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Experimental and Theoretical Evidence of Basic Site Preference in Polyfunctional Superbasic Amidinazine: N^1,N^1-Dimethyl-N^2-β-(2-pyridylethyl)formamidine

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The gas-phase basicity (GB) of the flexible polyfunctional N^1,N^1-dimethyl-N^2-β-(2-pyridylethyl)-formamidine (**1**) containing two potential basic sites (the ring *N*-aza and the chain *N*-imino) is obtained from proton-transfer equilibrium constant measurements, using Fourier-transform ion-cyclotron resonance mass spectrometry. Comparison of the experimental GB obtained for **1** with those reported for model amidines and azines indicates that the chain *N*-imino in the amidine group is the favored site of protonation. Semiempirical (AM1) and ab initio calculations (HF, MP2, and DFT), performed for **1** and its protonated forms, confirm this interpretation. These results are in contrast to those found previously for N^1,N^1-dimethyl-N^2-azinylformamidines (containing the amidine function directly linked to the azinyl ring), in which the ring *N*-aza is the most basic site in the gas phase. The separation of the two potential basic sites in **1** by the ethylene chain interrupts the resonance conjugation between the two functions and changes their relative basicities and, thus, the preferable site of protonation. It also increases the chelation effect against the proton and the gas-phase basicity of **1** in such a magnitude that consequently **1** may be classified as a superbase (GB = 241.1 kcal mol^{-1}). A transition state corresponding to the internal transfer of the proton (ITP) between the ring *N*-aza and the chain *N*-imino in **1** is investigated at the DFT(B3LYP)/6-31G** level. The energy barrier calculated for the ITP between the two basic sites is small and vanishes when zero-point vibrational terms and thermal corrections are applied to obtain the enthalpy or Gibbs energy of activation for the proton transfer. Additional calculations at the DFT-(MPW1K)/6-31G** level confirm this behavior. This indicates that the quantum-chemical ITP in **1** has a single-well character. The proton is located on the *N*-imino site, and the H-bond is formed with the *N*-aza site.

Introduction

Identification of the preferred basic site in the gas phase for polyfunctional nitrogen ligands, in particular for systems with biological activities or their models, is not straightforward solely on the ground of experimental measurements.[1] For this reason, theoretical computations performed in parallel to experiments are very useful.[2] They supply important information on the geometry of the neutral and its various possible protonated forms and on internal effects that might contribute to the gas-phase basicity. They predict also the tautomeric, conformational, and basic site preferences, which are important points in the context of transport properties and interactions of biomolecules in living organisms.

Amidinazines (Chart 1) can be considered as trifunctional nitrogen ligands. They contain three nitrogen atoms: the *N*-amino and *N*-imino in the chain amidine function and the *N*-aza in the ring. Each of these nitrogens is capable to attach a proton in the gas phase. In our previous papers,[3] it has been shown by experi-

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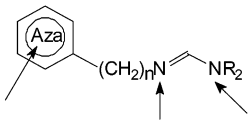
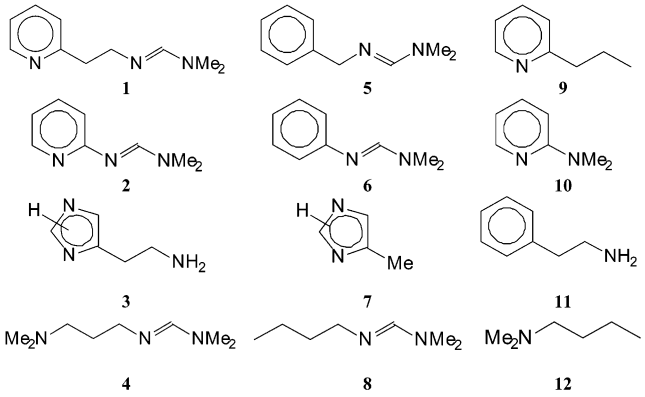
CHART 1



ments and computations that the ring *N*-aza is the favored site of protonation in amidinazines with the amidine function directly linked to the ring ($n = 0$, R = Me). The strong gas-phase basicity observed for the ring *N*-aza (GB of amidinazine is larger than that of the corresponding aminazine) has been explained by the transmission of the n−π conjugation effect (so-called "push−pull" effect) between the electron-donor amidine function (N=CHNR$_2$) and the electron-acceptor ring *N*-aza.[3]

