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# Gas-phase proton affinities of guanidines with heteroalkyl side chains

Zoran Glasovac [a,*], Vjekoslav Štrukil [a], Mirjana Eckert-Maksić [a], Detlef Schröder [b,*], Malgorzata Kaczorowska [c], Helmut Schwarz [c,*]

[a] *Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, POB 180, HR-10002 Zagreb, Croatia*
[b] *Institute of Organic Chemistry and Biochemistry, Flemingovo nám. 2, 16610 Prague 6, Czech Republic*
[c] *Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, 10623 Berlin, Germany*

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Dedicated to Dr. Thomas Weiske on the occasion of his 50th birthday.

**Abstract**

The gas-phase proton affinities (PAs) of four novel guanidine derivatives, with three of them incorporating heteroalkyl groups capable of forming intramolecular hydrogen bonds, are determined by the extended kinetic method. In addition, the PAs of two other guanidines are evaluated using the simple variant of the kinetic method. The proton affinities of the investigated bases fall in the range of 251–264 kcal mol$^{-1}$ and are thus 16–29 kcal mol$^{-1}$ larger than the proton affinity of the parent compound guanidine. It is shown that the formation of intramolecular hydrogen bonds, where possible, significantly contributes to the basicity of the guanidine bases under study.


*Keywords:* Density functional theory; Guanidine; Kinetic method; Mass spectrometry; Proton affinity

## 1. Introduction

Guanidine derivatives attract broad attention due to their versatile chemistry and interesting biochemical properties. Besides of being a building block of several biomolecules such as arginine, creatine phosphate, and purines [1], the guanidine subunit plays a significant role in the synthesis of a number of drugs [2]. Due to their high intrinsic basicities, guanidine derivatives are also used as powerful non-ionic organic bases or basic catalysts [3–6] in a number of organic reactions, to mention only the transesterification of vegetable oils [7–10], which is a key-step in the production of Biodiesel®. Substituted guanidine salts are also successfully applied as the ionic liquids in modern chemistry approaches [11,12].

From a theoretical point of view, particular attention has recently been paid to tailoring of novel superbases derived from the guanidine motif. In this respect, guanidines with side chains containing hetero-substituents are of outmost interest due to their capability of forming multiple intramolecular hydrogen bonds (IMHB). It is well known that the unusually high basicity of proton sponges is significantly influenced by the formation of intramolecular hydrogen bonds [13]. The tendency of diamines and diols to form IMHBs has been recognized for quite some time [14–18], but only recently, several papers of Raczynska et al. [19–23], Koppel and coworkers [24] and theoretical investigations of Maksić and coworkers [25–27] have shown that the existence of flexible intramolecular hydrogen bonds plays a significant role in the tailoring of organic superbases. A representative example is provided by a guanidine bearing three 3-(*N*,*N*-dimethylamino)propyl groups, for which a gas-phase basicity comparable to those of phosphazenes has been predicted [28].

Here, we report first results on the experimental determination of the gas-phase proton affinities (PAs) of some of these guanidine derivatives by means of tandem mass spectrometry. Specifically, our emphasis lies on compounds having 3-(*N*,*N*-dimethylamino)propyl- or 3-methoxypropyl substituents attached to the imino and/or amino nitrogen atoms (compounds **2**–**7**, Fig. 1). In addition, *N*,*N*′,*N*″-tripropylguanidine (**1**) is included as a reference compound which cannot form IMHB either in the neutral or in the protonated form, but has similar through-bond inductive effects operative in the guanidine core.

* Corresponding authors. Tel.: +385 1 4561 008; fax: +385 1 4680 195.
*E-mail address:* glasovac@emma.irb.hr (Z. Glasovac).

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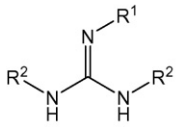


**1**: $R^1 = R^2 = (CH_2)_2CH_3$
**2**: $R^1 = (CH_2)_2CH_3$ ; $R^2 = (CH_2)_3N(CH_3)_2$
**3**: $R^1 = (CH_2)_3N(CH_3)_2$; $R^2 = (CH_2)_2CH_3$
**4**: $R^1 = R^2 = (CH_2)_3N(CH_3)_2$
**5**: $R^1 = (CH_2)_2CH_3$ ; $R^2 = (CH_2)_3OCH_3$
**6**: $R^1 = (CH_2)_3OCH_3$ ; $R^2 = (CH_2)_2CH_3$
**7**: $R^1 = R^2 = (CH_2)_3OCH_3$

Fig. 1. Structures of the guanidines **1–7**.

