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# $N_{\alpha},N_{\alpha}$ -Dimethylhistamine: A Biological Superbase in the Gas-Phase

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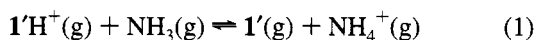
Received: June 14, 1994; In Final Form: March 8, 1995<sup>®</sup>

The gas-phase basicity ( $\Delta GB$ ) of the biological compound  $N_{\alpha},N_{\alpha}$ -dimethylhistamine (**1'**) relative to ammonia [defined as the standard Gibbs energy change for reaction 1 ( $1'H^+(g) + NH_3(g) \rightleftharpoons 1'(g) + NH_4^+(g)$ )] was measured by means of Fourier transform ion cyclotron resonance spectroscopy (FTICR). The various tautomer/conformers of **1'** and  $1'H^+(g)$  were studied by means of *ab initio* SCF-LCAO-MO calculations at the 6-31G//6-31G and 6-31G\*\*//6-31G\*\* levels. It was found that the combination of polarizability and chelation effects present in  $1'H^+(g)$  endows **1'** with an intrinsic basicity equal to that of  $N,N,N',N'$ -tetramethyl-1,8-naphthalenediamine (Proton Sponge).

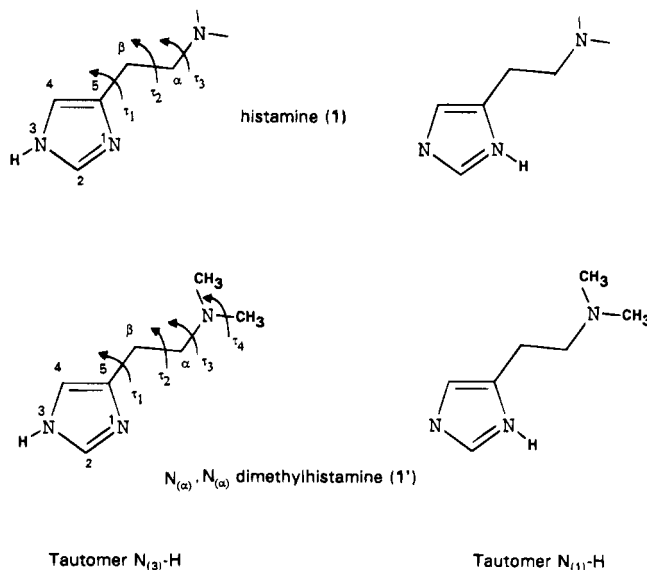
## Introduction

Experimental and theoretical results have recently been reported on the structure<sup>1–3</sup> and intrinsic (gas-phase) basicity<sup>2</sup> of 4(5)-(2-aminoethyl)imidazole (histamine, **1**; Figure 1). Several important features of **1(g)** and  $1'H^+(g)$  were singled out. Chelation, in particular, was found to profoundly affect the structure and stability of these species. This has prompted us to investigate the result of replacing the two amino hydrogens in **1** by methyl groups. The resulting compound,  $N_{\alpha},N_{\alpha}$ -dimethylhistamine<sup>4</sup> (**1'**; Figure 1), is also a natural compound,<sup>5</sup> endowed with high biological activity.<sup>6</sup> Current models on the binding of histamine to its  $H_2$  receptors involve proton relay<sup>6,7</sup> and bidentate chelation.<sup>8</sup> Furthermore, while the aqueous  $pK_a$ 's of these molecules are known,<sup>9,10</sup> we are not aware at this point of any experimental evidence indicating that **1** and **1'** bind to histamine receptors in an environment of bulk water. Actually, it is likely that these processes take place in protein cavities wherein the latter is probably absent. We thus expect our results to be potentially useful for the understanding of the acid–base equilibria of these compounds in molecular environments less efficient at delocalizing positive charge through hydrogen bonding (HyB) than bulk water.

Here we present and discuss the results of an *ab initio* SCF-LCAO-MO study of **1'** and  $1'H^+$ , together with the gas-phase basicity of **1'** relative to ammonia,  $\Delta GB(1')$ , determined experimentally by means of Fourier transform ion cyclotron resonance spectrometry (FTICR).<sup>11</sup>  $\Delta GB(1')$  is defined as the standard Gibbs energy change for reaction 1.



The *ab initio* study of **1'** and  $1'H^+$  was carried out first at the 6-31G//6-31G level,<sup>12</sup> for previous work<sup>1–3</sup> had shown it



**Figure 1.** Notation used in structural study of **1(g)** and **1'(g)** and their protonated forms.

to be quite satisfactory for the treatment of the structure and energetics of the various tautomer/conformers (T/C's) of **1** and  $1'H^+$ . Then, the structures of the most stable conformers found at this level were reoptimized at the 6-31G\*\*//6-31G\*\* level.

## Theoretical Treatment and Discussion

For the general discussion, the 6-31G//6-31G results (as summarized in Tables 1–4, given as supplementary material) will be used. Finer structural details and energetics will be examined by means of the 6-31G\*\*//6-31G\*\* data (Tables 5–7). Broadly speaking, the results obtained with both basis sets are quite similar. More precisely (i) with the exception of the  $N \cdots H$  distances in the chelated protonated forms, wherein the differences reach 0.1 Å, all other distances differ by 0.01–0.02 Å at the most, and (ii) differences in both series of angles range between  $-1.8^\circ$  and  $2.9^\circ$ , the signed and unsigned average values being  $0.5^\circ$  and  $1.0^\circ$ , respectively. As usual, dihedral

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<sup>®</sup> Abstract published in *Advance ACS Abstracts*, May 1, 1995.

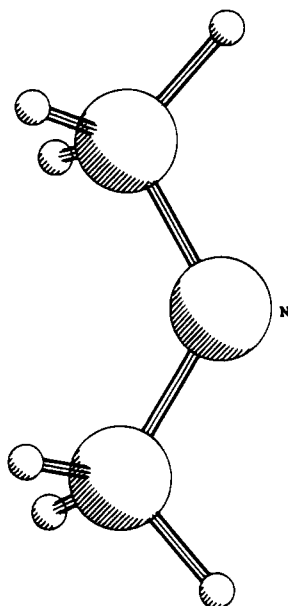


Figure 2. Conformation of the two methyl groups.

angles are more basis-sensitive, differences ranging between  $-10.6^\circ$  and  $14.0^\circ$ , with signed and unsigned averaged values of  $0.7^\circ$  and  $4.6^\circ$ , respectively.