The separation of the amidine function from the ring by a polymethylene chain interrupts this conjugation and may change the relative basicities of the nitrogen atoms. To study this effect, we chose N^1,N^1-dimethyl-N^2-β-(2-pyridylethyl)formamidine (**1**), in which the aza group is at the 2-position in the ring relative to the side chain, similarly as in previously studied N^1,N^1-dimethyl-N^2-2-pyridylformamidine (**2**). Amidinazine **1** also bears two nitrogen-containing basic groups separated by two methylene groups ($n = 2$). Therefore, **1** may be classified in the same family of flexible bidentate nitrogen ligands as histamine **3**, and its agonists (e.g., β-(2-pyridyl)ethylamine, substrate in synthesis of **1**), although the latter molecules bear an amine function instead of an imine. The structure and biological activity of **3** strongly depend on its environment (see ref 2i). Histamine may exist under the so-called "essential" (trans) or "scorpio" (gauche) conformations. It may be protonated at the ring *N*-aza or at the chain *N*-amino. Although there is a lack of crystallographic data for **3** interacting with the histamine-specific receptors (except from some X-ray structures of histamine-binding proteins),[2i] various models of interactions of **3** with the histamine specific receptors (H1, H2, H3, and H4) were proposed in the literature.[2j] Most of them are based on proton-transfer reactions. We may expect that **1** has properties in the gas phase similar to flexible bidentate nitrogen ligands such as histamine **3**, amidinamines, and guanidinamines (one *N*-imino and one *N*-amino),[1f] diamines (two *N*-amino),[4,5] and 2,2′-bipyridines (two *N*-aza),[6] which display a strong enhancement of basicity in the gas phase independently on the nitrogen hybridization (sp^2 or sp^3). With the aim of better understanding proton-transfer properties of flexible bidentate nitrogen-containing ligands in a nonpolar environment, gas-phase proton-transfer involving amidinazine **1** was considered as an interesting case study.

CHART 2



Other systems useful for interpretation of our results are shown in Chart 2. The gas-phase basicity measurements for **1** were carried out using the same Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer as for other superbasic amidines.[1f,3b] The experimental gas-phase substituent effects were analyzed in **1** and compared with those observed in model nitrogen bases (**2**−**12**). The empirical analysis of substituent effects was also based on the Taft and Topsom equation,[7] which was applied previously to formamidines and azines.[3b,8,9] This approach allows us to propose the favored site of protonation for **1** in the gas phase.

In parallel, quantum-chemical calculations were performed for **1** (free base and its monocations: the *N*-aza- and *N*-imino-protonated forms) using the semiempirical Austin Model 1 (AM1)[10] and ab initio methods: restricted Hartree−Fock (HF),[11] second-order Möller−Plesset perturbation (MP2),[12] and density functional theory (DFT)[13] with a hybrid exchange-correlation functional, B3LYP.[14] In ab initio calculations, the 6-31G** and 6-311++G** basis sets were used.[11] The computations give us the

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TABLE 1. Comparison of the Experimental GB Value Obtained for Amidinazine 1 with Those Reported for Other Nitrogen Bases[a] Shown in Chart 2 (in kcal mol^{-1})

base	GB[b]	base	GB[b]	base	GB[b]
1	241.1	**5**	234.8	**9**	220.8
2	232.9	**6**	229.4	**10**	225.0
3	229.5	**7**	220.1	**11**	215.7
4	241.7	**8**	234.5	**12**	224.2

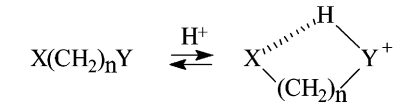
[a] Data from refs 1f, 3b, and 16. [b] In kcal mol^{-1}; absolute GB values are usually considered to be accurate to ±2−2.5 kcal mol^{-1}.[16]

possibilities to identify the most stable structures for the neutral and protonated forms, to support our conclusion (derived on the basis of experimental results) about the basic site preference in **1**, to predict the relative basicity between both sites, and to estimate the energy barrier for the internal transfer of the proton (ITP) from the *N*-imino to the *N*-aza site. Another hybrid exchange-correlation functional, MPW1K (modified functional of Perdew−Wang 1-parameter for kinetics described by Truhlar and co-workers[15]), was also used to characterize the ITP phenomenon.

Results and Discussion

Experimental Gas-Phase Basicity. The GB measurements performed for N^1,N^1-dimethyl-N^2-β-(2-pyridylethyl)formamidine (**1**) showed that amidinazine is more basic than the two reference bases (TMG and DBN) used in the experiment. The relative basicity between amidinazine **1** and TMG (GB = 238.4 kcal mol^{-1}, 1 cal = 4.184 J)[1f,16] was too large to perform an accurate determination of GB (ΔGB = 3 ± 1 kcal mol^{-1}). However, for DBN (GB = 241.0 kcal mol^{-1}),[1f] which is more basic than TMG, the equilibrium constant and the relative basicity for the proton-transfer reaction could be obtained with a better precision (ΔGB = 0.08 ± 0.10 kcal mol^{-1}). These experimental results indicate that amidinazine **1** belongs to the family of superbases in the gas phase, similar to DBN.[1f,17] Its GB value (241.1 kcal mol^{-1}) is larger than those of model nitrogen bases (**5**−**12**, Chart 2) given in Table 1. Although the uncertainties for the relative basicities ΔGB lie usually in the range 0.1−1 kcal mol^{-1}, the absolute GB values are considered to be accurate to about ±2−2.5 kcal mol^{-1}.[16] When a comparison is made with computed data (which are also absolute values for individual compounds) it seems reasonable to consider the latter uncertainty. Amidinazine **1** is also a stronger base than other polydentate nitrogen ligands, i.e., N^1,N^1-dimethyl-N^2-2-pyridylformamidine (**2**, GB = 232.9 kcal mol^{-1})[3b] and histamine (**3**, GB = 229.5 kcal mol^{-1}).[1f] In **2**, which does not possess a polymethylene chain (n = 0), the formamidine group is directly linked to the pyridyl ring. In **3**, the two potential basic sites, the ring *N*-imino and the chain *N*-amino, are separated by the same number of methylene groups as in **1** (n = 2). Surprisingly, the GB of **1** is close to that of aliphatic N^1,N^1-dimethyl-N^2-γ-(*N*,*N*-dimethylaminopropyl)formamidine (**4**, GB = 241.7 kcal mol^{-1}),[1f] in which the potential basic sites, the dimethylamino nitrogen at the end of the alkyl chain (propylene group, $CH_2CH_2CH_2$), and the amidine *N*-imino are separated by three carbons, similar to the ring *N*-aza and the chain *N*-imino in **1**.

