with no significant changes due to complexation by metal cations [45]. The DFT(B3LYP)/6-31G*//DFT(B3LYP)/6-31G* and DFT(B3LYP)/6-311+G**//DFT(B3LYP)/6-31G* calculated enthalpies, entropies and Gibbs free energies for the most stable conformations of histamine, 2-(β-aminoethyl)-pyridine and their adducts with Li^+ cation are given in Table 1.

3.5. Theoretical LCBs of HA and AEP

The theoretical LCB values (Table 2) for histamine and 2-(β-aminoethyl)-pyridine were estimated at the DFT(B3LYP)/6-31G*//DFT(B3LYP)/6-31G* and DFT(B3LYP)/6-311+G**//DFT(B3LYP)/6-31G* levels using Eqs. (5) and (6), and the G values calculated at 298 and 373 K for the Li^+ cation, the most stable neutral ligands (HA2-5 and AEP2) and their most stable adducts with Li^+ (HA1-Li^+ and AEP-Li^+). The LCB for the less stable HA1-2 tautomer is slightly higher than that for the most stable HA2-5. All these values confirm the remarkably strong lithium cation basicities and the chelation effects for HA and AEP in the gas-phase observed by experiments. The theoretical ΔLCB (difference between the LCBs for the most stable structures of HA and AEP) is close to that experimentally determined (Table 3) and they are almost the same as the relative experimental ΔLCB value (3.1 kcal mol^{-1}) between the LCB of imidazole and that of pyridine, which posses only one basic site, the N-aza atom. This is an additional indication that the ring N-aza site interacts more strongly with the lithium cation than with the chain N-amino in both ligands HA and AEP, pinpointing similarities between HA and AEP in binding the lithium cation.

Table 3
Comparison of theoretical and experimental ΔLCBs (in kcal mol^{-1})[a] at 373 K estimated between HA and AEP

Method	ΔLCB
DFT(B3LYP)/6-31G*//DFT(B3LYP)/6-31G*	4.1
DFT(B3LYP)/6-311+G**//DFT(B3LYP)/6-31G*	3.6
FT-ICR-MS (kinetic method)	>2

[a] ΔLCB = LCB(HA2-5) − LCB(AEP2).

4. Conclusions

Among the 22 conformations studied at the DFT(B3LYP)/6-31G* level, the lithium cation-histamine adduct has only one structure being truly more stable than the others. Similarly, for the lithium cation-2-(β-aminoethyl)-pyridine adduct, among seven conformations studied at the same level of theory, only one structure is significantly more stable. The most stable adducts have the "scorpion" conformation, where the lithium cation is almost equally chelated by two basic nitrogens with slight preference of the N-aza site. The remarkably high, calculated or experimentally determined, values of the lithium cation basicities for HA and AEP corroborate their strong chelating properties in the gas-phase. This chelation is similar to that observed pre-

viously for the proton. Conformational similarities between the HA and AEP adducts with Li^+ (and H^+) and also similarities between the LCB (and GB) values of HA and AEP can partially explain similarities of both ligands in binding with the H1 receptor.

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