For the sake of comparison, the PAs calculated by *ab initio* MO and DFT methods are presented also and the computed thermochemical properties are further used for assisting the analysis of the experimental data.

For this purpose, we applied the kinetic method developed by Cooks and coworkers [29,30]. Briefly, in this approach proton-bound dimers [$\mathbf{A}\cdot H^+\cdot\mathbf{B}$] of the compound of interest **A** and a reference base **B** of known PA are generated, mass-selected, and then subjected to collision-induced dissociation (CID); also the results of metastable ion spectra can be analyzed using the kinetic method [31]. According to the concept of the kinetic method, the ratio of the resulting ion abundances of the fragment ions $I(\mathbf{A}\cdot H^+)$ and $I(\mathbf{B}\cdot H^+)$, respectively, can be considered as a monitor for the difference of the proton affinities, i.e., $\Delta PA = -RT_{eff} \ln[I(\mathbf{A}\cdot H^+)/I(\mathbf{B}\cdot H^+)]$, where the effective temperature $T_{eff}$ represents a phenomenological measure of the mean internal energy of the ions which dissociate within the time-window characteristic of a particular analyzer and operating conditions [32–34].

## 2. Experimental and theoretical details

### 2.1. Chemicals

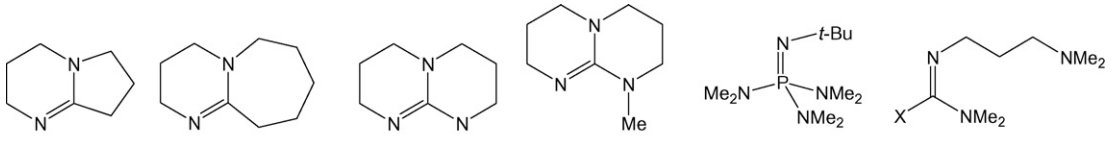
The guanidine derivatives were prepared by addition of the corresponding amines to the respective carbodiimides in boiling tetrahydrofuran and, after standard work-up, purified by vacuum distillation prior to measurements [35,36]. The reference bases (Fig. 2) 1,8-diazabicyclo[5.4.0]-undec-7-ene (**DBU**), 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (**TBD**), and 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-1-ene (**MTBD**) were purchased from Aldrich or Fluka and used without further purification.

### 2.2. Instrumentation

The measurements were conducted using a VG BIO-Q mass spectrometer which has been described elsewhere [37]. Briefly, the VG BIO-Q is a commercial instrument which consists of an electrospray ionization (ESI) source combined with a tandem mass spectrometer of QHQ configuration (Q stands for quadrupole and H for hexapole). In the present experiments, mmolar solutions of the guanidines **1–7** and an appropriate reference base (see below) in pure methanol were introduced through a fused-silica capillary to the ESI source via a syringe pump (ca. 5 μl/min) using nitrogen as nebulizing and drying gas at a source temperature of 80 °C. The ion source was adjusted to relatively soft ionization conditions, thereby maximizing the yields of the desired proton-bound dimers [38,39]. For CID, the ions of interest were mass-selected using Q1, interacted with xenon as a collision gas in the hexapole H under single-collision conditions (typically $2 \times 10^{-4}$ mbar) at variable collision energies ($E_{lab}$ = 0–6 eV), while scanning Q2 to monitor the ionic products. In the context of the kinetic method [40,41], the variation of the collision energy from nominally 0 to 6 eV in steps of 1 eV can be assumed to alter the effective temperatures of the dissociating ions. The resulting ion ratios were used for the determination of the proton affinities of the investigated bases. For the sake of completeness, we note that, besides for two protonated bases, no other signals were observed during the measurements indicating that neither side nor secondary reactions took place which might obscure the analysis [42].