The exceptionally high basicity of amidazine **1** suggests that both basic sites participate in the monoprotonation reaction 1. One site binds the proton and the other one interacts with the protonated function by formation of an intramolecular hydrogen bond (N···H−N$^+$), similar to other bidentate nitrogen ligands (e.g., diamines, proton sponges, amidinamines, guanidinamines, lysine, histamine, histidine, arginine, etc.).[1f,3c,4,5,8c,16,17] In general, the chelation of a proton in flexible bidentate nitrogen ligands increases the GB value by 5−20 kcal mol^{-1} in comparison to monodentate bases. Stronger chelation effects were observed for $n \geq 3$ than for $n < 3$. Stronger effects were also observed for diamines, amidinamines and guanidinamines as compared to the corresponding monoamines, amidines, and guanidines, respectively.



(1)

Although the chelation of a proton can explain the superbasicity of amidinazine **1**, it does not indicate which position is occupied by the proton between the two basic sites. In other words, which site is more basic and bonds more strongly to the proton, and which one is less basic and forms the intramolecular hydrogen bond. Therefore, we compared the experimental GB value obtained for **1** with those reported for model compounds, and we performed a detailed analysis of substituent effects in **1** and in model formamidines and pyridines to gain insights on the position of the proton in this polydentate base.

Evidence of the Preferred Site of Protonation Based on Experimental Data. Experimental and theoretical studies performed for a series of model N^1,N^1-dimethylformamidines, RN=CHNMe$_2$ (R = alkyl, aryl, arylalkyl) have shown that the *N*-imino in the amidine function is certainly the preferred site of protonation in the gas phase.[1f,8,17] Its gas-phase basicity is larger by ca. 25 kcal mol^{-1} than that of the *N*-amino. The basicity difference is attributable to the n-π conjugation effect (2), which increases the basicity of the *N*-imino and decreases the basicity of the *N*-amino.[18] For this reason, in polyfunctional amidinazine **1**, two potential basic sites (the ring *N*-aza and the chain *N*-imino) have been considered.

(2)

The comparison of the GB value found for N^1,N^1-dimethyl-N^2-benzylformamidine (**5**, GB = 234.8 kcal mol^{-1})[1f] with that reported for 2-*n*-propylpyridine (**9**, GB = 220.8 kcal mol^{-1})[16] indicates that in model bases the *N*-imino is more basic than the *N*-aza by 14 kcal mol^{-1}. A similar GB difference equal to ca. 10 kcal mol^{-1} was observed between N^1,N^1-dimethyl-N^2-*n*-butylformamidine

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(**8**, GB = 234.5 kcal mol^{-1})[1d] and *N*,*N*-dimethyl-*n*-butylamine (**12**, GB = 224.2 kcal mol^{-1}).[16] The separation of basic sites in **4** by a polymethylene chain eliminates resonance effects between the basic functions and strongly reduces the field/inductive effects of the heteroatoms. As a consequence, the *N*-imino in the amidine group (as the more basic) retains the proton by a bond with a marked covalent character, and the *N*-amino at the end of the *n*-propylene chain (as the less basic) interacts with the proton by formation of an intramolecular H-bond.[1f,8c,16] A similar conclusion has been derived for histamine (**3**), in which the ring *N*-imino (analogue to the imino nitrogen in the amidine group) retains the proton and the chain *N*-amino forms the H-bond.[1a,f,16] 4(5)-Methylimidazole (**7**, GB = 220.1 kcal mol^{-1}) is more basic than *β*-phenylethylamine (**11**, GB = 215.7 kcal mol^{-1}).[16] These observations for flexible polydentate ligands together with a large value of GB for **1** (close to that of **4**) suggest that the *N*-imino in the amidine group is the preferred site of protonation in **1**, similarly as in **3** and **4**.