The main geometrical parameters for **1'** and **1'H<sup>+</sup>** are shown in Figure 1 (notations for **1** are the same as in ref 2). In both cases, the origin of the conformational coordinates is taken with respect to the *syn* configuration:  $\tau_1$  is taken with N1 in a *syn* configuration with respect to C( $\alpha$ ).<sup>17</sup>  $\tau_3^1$  and  $\tau_3^2$  correspond to the dihedral angles of both N-CH<sub>3</sub> groups,  $\tau_3^2$  being defined with respect to  $\tau_3^1$ .  $\tau_4^1$  and  $\tau_4^2$  define the configurations of the three hydrogens on each methyl group. For a given T/C the set of  $\tau_1$ ,  $\tau_2$ ,  $\tau_3$  values is found to be quite insensitive to changes in the optimized values of  $\tau_4$ , namely  $\tau_4^1$  and  $\tau_4^2$ . Thus, the optimization of these angles was limited to the neighborhood of  $\tau_4^1 = -60^\circ$  and  $\tau_4^2 = 60^\circ$ , corresponding to an *anti* configuration for the two hydrogens on different methyl groups and laying on the CNC plane (Figure 2). This was the only restriction applied in the geometry optimization.

Two main groups of conformers are found for  $\tau_2$  values near  $60^\circ$  (*gauche*, G) and  $180^\circ$  (*trans*, T). Following Brown,<sup>1</sup> the range of variation of angles  $\tau_1$  and  $\tau_3$  is divided into sections, labeled I-V and a-c, respectively.

The structural parameters and energies pertaining to the various T/C's of **1'** are given in Tables 1 (N2-H tautomer) and 2 (N3-H tautomer), which are in the supplementary material. These structural parameters are determined at the 6-31G//6-31G level.

Figure 3 portrays the various conformers for the N<sub>(1)</sub>-H tautomer. The most stable one (G-IVa) corresponds to a nuclear arrangement involving an internal hydrogen bond, N<sub>(1)</sub>-H...N( $\alpha$ ). This bond is bent (angle N<sub>(1)</sub>-H...N( $\alpha$ ) =  $123.1^\circ$ ), and according to Kern and Allen's rule<sup>18a</sup> its stability can be estimated at *ca.* 55% of the hypothetical linear arrangement.<sup>18b</sup> Table 1 of the supplementary material shows also a significant stretching of the N<sub>(1)</sub>-H bond. Energetically, at the 6-31G level, chelation contributes to make G-IVa some 5 kcal/mol more stable than the other (unchelated) G conformers of the same tautomer. We find three different T conformers with similar values for  $\tau_1$  and  $\tau_2$  and differing mostly in  $\tau_3$ . They are some 3.8 kcal/mol less stable than G-IVa. It is of interest that the angle C( $\alpha$ )C( $\beta$ )C(5) is larger in G than in T conformers, likely

reflecting an enhanced repulsion between the NMe<sub>2</sub> and the imidazole moieties. This possibly explains why the angles N( $\alpha$ )C( $\alpha$ )C( $\beta$ ) and C(CH<sub>3</sub>)N( $\alpha$ )C( $\alpha$ ) are largest in the c region of the  $\tau_3$  manifold.

The five T and five G conformers for the N<sub>(3)</sub>-H tautomer are presented in Figures 4 and 5, respectively. In what follows, all energies are positive and referred to the N<sub>(1)</sub>-H/G-IVa tautomer/conformer. The energies of the G conformers are in the range 2.7–5.9 kcal/mol, the most stable conformer being IIa. As for the N<sub>(1)</sub>-H tautomer, the C( $\alpha$ )C( $\beta$ )C(5) angles are larger for the G than for the T conformers and the N( $\alpha$ )C( $\alpha$ )C( $\beta$ ) and C(CH<sub>3</sub>) angles are largest in the c region of the  $\tau_3$  manifold, the reasons for this being likely the same. The energies of the T conformers are very similar and close to 2.8 kcal/mol, thus showing the small influence of the angles  $\tau_1$  and  $\tau_2$  on the stabilities of the T conformers of the N<sub>(3)</sub>-H tautomer. With respect to the case of **1**, the number of stationary points is larger, probably because in **1'** configurations are not "frozen" by HyB (however weak) between the hydrogens of the amino group and the  $\pi$  system of the ring.<sup>1-3</sup> The total energies and geometries of the eight most stable T/C's of **1'** at the 6-31G\*\*//6-31G\*\* level are shown in Table 5. Data for **1'H<sup>+</sup>** are collected in Table 3 in the supplementary material. The most stable structures for this species (A<sup>+</sup> and B<sup>+</sup>) are depicted in Figure 6. For comparison purposes, the unchelated form C<sup>+</sup> and E<sup>+</sup> are also shown. For **1'H<sup>+</sup>**, the most stable structure is B<sup>+</sup>, with a chelated N<sub>(3)</sub>-H G configuration. Above it, we find structure A<sup>+</sup>. It is also chelated, but now protonation takes place in the imidazole ring.