### 2.3. Computational methods

The PAs were calculated using the MP2/6-311 + G(d,p)//HF/6-31G(d) and B3LYP/6-311 + G(2df,p)//B3LYP/6-31G(d) methods with the Gaussian 03 program suite [43]. For each of the bases, several conformations of the neutral and the protonated form were examined and the lowest-energy structures were selected for the calculations of the proton affinity. The minima on the Born-Oppenheimer potential-energy surfaces were further verified by analysis of the vibrational frequencies performed at the level at which the geometry optimization was made. The resulting frequencies were used for the calculation of zero-point energies and thermal corrections without any scaling in the case of the DFT calculations, whereas a scaling factor of 0.9135 was used for the MP2 results [44]. Thermal corrections of enthalpies to 298 K were applied without corrections for internal rotations. Structures were visualized and generated by MOLDEN 4.0 [45].



**DBN** **DBU** **TBD** **MTBD** **P1tBu**

**FDM** (X = H)
**TMG** (X = $N(CH_3)_2$)
**ADM** (X = $CH_3$)

Fig. 2. Structures of the reference bases used in kinetic measurements.

## 3. Results and discussion

For the analysis of the experimental results, two variants of the kinetic method were considered. The simple variant of the kinetic method [40] is based on the assumption that in the dissociations of [**A**·H$^+$·**B**] all unknown and the reference compounds have similar entropic effects and thus cancel out. This approach turned out inadequate in most cases examined here. This is not surprising in view of the rigidity of the bicyclic structures of the reference bases used vis-a-vis the conformational flexibility of the investigated guanidine derivatives [46]. Moreover, the chains in guanidines substituted with heteroalkyl groups are less flexible than those in **1** due to the formation of the IMHB in the former species. This particularly holds true for the protonated forms, which, as a rule, exhibit stronger intramolecular hydrogen bonds than their neutral counterparts [28]. Concomitantly, a decrease in entropy upon protonation of all heteroalkyl guanidine derivatives with respect to guanidine **1** might be expected. Another point worthy of noting is that the number of IMHBs in bases **4** and **7** increases upon protonation. In most of the experiments, we therefore applied the extended kinetic approach [47,48] with the statistical corrections developed by Armentrout [49] in order to remove the covariance between the slope and intercept. Accordingly, we are only left with the assumption of similar entropies of protonation of the reference bases, which appears reasonable for the bicyclic reference bases chosen. Recently, Zheng and Cooks employed a modified entropy-corrected method which can be used for determining thermochemical properties of structurally dissimilar compounds [50]. This approach would be perhaps more suitable for the investigation of compounds for which the number of IMHBs differ in the protonated and non-protonated forms, i.e., if strong entropy effects upon protonation are expected. In the present study, such situations may be expected only in the case of compounds **4** and **7** for which two IMHBs are expected in neutral form, while a third IMHB is formed upon protonation. In this work, we applied the entropy-corrected approach only in order to estimate the entropy of protonation ($\Delta S_p$) of guanidine **2** for the sake of comparison with the values obtained by the extended kinetic method (see below).

The reference bases of suitably large and known gas-phase basicities employed for the generation of proton-bound heterodimers of the type [**A**·H$^+$·**B**] are shown in Fig. 2. Among them, the phosphazene **P1tBu**, in spite of its large basicity, could not be used, because it failed to form dimers either with guanidine bases (heterodimers) or with itself (homodimer) [51]. On the other hand, the dimethylaminopropyl derivatives of *N*,*N*-dimethylformamidine (**FDM**), *N*,*N*-dimethylacetamidine (**ADM**), and *N*,*N*,*N*′,*N*′-tetramethylguanidine (**TMG**) as well as bicyclic **DBN** gave too weak or no signals of heterodimers with the guanidines under study. Consequently, the set of reference bases had to be limited to the bicyclic imidine **DBU** and guanidine derivatives **TBD** and **MTBD**. In order to improve the internal consistency in the determination of the PAs, some of the guanidines of lower PAs were also taken as reference bases for determination of PAs of the other members of the series. In this way we were able to evaluate the PAs of all bases except that of **4**, for which none of the used reference bases was found to be sufficiently basic, i.e., **4**·H$^+$ was obtained as the exclusive fragment upon CID of the respective dimers.