A different situation has been observed for amidinazine **2**, which does not contain a polymethylene chain ($n = 0$) and for which the amidine group is linked directly to the pyridine ring.[3] Although N^1,N^1-dimethyl-N^2-phenylformamidine (**6**, GB = 229.4 kcal mol^{-1}) is more basic than 2-*N*,*N*-(dimethylamino)pyridine (**10**, GB = 225.0 kcal mol^{-1}), the ring N-aza is the favored site of protonation in **2**. A strong resonance conjugation between the aza and amidine groups changes the basicity order of the conjugated sites and, as a consequence, changes the basic site preference in **2**.

An additional support to the conclusion concerning the preferred site of protonation in **1** can be derived from the analysis of substituent effects. If one assumes that protonation occurs at the ring *N*-aza in **1**, the estimated (microscopic) gas-phase basicity of this site can be predicted from the effects of the $(CH_2)_2N{=}CHNMe_2$ group on the GB of pyridine. Fortunately, the gas-phase substituent effects in pyridines[9] have well been described by Taft and co-workers, see relation (3).[7,19,20] The estimated effect of the $(CH_2)_2N{=}CH{-}NMe_2$ group (δGB = 5.4 kcal mol^{-1}) is almost the same as that observed for the Et group (δGB = 5.3 kcal mol^{-1}).[16] The estimated GB value for the protonation of the ring *N*-aza in **1** (ca. 220 kcal mol^{-1}) is lower than the experimental (macroscopic) GB of **1** (241.1 kcal mol^{-1}) by ca. 21 kcal mol^{-1}. Such a large difference cannot be assigned to the chelation effect of the proton by the sp^2 hybridized nitrogens. In the case of bidentate nitrogen ligands, in which the ring *N*-aza binds a proton, the chelation effect has been found to be no larger than 10 kcal mol^{-1}.[3,6] The same is true for polyfunctional amidines.[1f,8c]

$$-\delta\mathrm{GB} = \rho_\alpha\sigma_\alpha + \rho_\mathrm{F}\sigma_\mathrm{F} + \rho_\mathrm{R}\sigma_\mathrm{R} + \epsilon \qquad (3)$$

Conversely, if one assumes that protonation in **1** takes place at the *N*-imino in the amidine function, its basicity could be estimated from the effect of the $(CH_2)_2$(2-pyridyl) group, which influences the GB of the amidine group. Lack of the σ_i constants for the 2-$(CH_2)_2$(2-pyridyl) group makes the direct estimation of its effect difficult. However, taking into account an observation that the substituent effect of the $(CH_2)_2N{=}CHNMe_2$ group is close to that of Et, one can assume that the substituent effect of the $(CH_2)_2$(2-pyridyl) group is not very different from that of the $(CH_2)_2$Ph and/or Et groups. An application of eq 3 to the series of N^1,N^1-dimethyl-N^2-alkylformamidines ($RN{=}CHNMe_2$)[8b,c] enables estimation of δGB for R = $(CH_2)_2$Ph and Et. Indeed, the estimated effect of the $(CH_2)_2$Ph group (δGB = 6.4 kcal mol^{-1}) is close to the effect calculated for the Et group (δGB = 6.0 kcal mol^{-1}). These estimations indicate that the GB value of **1** estimated for the *N*-imino protonation (ca. 234 kcal mol^{-1}) is lower than the experimental GB (241.1 kcal mol^{-1}) by ca. 7 kcal mol^{-1}. The difference between the estimated GB(*N*-imino) and the experimental GB(**1**) is of the same order of magnitude as the chelation effect of the proton observed for the bidentate nitrogen ligands (5−11 kcal mol^{-1}), in which the amidine function is the more basic site.[1f,8,17] These empirical estimations lead to the conclusion that in the bidentate amidinazine **1**, the chain *N*-imino in the amidine group forms a bond of a covalent character with a proton and the ring *N*-aza enhances the proton binding by a H-bond formation.

Stable Conformations Found for Neutral and Protonated Forms by Quantum-Chemical Calculations. All calculations were conducted on the *E* configuration of the C=N double bond in the amidine group. This configuration has been found in the case of previously studied formamidines and amidinazines.[1c,2c,3,8,18,21] Due to the high flexibility of the side chain in amidinazine **1**, more than 400 initial conformations were considered for the neutral and monoprotonated (the ring *N*-aza and the chain *N*-imino) forms of **1**. Such a large number of conformations results from possible rotations around the single bonds in the side chain (the angles were systematically changed in steps by 30°).

To preselect the most stable conformations of **1** and its monocations, the AM1 semiempirical method[10] was applied. The geometries of all conformations (considered in this paper) were optimized without any symmetry constraint, and the most stable structures were identified. Next, the preselected structures were fully reoptimized without symmetry constraints using the HF and DFT(B3LYP) methods[11,13,14] and the 6-31G** basis set. To verify the effect of the basis set on geometrical parameters in **1**, the calculations were additionally performed at the HF//6-311++G** level. The reoptimized geometries have no symmetry (*C*1), and all vibrational frequencies are real. After ab initio reoptimizations, the structures of the neutral and protonated forms were found to be similar to those found at the AM1 level.