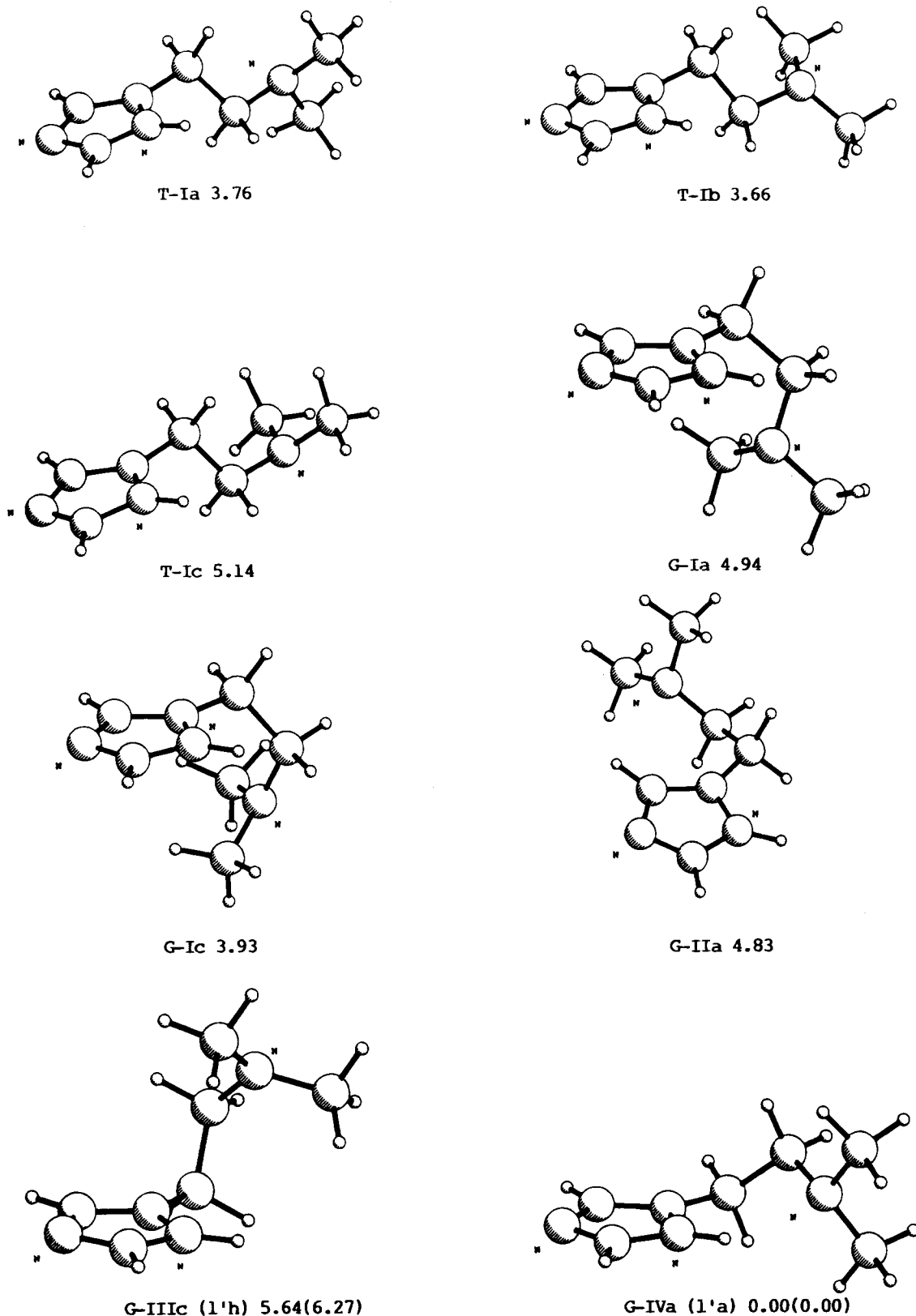
The ranking of stabilities in **1H<sup>+</sup>** was found<sup>2,3</sup> to be the opposite, the energy gap being small, however. These differences between **1H<sup>+</sup>** and **1'H<sup>+</sup>** likely reflect the large increase in the intrinsic basicity of the amino nitrogen brought about by the N-methyl substitution.<sup>19</sup> This effect overrides differences in HyB stabilization energies. Thus, the strength of the HyB in B<sup>+</sup> is lower than that in the corresponding tautomer of **1H<sup>+</sup>**, as seen by comparing the distances N( $\alpha$ )-H and N<sub>(1)</sub>...H in **1'H<sup>+</sup>**/**1H<sup>+</sup>**: 1.034/1.048 Å, 1.776/1.719 Å. Interesting, the opposite holds for the A<sup>+</sup> structures. The hydrogen bonds in both A<sup>+</sup> and B<sup>+</sup> are bent:  $133.6^\circ$  and  $145.2^\circ$ , respectively. Using Kerns and Allen's rule,<sup>18a</sup> it follows that chelation is stronger in B<sup>+</sup> than in A<sup>+</sup>. The opposite applies to **1H<sup>+</sup>**.

The T/C's of the cation are also calculated at the 6-31G\*\*//6-31G\*\* level (Table 2 in the supplementary material). The difference of energy between A<sup>+</sup> and B<sup>+</sup> is slightly larger with this basis set, because the hydrogen bonds are stronger at the 6-31G level, especially A<sup>+</sup>.

For the purpose of comparing theoretical and experimental results, a number of isodesmic reactions<sup>20</sup> were devised. They involve imidazole (**2**) and ethyldimethylamine (**3**) and their protonated forms. Structural and energetic data for **2**, **2H<sup>+</sup>**, **3**, and **3H<sup>+</sup>** are shown in Table 7 (and in Table 4 of the supplementary material). As shown in parentheses in Tables 1 and 2 in the supplementary material and in Table 5, a more compact notation is used for the most stable T/C's of **1'**, **1'-1'g**. The species **1'h** does not belong to this set but has been included in order to illustrate conformational effects.

The energetics of the isodesmic reactions 9–13 are summarized in Table 8.

Assuming equal entropies for species **1'a–1'g**, reactions 2–7 lead to the following distributions of T/C's in a gaseous sample of **1'(g)** at 333 K (nominal temperature of the FTICR experiments) at the 6-31G (6-31G\*\*) level: **1'a**, 90.3 (89.7); **1'b**, 1.5

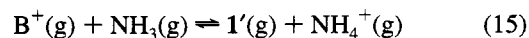
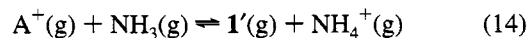


**Figure 3.** Conformers of the *N*<sub>1</sub>-H tautomer of 1'(g); potential energy in kcal/mol at the 6-31G//6-31G and 6-31G\*\*//6-31G\*\* (values in parentheses) levels.