### 3.1. Proton affinity measurements

We shall commence the discussion by consideration of the results obtained for compounds **1**, **2**, **5**, and **6** for which proton-bound heterodimers were experimentally accessible and which showed competing channels for neutral losses. In the determination of the proton affinity of the guanidine **1**, the compounds **DBU**, **TBD**, and **MTBD** were used as reference bases. Similarly, in case of **5**, three reference bases were used (**1**, **TBD**, and **MTBD**), whereas for **2** and **6** the measurements employed only two reference bases (**MTBD** and **5** in case of **2**; **5** and **2** in case of **6**). CID spectra of the proton-bound heterodimers were recorded at several collision energies ($E_{lab}$) in order to change the effective temperature in ion dissociation; the variations exceeded 40 % in all cases. The results obtained for the parent compound **1** and the heteroalkyl guanidine derivatives **2**, **5**, and **6** are given in Table 1.

First, the PAs of all compounds were determined using the simple kinetic method according to Eq. (1):

$$\ln\frac{k_1}{k_2} = \ln\frac{[\mathbf{B}_i \cdot \mathrm{H}^+]}{[\mathbf{A} \cdot \mathrm{H}^+]} = \ln\frac{x_{\mathbf{B}_i\cdot\mathrm{H}^+}}{x_{\mathbf{A}\cdot\mathrm{H}^+}} \approx \frac{\Delta(\mathrm{PA})}{RT_{\mathrm{eff}}} = \frac{\mathrm{PA}(\mathbf{B}_i)}{RT_{\mathrm{eff}}} - \frac{\mathrm{PA}(\mathbf{A})}{RT_{\mathrm{eff}}} \quad (1)$$

Plotting $\ln(x(\mathbf{B}_i\cdot\mathrm{H}^+)/x(\mathbf{1}\cdot\mathrm{H}^+))$ versus PA(**B**) for each of the applied collision energies resulted in a regression line with the slope of $1/RT_{\mathrm{eff}}$ and PA(**A**) as the *x*-intercept (Fig. 3). As the *x*-intercepts of the linear plots obtained show a systematic shift on the *x*-axis, entropic effects cannot be neglected in this case [52]. Together with the PAs of the reference bases, the data obtained at the different sets of collision energies can be used to derive PA(**1**) which was then corrected to 298 K by assuming a linear dependence of the measured PAs versus $T_{\mathrm{eff}}$ (Fig. 4). This procedure resulted in a value of $\mathrm{PA}(\mathbf{1})_{298} = 251.8\ \mathrm{kcal\ mol^{-1}}$. By applying the same approach, the PAs of **2**, **5** and **6** at 298 K

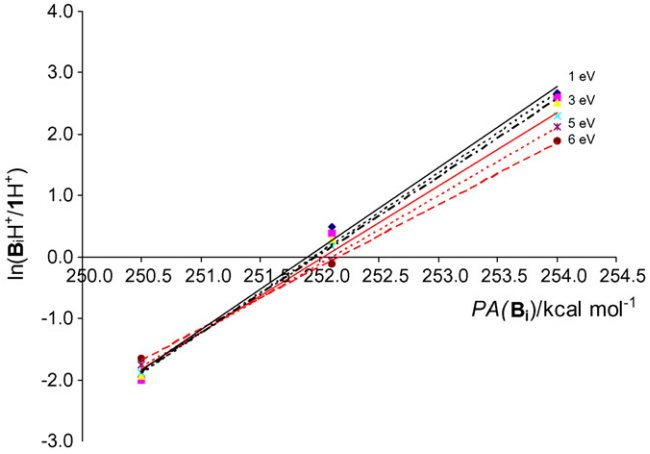



Fig. 3. Plot of $\ln(\mathbf{B}_i\cdot\mathrm{H}^+/\mathbf{1}\cdot\mathrm{H}^+)$ vs. the PA of the reference bases **B** at different collision energies ($E_{lab}$).