Generally, the level of calculations and the basis set have no significant influence on the conformational

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(20) (a) For the estimation of the GB corresponding to the N-aza in **1**, the following parameters were taken: the ρ_i recalculated according to the data given for 2-substituted pyridines in the recent compilation of Hunter and Lias[16] ($\rho_\alpha = 9.1 \pm 0.7$, $\rho_\mathrm{F} = 29.3 \pm 0.8$, $\rho_\mathrm{R} = 13.9 \pm 0.8$, $\epsilon = -0.1 \pm 0.4$, $n = 15$, $r = 0.998$, $s = 0.6$),[3b] and the σ_i reported for the $(CH_2)_2N{=}CH{-}NMe_2$ ($\sigma_\alpha = -0.52$, $\sigma_\mathrm{F} = 0.015$, and $\sigma_\mathrm{R} = -0.07$).[1c,19] (b) Raczyńska, E. D. *J. Chem. Res., Synop.* **1997**, 214. (c) For the estimation of the GB corresponding to the N-imino in **1**, the following parameters were used: the ρ_i recalculated according to the recently revised GB values for N^1,N^1-dimethyl-N^2-alkylformamidines,[1f] ($\rho_\alpha = 12.2 \pm 0.9$, $\rho_\mathrm{F} = 45.9 \pm 1.4$, $\epsilon = 4.5 \pm 0.6$, $n = 17$, $r = 0.996$, $s = 0.5$), and the σ_i constants reported for the $(CH_2)_2$Ph ($\sigma_\alpha = -0.65$, and $\sigma_\mathrm{F} = 0.03$) and Et groups ($\sigma_\alpha = -0.49$, and $\sigma_\mathrm{F} = 0.00$).[19]

(21) Krygowski, T. M.; Woźniak, K. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons Ltd: New York, 1991; Vol. 2, Chapter 2.

preferences. All the most stable structures are stabilized by an intramolecular H-bond. In the neutral form, the amidine CH interacts with the ring N-aza, with the distance between the interacting atoms (H···N) equal to 2.7 (AM1), 2.5 (HF/6-31G**), 2.6 (HF/6-311++G**), and 2.4 Å (DFT(B3LYP)/6-31G**). This is a typical distance for the CH···N hydrogen bond.[22] For the monocations, the protonated group interacts with the free basic site forming the NH^+···N bonds. In the *N*-aza protonated forms, the distance between the hydrogen of the ring *N*-azaH^+ and the chain *N*-imino is equal to 2.0 (AM1), 1.8 (HF/6-31G** and HF/6-311++G**), and 1.6 Å (DFT-(B3LYP)/6-31G**). In the *N*-imino-protonated form, the distance between the hydrogen of the chain *N*-iminoH^+ and the ring *N*-aza is equal to 2.4 (AM1), 2.0 (HF/6-31G**), 2.1 (HF/6-311++G**), and 1.8 Å (DFT(B3LYP)/6-31G**). In both protonated forms, the NH^+···N bonds are shorter than the CH···N bond in the neutral form, reflecting the stronger intramolecular interactions in the monocations than in the neutral form. The different types of H-bonds (CH···N vs NH^+···N) explain also different conformational preferences by the neutral and protonated forms of amidinazine **1**.

Evidence of Preferred Site of Protonation Based on Theoretical Calculations. In quantum-chemical calculations, amidinazine **1** was considered as a nitrogen ligand with two potential basic sites, the ring *N*-aza and the chain *N*-imino. Therefore, thermodynamic parameters were calculated for the neutral and the two protonated forms (*N*-aza and *N*-imino) using the HF and DFT(B3LYP) methods[11,13,14] and the 6-31G** basis set. To verify the effect of the basis set on thermodynamic parameters, calculations were additionally performed at the HF//6-311++G** level. The single point energies were also calculated for the neutral and protonated forms of **1** at the MP2/6-31G**, MP2/6-311++G**, and DFT-(B3LYP)/6-311++G** levels using geometries optimized at the HF/6-31G**, HF/6-311++G**, and DFT(B3LYP)/6-31G** levels.[11−14] A comparison of the total and relative energies calculated for the protonated forms (*N*-imino and *N*-aza) indicates that the *N*-imino is a more basic site than the *N*-aza in **1** by ca. 5−12 kcal mol^{-1}. An extension of the basis set to 6-311++G** has no significant effect on the relative energies.

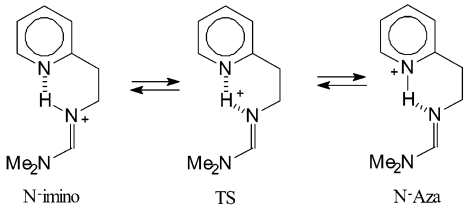
The proton affinity (PA) of the two basic sites in **1** (*N*-aza and *N*-imino) was estimated at the AM1 level[23] from the heats of formation, and at the ab initio levels from the enthalpies calculated for the neutral and protonated forms. The gas-phase basicity (GB) was calculated at the ab initio levels from the corresponding PA and the entropy term $T\Delta S$. Table 2 summarizes the calculated PA and GB values for the *N*-aza and *N*-imino in **1**. The AM1 model gives lower PA values than the HF and DFT methods, and all the methods give overestimated values of PA as compared to the experimental result. However, the relative values of PA and GB are similar among different methods. All of them indicate that the *N*-imino is a more basic site than the *N*-aza (by 5−12 kcal mol^{-1}), similar to the estimation based on empirical models.