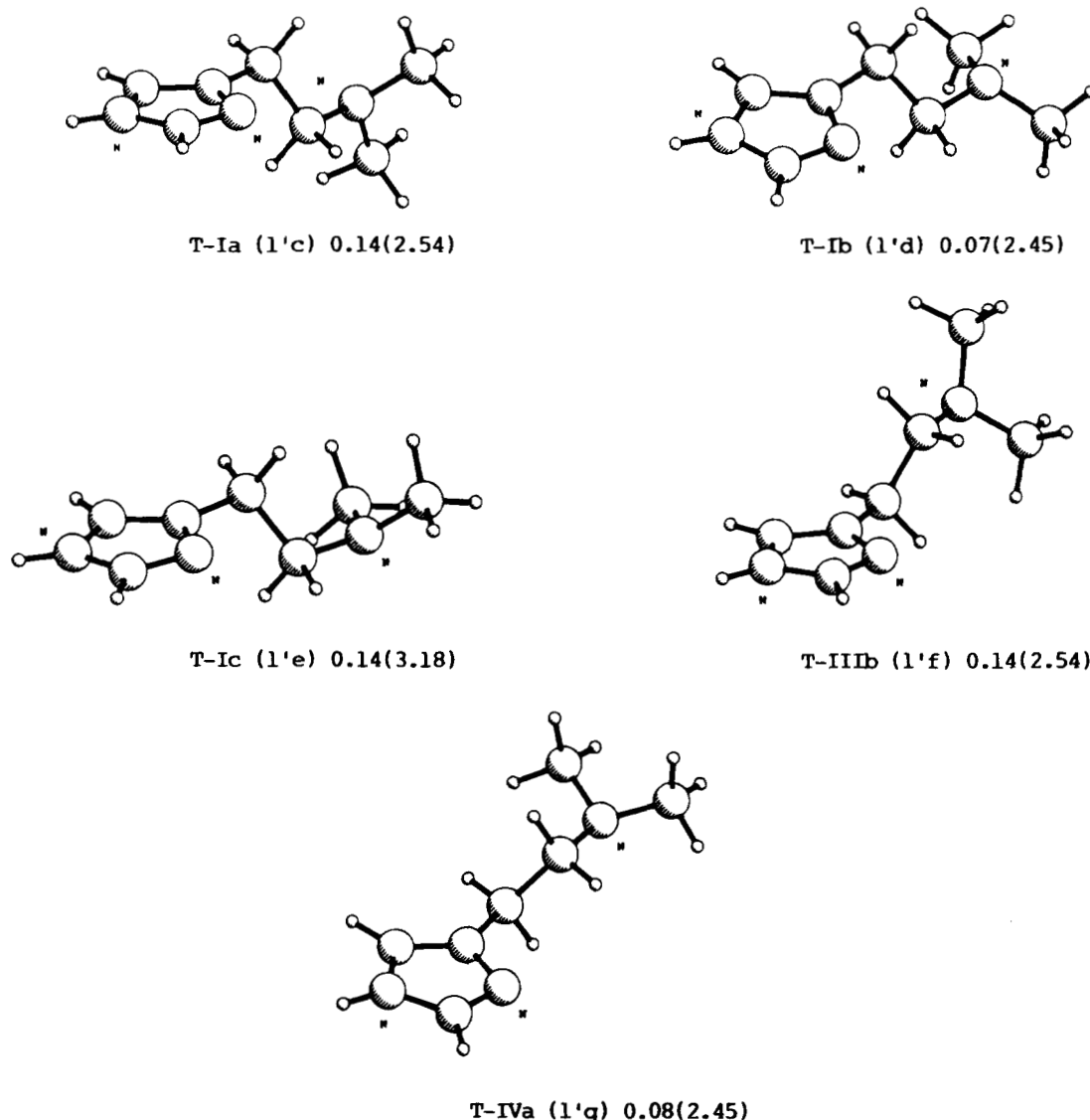
(1.5); 1'd, 1.4 (2.2); 1'g, 1.3 (2.2); 1'c, 1'e, and 1'f, 1.2 (1.8, 0.7, and 1.9, respectively).

The results can be linked to experimental proton affinities relative to ammonia (standard enthalpy changes for reaction 1, ΔPA, by using the experimental values ΔPA (2) = 21.0 kcal/mol and ΔPA(3) = 25.1 kcal/mol.<sup>21</sup> Using these values, together with data from Table 8, we derive the energy changes

for reactions 14 and 15: Δ*E*(14) = 33.0 (32.8) kcal/mol and Δ*E*(15) = 41.8 (40.1) kcal/mol at the 6-31G (6-31G\*\*) level.



Notice that both basis sets lead to quite comparable results.



**Figure 4.** *Trans* conformers of the N3-H tautomer of 1'(g); potential energy in kcal/mol at the 6-31G//6-31G and 6-31G\*\*//6-31G\*\* (values in parentheses) levels.

Assuming reasonably close entropy changes for these two reactions, it is clear that B<sup>+</sup> is by far the most likely structure for 1'H<sup>+</sup>(g). Species C<sup>+</sup>, D<sup>+</sup>, and E<sup>+</sup> are unchelated and unlikely to exist in appreciable quantities in an actual sample of 1'H<sup>+</sup>(g) under our working conditions. They are useful, however, because they allow us to get an insight into the stabilizing role played by chelation. Notice that species D<sup>+</sup>, which shares with 1'h the energetically unfavorable conformation about the bond (as defined by  $\tau_1$ ), is appreciably less stable than C<sup>+</sup> and E<sup>+</sup>, thus reflecting the unfavorable skeletal conformation. The importance of chelation at increasing stability of 1'H<sup>+</sup>, irrespective of the protonation site, is shown by the values of  $\Delta E(11)$  and  $\Delta E(13)$  (Table 8).

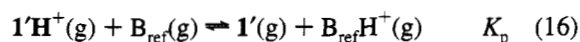
### Experimental Results and Conclusions

The sample of 1' used in this work was synthesized by selective methylation of histamine, as described by Ham.<sup>22</sup> FTICR experiments were performed on a modified CMS-47 mass spectrometer used in previous studies.<sup>23</sup> The high-field strength (4.7 T) of its superconducting magnet easily allows the monitoring of proton exchange processes for 20 s or more under nominal pressures of  $(1-2) \times 10^{-6}$  mbar. The main modification in the spectrometer is the insertion of Balzers BVB 063H butterfly valve between the high-vacuum turbomolecular

