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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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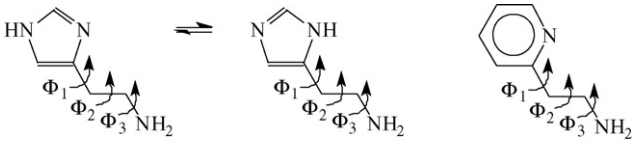
N-aza atom in the ring and the N-amino atom in the aliphatic side chain. AEP is a bifunctional nitrogen ligand that has sites very similar in basicity, the ring N-aza and the chain N-amino. The ethylamino side chains of both compounds may adopt a large number of conformations. They display rotational 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