TABLE 2. PA and GB (at 298.15 K, in kcal mol^{-1}) Calculated for the *N*-Aza and *N*-Imino Sites in Title Amidinazine at the AM1, HF, and DFT Levels

level of computations	PA			GB		
	N-aza	*N*-imino	ΔPA[a]	*N*-aza	*N*-imino	ΔGB[b]
AM1	230.5	242.9	12.4			
HF/6-31G**	253.6	261.6	8.0	245.8	254.0	8.2
HF/6-311++G**	248.8	257.0	8.2	240.9	249.7	8.8
DFT(B3LYP)/-6-31G**	254.0	258.4	4.4	245.4	250.4	4.9

[a] ΔPA = PA(*N*-imino) − PA(*N*-aza). [b] ΔGB = GB(*N*-imino) − GB(*N*-aza).

SCHEME 1



Energy Barrier for Proton Transfer in the Protonated Form. The potential energy surface for the internal transfer of the proton (ITP) was examined with the aim to characterize its shape. On the basis of the existence of two geometrically stable protonated forms (see above), the presence of an energy barrier is expected for a proton transfer from the chain *N*-imino to the ring *N*-aza in the protonated form of **1** (a double well potential).[24] However, the homonuclearity of the resonance-assisted N−H···N bond, the strong basicity of the two basic sites (Table 2) and a relatively short distance between the nitrogen atoms (N···N equal to 2.7 and 2.6 in the *N*-imino- and *N*-aza-protonated form, respectively) suggest that the energy barrier for ITP in **1** could be very small.[25] In such a case, the Gibbs free energy profile may possess a single well character. For this reason, a transition state (TS in Scheme 1) was searched at the DFT(B3LYP)/6-31G** level. The harmonic vibrational analysis performed for this stationary point confirmed its character of a first-order saddle point with a single imaginary frequency. The structure of TS (the Φ_1, Φ_2, Φ_3, Φ_4, and $\Phi_{4'}$ angles equal to 33.4, −52.4, −135.1, −174.0 and 0.7°, respectively) was found to be closer to that calculated for the N-aza protonated form (the Φ_1, Φ_2, Φ_3, Φ_4, and $\Phi_{4'}$ angles equal to 34.2, −56.1, −132.3,

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TABLE 3. Comparison of Thermodynamic Properties for the Transition State (TS) and the *N*-Aza-Protonated Form (*N*-aza) Relative to Those of the *N*-Imino-Protonated Form Calculated at the DFT(B3LYP)/6-31G Level[a]**

relative property	TS	*N*-aza
ΔE	5.9	5.3
$\Delta(E + \text{ZPVE})$	3.0	4.5
ΔH	2.8	4.4
ΔG	3.5	4.9

[a] In kcal mol^{-1}.

−172.2, and 0.4°, respectively) than to that for the *N*-imino- protonated form (the Φ_1, Φ_2, Φ_3, Φ_4, and $\Phi_{4'}$ angles equal to 40.4, −61.1, −134.0, 179.2, and 0.3°, respectively). The distance between the proton and the ring *N*-aza in TS (1.220 Å) is shorter than that between the proton and the chain *N*-imino (1.360 Å) indicating that the TS geometry is closer to that of the less stable *N*-aza form (Scheme 1), which is in agreement with the Hammond postulate.[26]

The DFT-calculated thermodynamic quantities for the barrier (such as the relative electronic energy, the relative sum of the electronic and the zero-point vibrational energies, the relative enthalpy, and the relative Gibbs energy, which are denoted as ΔE, $\Delta(E + \text{ZPVE})$, ΔH, and ΔG, respectively) between the TS (first-order saddle point) and the minimum energy structure of the *N*-imino-protonated form are listed in Table 3. For comparison, analogous relative thermodynamic quantities between the minima of the *N*-aza- and *N*-imino-protonated forms are also given in Table 3. As expected, the electronic energy of TS is higher than that of both the *N*-imino and *N*-aza tautomers. However, the barrier disappears after addition of the zero-point vibrational correction, and it is also missing on the enthalpy and Gibbs free energy surfaces.

It is known that the B3LYP method underestimates barriers for proton-transfer reactions,[15] and the lack of a barrier may be an artifact of the B3LYP method. For this reason, we performed additional geometry optimizations using a hybrid exchange-correlation potential MPW1K, which was parametrized by Truhlar and coworkers to reproduce barrier heights for chemical reactions.[15] Calculations were carried out using the 6-31G** basis set. The electronic energy of the TS is also higher than that of both the *N*-imino (by 6.3 kcal mol^{-1}) and *N*-aza isomers (by 0.6 kcal mol^{-1}). However, upon addition of the zero-point vibration energy, and the thermal terms, the Gibbs energy barrier for ITP (3.9 kcal mol^{-1}) is smaller than the relative Gibbs energy between the protonated forms (5.1 kcal mol^{-1}).