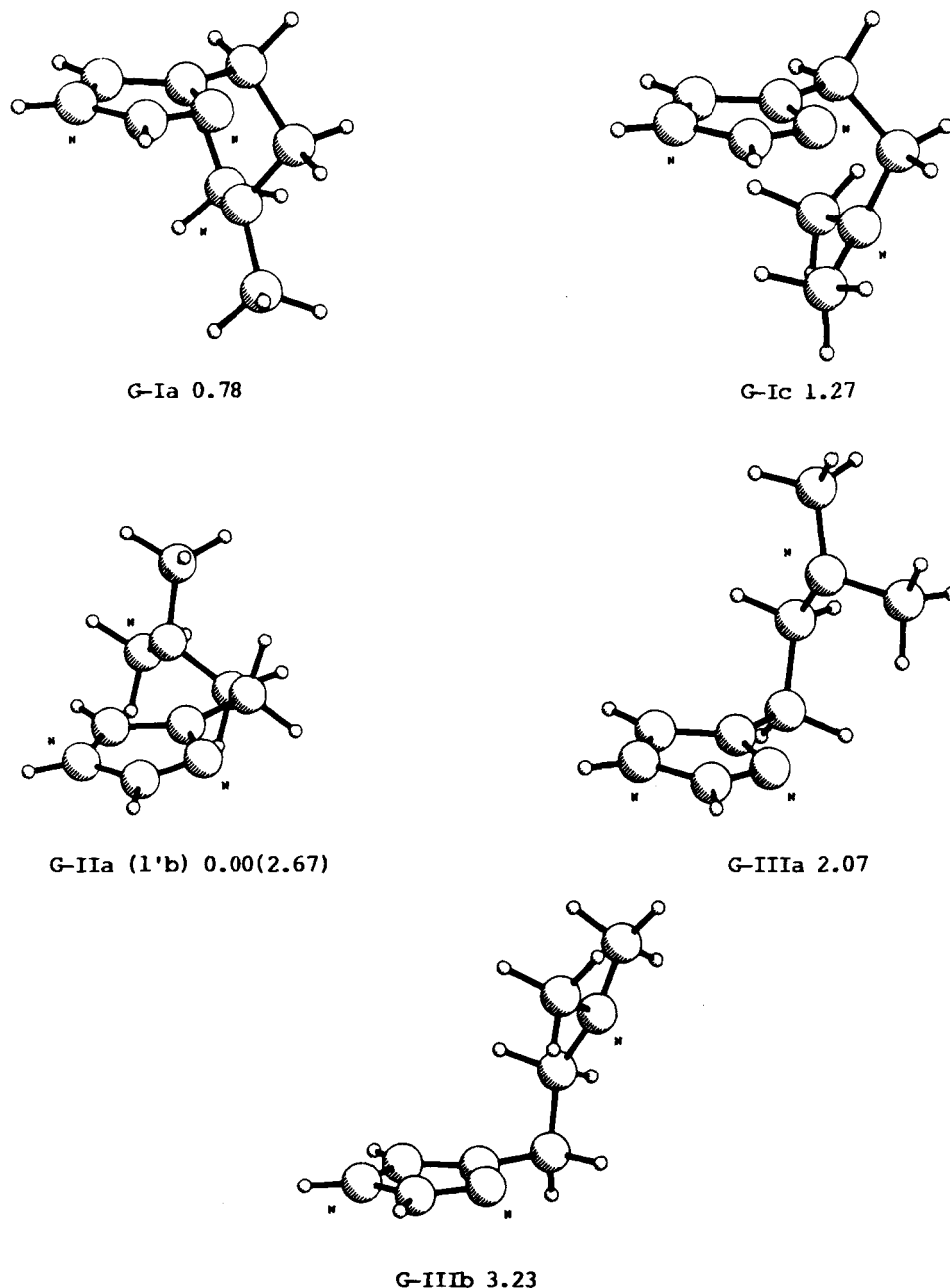
pump and the section containing the ion-trapping cell and the Bayard-Alpert ionization gauge. This allows the efficient reduction of the gas flow, thus minimizing the pressure gradient between the cell and the head of the ionization gauge. In every case, the readings provided by the Bayard-Alpert gauge were calibrated against an MKS baraton capacitance manometer. The nominal average temperature of the cell is 333 K. Usual reaction times were 10–15 s with samplings every 0.5 or 1 s. The spectra used for quantitative equilibrium studies were obtained using the rapid scan/cross correlation technique,<sup>24</sup> as it is known to yield accurate relative ion intensities.

Although kinetic studies are important, in our case, attention was primarily focused on thermodynamic aspects, and so detailed kinetic information was not obtained. This notwithstanding, it was observed that 1 s after the ionization pulse, the ratio of the relevant ion intensities did not differ from the values obtained after 5–20 s by more than 5–10% (with pressures in the range indicated above).

Experimentally, we determined the equilibrium constant  $K_p$  for equilibrium 16:



wherein B<sub>ref</sub> are selected reference bases.



**Figure 5.** *Gauche* conformers of the N3-H tautomer of 1'(g); potential energy in kcal/mol at the 6-31G//6-31G and 6-31G\*\*//6-31G\*\* (values in parentheses) levels relative to 1'a.

The gas-phase basicity of 1' relative to ammonia,  $\Delta\text{GB}(1')$ , that is, the standard Gibbs energy change for reaction 1, is given by eq 17:

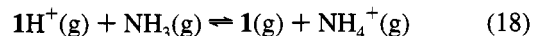
$$\Delta\text{GB}(1') = \Delta\text{GB}(\text{B}_{\text{ref}}) + \delta\Delta\text{GB}(1') \quad (17)$$

where  $\delta\Delta\text{GB}(1') = -RT \ln K_p$ . Experimental  $K_p$  values were the average of at least six different experiments carried out using different pressure ratios and total pressures of the neutral species. In every case, double resonance experiments confirmed the existence of the proton exchange embodied in reaction 16.

As reference bases, we used *N,N,N',N'*-tetramethyl-1,3-diaminopropane (TMP,  $\Delta\text{GB} = 38.8$  kcal/mol<sup>25</sup>), 1,1,3,3-tetramethylguanidine (TMG,  $\Delta\text{GB} = 42.0$  kcal/mol<sup>25</sup>), and *N,N,N',N'*-tetramethyl-1,4-diaminobutane (TMB,  $\Delta\text{GB} = 41.6$  kcal/mol, this work). A multiple-overlap study of these references and 1' was carried out. The results are summarized in Figure 7 and are seen to be quite self-consistent. The resulting value of  $\Delta\text{GB}(1')$  is  $41.3 \pm 0.2$  kcal/mol.

The FTICR experiments do not lead directly to proton affinities. The determination of  $\Delta\text{PA}(1')$  thus requires an independent estimation of the entropy change pertaining to reaction 1.

On the basis of the previous experimental determinations,<sup>26</sup> we had estimated<sup>2</sup> the entropy change,  $\Delta S$ , for reaction 18 at ca. 3.25 cal/(mol·K).

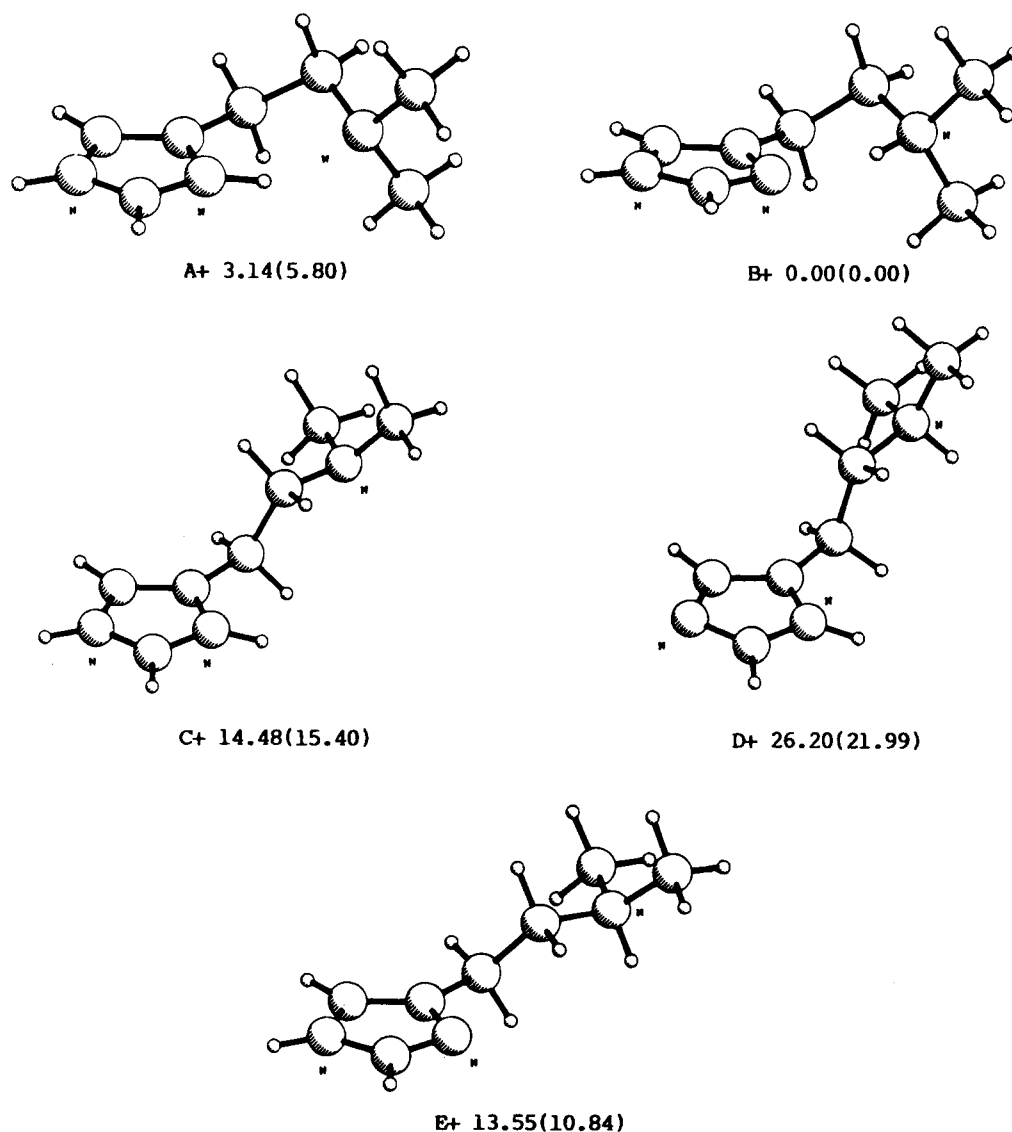


This value includes two main contributions: one originates in the ratio of symmetry numbers of  $\text{NH}_3$  (3) and  $\text{NH}_4^+$  (12) and amounts of  $-R \ln 4$  ( $-2.75$  cal/(mol·K)). The other, positive, is associated with the cyclation entropy of  $\text{1H}^+$  and amounts to 6 cal/(mol·K).<sup>2</sup> Here, again, a value of 6 cal/(mol·K) is taken for the cyclation entropy of  $\text{1'H}^+(\text{g})$ . The reason for this choice is as follows: according to Aue and Bowers,<sup>27</sup> the entropy changes for the gas-phase protonation of the couples of  $\alpha,\omega$ -diamines  $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NH}_2/\text{H}_2\text{N}(\text{CH}_2)_n\text{NH}_2$  and  $\text{Me}_2\text{N}-$

**TABLE 5: Relevant Geometrical Parameters<sup>a</sup> (6-31G\*\*//6-31G\*\*) for the Eight Significant Conformers of the N<sub>(1)</sub>-H and N<sub>(3)</sub>-H Tautomers of N,N-Dimethylhistamine**

| parameter  | G-IIIc (1'h) | G-IVa (1'a) | T-Ia (1'e) | T-Ib (1'd) | T-Ic (1'e) | T-IIIb (1'f) | T-IVa (1'g) | G-IIa (1'b) |
|--|--------------|-------------|------------|------------|------------|--------------|-------------|-------------|
| C <sub>(β)</sub> C <sub>(5)</sub>                                  | 1.501        | 1.498       | 1.499      | 1.499      | 1.498      | 1.499        | 1.493       | 1.502       |
| C <sub>(α)</sub> C <sub>(β)</sub>                                  | 1.545        | 1.532       | 1.532      | 1.531      | 1.541      | 1.532        | 1.534       | 1.528       |
| N <sub>(α)</sub> C <sub>(α)</sub>                                  | 1.446        | 1.461       | 1.455      | 1.453      | 1.450      | 1.455        | 1.460       | 1.455       |
| N <sub>(α)</sub> (CH <sub>3</sub> ) <sup>1</sup>                   | 1.446        | 1.452       | 1.448      | 1.447      | 1.443      | 1.447        | 1.454       | 1.448       |
| N <sub>(α)</sub> (CH <sub>3</sub> ) <sup>2</sup>                   | 1.440        | 1.451       | 1.447      | 1.447      | 1.444      | 1.448        | 1.455       | 1.448       |
| HN <sub>(1)</sub>  | 0.992        | 0.995       | 0.992      | 0.992      | 0.992      | 0.992        | 0.992       | 0.992       |
| C <sub>(β)</sub> C <sub>(5)</sub> N <sub>(1)</sub>                 | 123.2        | 123.1       | 121.4      | 121.4      | 121.2      | 121.4        | 121.3       | 119.6       |
| C <sub>(α)</sub> C <sub>(β)</sub> C <sub>(5)</sub>                 | 116.2        | 114.0       | 112.1      | 111.9      | 111.7      | 112.1        | 112.2       | 116.0       |
| N <sub>(α)</sub> C <sub>(α)</sub> C <sub>(β)</sub>                 | 119.1        | 113.6       | 112.9      | 113.1      | 116.9      | 112.9        | 112.4       | 115.4       |
| C(CH <sub>3</sub> ) <sup>1</sup> N <sub>(α)</sub> C <sub>(α)</sub> | 117.2        | 112.6       | 113.1      | 111.7      | 114.9      | 111.7        | 115.0       | 113.5       |
| C(CH <sub>3</sub> ) <sup>2</sup> N <sub>(α)</sub> C <sub>(α)</sub> | 115.5        | 111.4       | 111.7      | 113.4      | 114.9      | 113.1        | 114.6       | 110.9       |
| τ <sub>1</sub>   | 254.7        | 312.4       | 67.4       | 61.9       | 66.3       | 292.7        | 300.6       | 159.2       |
| τ <sub>2</sub>   | 67.3         | 66.0        | 176.7      | 186.6      | 183.1      | 183.5        | 176.4       | 60.1        |
| τ <sub>3</sub>   | 282.3        | 75.5?       | 73.7       | 161.2      | 294.7      | 160.5        | 72.4        | 62.2        |
| τ <sub>3</sub> <sup>2</sup> <sup>b</sup>                           | 138.0        | 124.2?      | 125.9      | 126.4      | 133.4      | 125.9        | 126.4       | 126.0       |
| τ <sub>4</sub> <sup>1</sup>  | -43.3        | -58.6       | -58.8      | -57.4      | -48.8      | -57.9        | -59.3       | -62.5       |
| τ <sub>4</sub> <sup>2</sup>  | 45.9         | 59.0        | 58.1       | 59.3       | 48.4       | 58.9         | 57.4        | 57.3        |
| total energy <sup>c</sup>  | -435.98277   | -435.99276  | -435.98872 | -435.98885 | -435.98769 | -435.98872   | -435.98885  | -435.98851  |