These results suggest that at 298 K the probability of finding the proton on the side of the ring *N*-aza is negligible and that the proton is localized on the *N*-imino side of the chain. The geometrically stable *N*-aza-protonated form is metastable thermodynamically. Zero-point vibrations and thermal corrections (which model experimental conditions) are sufficient to remove the barrier between the *N*-aza- and *N*-imino-protonated forms. We conclude that the surfaces of enthalpy and Gibbs energy have a single well character.

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The stability difference between the two protonated forms can be explained by two opposite resonance effects operating in the monocations. The protonation of the *N*-imino site, located in the n−π conjugated amidine function, increases the resonance effect in the molecule,[21a] whereas the protonation of the *N*-aza site in the aromatic pyridine moiety decreases the aromaticity of the ring.[27] The two basic heteroatoms of the same element, both in the sp^2 hybridization, are chemically different in the protonation reaction. The *N*-imino can form a covalent bond with the proton, while the *N*-aza can form an intramolecular hydrogen bond. The distance between the basic sites in TS (N···N equal to 2.5) is slightly smaller than in the *N*-imino-protonated form (2.7) indicating that the intramolecular H-bond in the thermodynamically stable monocation can be considered relatively strong. It is similar to that observed for protonated proton sponges.[25b]

Conclusion

Both the experimental and theoretical studies on the basic site preferences in polyfunctional amidinazine **1** indicate that the chain *N*-imino site is favored in the gas phase contrary to the previously studied amidinazine **2**, in which the ring *N*-aza is the preferred site of protonation. The separation of the amidine group from the pyridyl ring by a polymethylene chain interrupts the resonance conjugation between the basic functions, reduces their field/inductive effect and changes the relative basicities. The higher flexibility of **1** than **2**, and the extra stability of the monocation resulting from the formation of a more stable intramolecular H-bond strongly increase the gas-phase basicity of **1**, which can be qualified as a superbase (PA(**1**) > 240 kcal mol^{-1}). The chelation effect of the proton is similar to that observed in histamine **3** and in amidinamine **4**. From model compounds, it was estimated that this effect increases the basicity of the *N*-imino site by ca. 7 kcal mol^{-1}. A barrier for ITP (*N*-aza → *N*-imino) is only 0.6 kcal mol^{-1} on the electronic potential energy surface and the barrier disappears after inclusion of zero-point vibrational corrections and thermal contributions to enthalpy and Gibbs energy. Thus the enthalpy and Gibbs energy surfaces for a proton have a single well character. The proton is localized on the *N*-imino site and a hydrogen bond is formed with the *N*-aza site. A similar behavior was observed for histamine **3** and its agonists. A more basic nitrogen atom binds covalently the proton and a less basic nitrogen atom stabilizes the protonated site through H-bonding. The proton location in the protonated histamine was shown to be dependent on the medium.[2i] We postulate that the chelation effect of the proton might be similar in **1** and in histamine: (i) two basic sites of similar strength (if we expect the difference in hybridization of the side chain nitrogen), (ii) a similar distance between the two nitrogen atoms with a flexible link, and (iii) a small or absent activation energy for the ITP. One can expect that the Gibbs energy barrier to transfer the proton is also small

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or absent in histamine. Consequently, when the environment [more (H1 and H2) or less polar pockets (H3 and H4) of histamine receptors] of the protonated molecule is changed, a fast exchange of the protonated sites can take place. Until now, the calculations on protonation of histamine considered essentially the energetic aspects but neglected the kinetics features of the ITP. We suggest that this aspect is relevant to the biological activity of such kind of molecules and should be taken into account in developing models of interaction between active molecules and receptors.

Experimental Section

Chemicals. Reagents for synthesis and reference bases for GB measurements were commercial compounds. Amidinazine **1** were synthesized according to known procedure, applied previously to N^1,N^1-dimethylformamidines, RN=CHNMe$_2$,[8,28] by heating an equimolar mixture of *N*,*N*-dimethylformamide dimethylacetal and β-(2-pyridyl)ethylamine at 60−70 °C without solvent. The reaction was controlled by TLC on silica gel plates using a mixture of chloroform and ethyl acetate as eluent and ultraviolet light for visualization. After evaporation of MeOH, amidinazine was purified by distillation under reduced pressure. Its structure was confirmed by infrared and mass spectra.

Infrared spectra (FT-IR, KBr cell of 0.627 mm) recorded in the ν(C=N) frequency region for amidinazine in CCl4 solution at room temperature, showed a band at 1654 cm^{-1}, to be compared to the value for N^1,N^1-dimethyl-N^2-benzylformamidine, PhCH2N=CHNMe$_2$ (1654 cm^{-1}).