<sup>a</sup> Bond distances in Å, and bond angles in deg. <sup>b</sup> The dihedral angle is taken with respect to the previous methyl angle. <sup>c</sup> Energies in atomic units.



**Figure 6.** Selected tautomer/conformers of 1'H<sup>+</sup>(g); potential energy in kcal/mol at the 6-31G//6-31G and 6-31G\*\*//6-31G\*\* (values in parentheses) levels relative to B<sup>+</sup>.

(CH<sub>2</sub>)<sub>n</sub>NMe<sub>2</sub>/H<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub> (2 ≤ n ≤ 4) are independent of the N-methyl substitution. For reasons indicated in ref 2, the case of n = 2 was considered to be a convenient model for

reaction 18. Thus, at 333 K (the nominal working temperature), the TΔS term for reaction 1 is at least 1.1 kcal/mol. A lower limit of ΔPA(1') is thus 42.3 kcal/mol, in remarkably good

**TABLE 6: Relevant Geometrical Parameters<sup>a</sup> (6-31G\*\*//6-31G\*\*) for Five Relevant Tautomer/Conformers of the N<sub>α</sub>,N<sub>α</sub>-Dimethylhistamine Monocation**

| parameter  | N <sub>(1,3)</sub> -H(A <sup>+</sup> ) | N <sub>(3)</sub> -H(B <sup>+</sup> ) | N <sub>(1,3)</sub> -H(C <sup>+</sup> ) | N <sub>(1)</sub> -H(D <sup>+</sup> ) | N <sub>(3)</sub> -H(E <sup>+</sup> ) |
|--|--|--------------------------------------|--|--------------------------------------|--------------------------------------|
| C <sub>(β)</sub> C <sub>(5)</sub>                                  | 1.502                                  | 1.503                                | 1.498                                  | 1.497                                | 1.500                                |
| C <sub>(α)</sub> C <sub>(β)</sub>                                  | 1.535                                  | 1.529                                | 1.539                                  | 1.532                                | 1.528                                |
| N <sub>(α3)</sub> C <sub>(α)</sub>                                 | 1.464                                  | 1.504                                | 1.443                                  | 1.511                                | 1.509                                |
| N <sub>(α)</sub> (CH <sub>3</sub> ) <sup>1</sup>                   | 1.461                                  | 1.486                                | 1.452                                  | 1.494                                | 1.491                                |
| N <sub>(α)</sub> (CH <sub>3</sub> ) <sup>2</sup>                   | 1.461                                  | 1.486                                | 1.453                                  | 1.495                                | 1.493                                |
| HN <sub>(1)</sub>  | 1.012                                  | 1.876                                | 0.998                                  | 0.993                                |                                      |
| HN <sub>(3)</sub>  | 0.997                                  | 0.995                                | 0.998                                  |                                      | 0.994                                |
| HN <sub>α</sub>  | 2.023                                  | 1.023                                |  | 1.008                                | 1.008                                |
| C <sub>(β)</sub> C <sub>(5)</sub> N <sub>(1)</sub>                 | 121.3                                  | 120.4                                | 122.6                                  | 124.1                                | 119.1                                |
| C <sub>(α)</sub> C <sub>(β)</sub> C <sub>(5)</sub>                 | 113.1                                  | 112.9                                | 112.7                                  | 110.2                                | 109.1                                |
| N <sub>(α)</sub> C <sub>(α)</sub> C <sub>(β)</sub>                 | 113.3                                  | 113.1                                | 111.4                                  | 113.7                                | 113.1                                |
| C(CH <sub>3</sub> ) <sup>1</sup> N <sub>(α)</sub> C <sub>(α)</sub> | 112.5                                  | 113.2                                | 113.4                                  | 113.3                                | 113.4                                |
| C(CH <sub>3</sub> ) <sup>2</sup> N <sub>(α)</sub> C <sub>(α)</sub> | 110.8                                  | 111.4                                | 112.1                                  | 111.0                                | 111.1                                |
| τ <sub>1</sub>   | 322.0                                  | 318.8                                | 286.8                                  | 275.3                                | 308.5                                |
| τ <sub>2</sub>   | 60.1                                   | 59.9                                 | 171.0                                  | 176.2                                | 163.4                                |
| τ <sub>3</sub> <sup>1</sup>  | 74.7                                   | 70.9                                 | 74.0                                   | 65.8                                 | 64.3                                 |
| τ <sub>3</sub> <sup>2</sup> <sub>b</sub>                           | 123.7                                  | 126.2                                | 126.9                                  | 125.5                                | 126.1                                |
| τ <sub>4</sub> <sup>1</sup>  | -60.2                                  | -59.2                                | -59.6                                  | -61.0                                | -60.1                                |
| τ <sub>4</sub> <sup>2</sup>  | 59.3                                   | 59.0                                 | 55.1                                   | 53.5                                 | 56.5                                 |
| total energy <sup>c</sup>  | -436.39750                             | -436.40675                           | -436.38221                             | -436.37170                           | -436.38947                           |

<sup>a</sup> Bond distances in Å, and bond angles in deg. <sup>b</sup> The dihedral angle is taken with respect to the previous methyl angle. <sup>c</sup> Energies in atomic units.

**TABLE 7: Total Energies for Imidazole (2)<sup>a</sup> and Its Protonated Form and Selected Dihedral Angles<sup>b</sup> [6-31G//6-31G and 6-31G\*\*//6-31G\*\* (in Parentheses)] and Total Energies for N<sub>α</sub>,N<sub>α</sub>-Dimethylethylamine (3) and Its Protonated Form**

| parameter                                | 2            | 2H <sup>+</sup> | 3             | 3H <sup>+</sup> |
|--|--------------|-----------------|---------------|-----------------|
| τ <sub>1</sub>                           |              |                 | 59.5 (52.5)   | 59.1 (55.1)     |
| τ <sub>2</sub>                           |              |                 | 7.8 (7.8)     | 6.5 (7.0)       |
| τ <sub>3</sub> <sup>1</sup>              |              |                 | 65.9 (67.8)   | 66.9 (65.0)     |
| τ <sub>3</sub> <sup>2</sup> <sub>c</sub> |              |                 | 133.1 (126.2) | 125.1 (125.8)   |
| τ <sub>4</sub> <sup>1</sup>              |              |                 | -57.0 (-60.2) | -60.6 (-60.5)   |
| τ <sub>4</sub> <sup>2</sup>              |              |                 | 53.6 (57.6)   | 57.8 (57.1)     |
| total energy <sup>d</sup>                | -224.70975   | -225.10344      | -212.20864    | -212.60027      |
| (total energy <sup>d</sup> )             | (-224.82430) | (-225.21063)    | (-212.32074)  | (-212.71068)    |

<sup>a</sup> The values are taken from ref 2. <sup>b</sup> Bond distances in Å, and bond angles in deg. <sup>c</sup> The dihedral angle is taken with respect to the previous methyl angle. <sup>d</sup> Energies in atomic units.

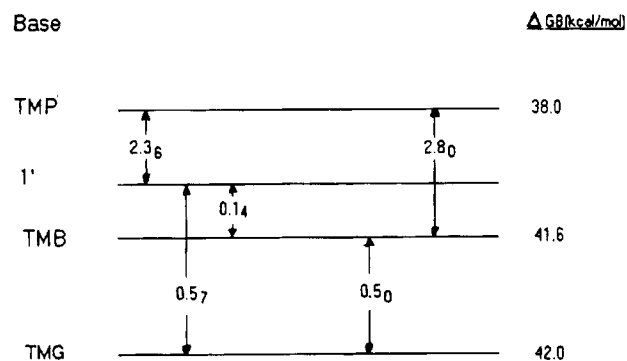
**TABLE 8: Calculated (6-31G//6-31G and 6-31GH\*\*//6-31G\*\*) Energy Changes for Isodesmic Reactions 2–13**

| eq no. | reaction                                   | ΔE(6-31G) <sup>a</sup> | ΔE(6-31G**) <sup>a</sup> |
|--------|--|------------------------|--------------------------|
| 2      | 1'a → 1'b                                  | 2.71                   | 2.71                     |
| 3      | 1'a → 1'c                                  | 2.85                   | 2.57                     |
| 4      | 1'a → 1'd                                  | 2.78                   | 2.45                     |
| 5      | 1'a → 1'e                                  | 2.85                   | 3.20                     |
| 6      | 1'a → 1'f                                  | 2.85                   | 2.56                     |
| 7      | 1'a → 1'g                                  | 2.78                   | 2.45                     |
| 8      | 1'a → 1'h                                  | 5.64                   | 6.27                     |
| 9      | A <sup>+</sup> + 2 → 1'a + 2H <sup>+</sup> | 12.82                  | 11.55                    |
| 10     | B <sup>+</sup> + 3 → 1'b + 3H <sup>+</sup> | 19.96                  | 17.44                    |
| 11     | 1'a + 2H <sup>+</sup> → C <sup>+</sup> + 2 | -1.48                  | -1.95                    |
| 12     | 1'h + 3H <sup>+</sup> → D <sup>+</sup> + 3 | 3.31                   | 0.69                     |
| 13     | 1'a + 3H <sup>+</sup> → E <sup>+</sup> + 3 | -3.70                  | -4.20                    |

<sup>a</sup> Energies in kcal/mol.

agreement with the calculated values. This estimate of TΔS is, actually, quite conservative. Thus, if we use the experimental values of the cyclation entropies of α,ω-diamines experimentally determined by Kebarle,<sup>26b</sup> a value of *ca.* 5.1 kcal/mol is obtained for TΔS. This would lead to a somewhat larger ΔPA value for 1': 46.4 kcal/mol.

In the case of N,N,N',N'-tetramethyl-1,8-naphthalenediamine (Proton Sponge), ΔGB amounts to 40.9 kcal/mol,<sup>21</sup> essentially the same value as ΔGB(1'). Thus, the combination of the high HyB basicity of the imidazole moiety and the important intrinsic basicity of the substituted amino group makes 1'(g) a superbases. These results also show, in the case of polyfunctional bases leading to chelated protonated species, the possibility of easily

**Figure 7.** Multiple overlap diagram pertaining to the experimental determination of ΔGB(1').

shifting the protonation site by appropriate substitutions around one of the basic centers.

Last, these studies have revealed some very important differences between 1 and 1'. Thus, in 1H<sup>+</sup>(g) there is a delicate balance between the intrinsic basicities of the ring and side-chain nitrogens and the stabilization provided by chelation,<sup>2,3</sup> this balance being easily tipped off by the solvent. Here, the N-methylation enhances the intrinsic basicity of 1' but at the same time "locks" the proton on the N(CH<sub>3</sub>)<sub>2</sub> group, both in solution and in the gas phase.

**Acknowledgment.** This work was supported by DGICYT Grants PB90-0279 and PB93-0320-CO2-01. The authors are grateful to the Centro de Supercomputación de Galicia for



providing computational facilities. We thank one of the reviewers for valuable comments.

**Supplementary Material Available:** Tables 1–4 showing geometric parameters and total energies (4 pages). Ordering information is given on any current masthead page.

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JP9414665