Mass spectra (FT-ICR mass spectrometer, electron ionization (EI), 70 eV) were recorded before gas-phase basicity measurements under the same conditions as described previously[29] at sufficiently low pressure to avoid ion/molecule reactions. The mass spectrum confirmed the general mass spectral fragmentation observed for heteroalkyl derivatives of RN=CHNMe$_2$ (Scheme 1 in ref 29a). The $[NMe_2]^+$ (m/z = 44) ion is the base peak, similarly as for other N^1,N^1-dimethylformamidines. There are also other fragments, which are characteristic in the mass spectrum of any N^1,N^1-dimethylformamidine: the $[M]^+$ (m/z = 178 (intensity 12)), $[M - H]^+$ (m/z = 177 (15)), $[M - NMe_2]^+$ (m/z = 134 (45)), $[M - NHCHNMe_2]^+$ (m/z = 106 (60)), $[C_4H_9N_2]^+$ (m/z = 85 (46)), $[C_3H_7N_2]^+$ (m/z = 72 (6)), $[C_3H_8N]^+$ (m/z = 58 (16)) $[C_2H_4N]^+$ (m/z = 42 (31)) ions. Characteristic fragments for the alkylaryl (particularly ethylazinyl) group are also present in the mass spectrum of **1**: the $[C_6H_7N]^+$ (m/z = 93 (14)), $[C_5H_5N]^+$ (m/z = 79 (9)), $[C_5H_4N]^+$ (m/z = 78 (15)), $[C_5H_5]^+$ (m/z = 65 (5)), $[C_4H_3]^+$ (m/z = 51 (7)) ions.

GB Measurements. Gas-phase basicity was determined using the same FT-ICR mass spectrometer,[30] and the same procedure as described previously.[3b,8] The GB value was obtained from the equilibrium constants for the proton-transfer reaction (4) between the amidinazine (B) and a reference base (Ref) using relation (5). Two reference bases were used: 1,1,3,3-tetramethylguanidine (TMG) and 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN). The measurements were carried out at a FT-ICR cell temperature of 338 K.[31]

$$BH^+ + Ref \rightleftarrows B + RefH^+ \quad (4)$$

$$GB(B) = GB(Ref) + \Delta G(4) \quad (5)$$

Computational Details

The AM1 calculations[10] for various conformations of amidinazine **1** were performed using the HyperChem program.[32] For the most stable structures, selected at the AM1 level, ab initio calculations were carried out at the HF, MP2, and DFT-(B3LYP) levels[11−14] using the Gaussian 98 program.[33] The PA was estimated at the AM1 level (eq (6)) using the heats of formation ($\Delta_f H°$) calculated for the neutral and protonated forms, and the experimental $\Delta_f H°$ for the proton, $\Delta_f H°(H^+, g, 298.15\ K) = 367.2$ kcal mol^{-1}.[23] At the ab initio levels, the PA was estimated as a direct enthalpy change of the deprotonation reaction: $BH^+ \rightarrow B + H^+$ using eq (7). Equation (7) includes the changes in electronic energy, in zero-point vibrational energy, thermal corrections to energy, and the work term [Δ(pV)]. For the proton, only the translational energy term is not equal to zero ($^3/_2RT$ = 0.889 kcal mol^{-1} at 298.15 K). At ab initio levels, the gas-phase basicity (GB), eq (8), was calculated from the corresponding value of PA and the entropy term $T\Delta S = T[S(B) + S(H^+) - S(BH^+)]$, where T = 298.15 K and S is the sum of rotational, vibrational, and translational entropies. For the proton, only the translational entropy is not equal to zero [$S_{transl}(H^+) = 26.040$ cal mol^{-1} K^{-1}].[16]

$$PA = \Delta_f H°(B) + \Delta_f H°(H^+) - \Delta_f H°(BH^+) \quad (6)$$

$$PA = \Delta_r H_{298} = H_{298}(B) + H_{298}(H^+) - H_{298}(BH^+) \quad (7)$$

$$GB = PA - T\Delta S \quad (8)$$

The transition state for the proton transfer between the two possible sites of protonation in the "scorpio" conformations of the protonated forms was investigated at the DFT(B3LYP)/6-31G** level using the following procedure. First, the saddle point search was performed at the PM3 level,[34] using the package MOPAC2000.[35] The resulting PM3 structure was used as an initial geometry for the B3LYP/6-31G** optimization. The energy barrier for ITP was additionally computed using the modified[15] functional of Perdew−Wang (MPW1K) and the same basis set (6-31G**).

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Supporting Information Available: The most stable structures for the neutral and protonated (*N*-imino and *N*-aza) forms of **1**. Tables containing (i) rotational angles in the most stable structures of **1**, (ii) CN bond lengths in the most stable structures of **1**, (iii) total and relative energies for the protonated forms of **1**, and (iv) relative thermodynamic parameters for the protonated forms of **1**. Complete details of computational methods and results: DFT(B3LYP)/6-31G** and DFT(MPW1K)/6-31G**. This material is available free of charge via the Internet at http://pubs.acs.org.

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