Table 1
CID branching ratios for the fragmentation of the mass-selected proton-bound dimers of the guanidines **1**, **2**, **5**, **6**, and **7** with selected reference bases ($\mathbf{B}_i$) at various collision energies ($E_{lab}$)

| $\mathbf{B}_i$ | $E_{lab}$ (eV) | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| $\ln(x(\mathbf{B}_i{\cdot}H^+)/x(\mathbf{1}{\cdot}H^+))$ | | | | | | |
| **DBU** | −1.97 ± 0.07 | −2.00 ± 0.16 | −1.94 ± 0.10 | −1.88 ± 0.11 | −1.76 ± 0.10 | −1.66 ± 0.11 |
| **TBD** | 0.49 ± 0.37 | 0.38 ± 0.22 | 0.28 ± 0.09 | 0.18 ± 0.10 | −0.07 ± 0.21 | −0.11 ± 0.09 |
| **MTBD** | 2.66 ± 0.27 | 2.59 ± 0.27 | 2.51 ± 0.32 | 2.30 ± 0.48 | 2.12 ± 0.34 | 1.88 ± 0.11 |
| $\ln(x(\mathbf{B}_i{\cdot}H^+)/x(\mathbf{2}{\cdot}H^+))$ | | | | | | |
| **5** | −3.09 | −3.07 | −2.88 | −2.86 | −2.67 | −2.61 |
| **MTBD** | −5.05 | −5.38 | −5.03 | −4.48 | −4.01 | −3.91 |
| $\ln(x(\mathbf{B}_i{\cdot}H^+)/x(\mathbf{5}{\cdot}H^+))$ | | | | | | |
| **1** | −5.41 | −5.05 | −4.32 | −4.20 | −3.71 | −3.33 |
| **TBD** | −3.39 | −3.41 | −3.25 | −2.76 | −2.40 | −2.27 |
| **MTBD** | −3.00 | −2.82 | −2.42 | −2.27 | −1.93 | −1.84 |
| $\ln(x(\mathbf{B}_i{\cdot}H^+)/x(\mathbf{6}{\cdot}H^+))$ | | | | | | |
| **2** | −2.24 ± 0.07 | −2.09 ± 0.09 | −1.97 ± 0.06 | −1.76 ± 0.02 | −1.57 ± 0.07 | −1.51 ± 0.01 |
| **5** | −5.28 ± 0.43 | −4.88 ± 0.27 | −4.71 ± 0.54 | −4.27 ± 0.35 | −4.07 ± 0.37 | −3.76 ± 0.21 |
| **3**[a] | 4.88 | 5.10 | 4.81 | 4.76 | 4.69 | 4.64 |
| **7**[a] | – | 3.68 | 3.40 | 3.48 | 3.38 | 2.86 |
| $\ln(x(\mathbf{B}_i{\cdot}H^+)/x(\mathbf{7}{\cdot}H^+))$ | | | | | | |
| **3** | 1.48 | 1.36 | 1.33 | 1.29 | 1.36 | 1.33 |

[a] CID branching ratios used in calculations of PAs for guanidines **3** and **7**.

were derived as 258.6, 257.6, and 259.7 kcal mol$^{-1}$, respectively. The relevant data for all four bases are summarized in Table 2.

We note in passing that for compound **2** the difference between $PA_{avg}$ and $PA_{298}$ is significantly larger than for **1**, **5**, and **6**, which algebraically is due to the larger $T_{eff}$ found in the measurements involving **2** (between 800 and 1300 K compared to values of about 350–550 K for **1** and **6** and 670–1000 K in the case of **5**). From a chemical point of view, the larger values of $T_{eff}$ for **2** can be regarded as yet another indication for the significance of entropic effects upon *N*,*N*-dimethylaminopropyl substitution, most likely due to a recoil of the amino group to the guanidine core in the protonated form.

Having established that the entropic effects should be taken into account, the experimental data for **1** were analyzed employing the extended kinetic method. The relationship on which this method is based is given in Eq. (2) [41]:

$$\ln\frac{k_1}{k_2} = \ln\frac{[\mathbf{B}_i\mathrm{H}^+]}{[\mathbf{A}\mathrm{H}^+]} = \frac{\mathrm{PA}(\mathbf{B}_i) - \mathrm{PA}(\mathbf{B})_{avg}}{RT_{eff}} - \frac{\mathrm{PA}(\mathbf{A}) - \mathrm{PA}(\mathbf{B})_{avg}}{RT_{eff}} - \frac{\Delta(\Delta S)}{R} \quad (2)$$

$$\text{slope} = \frac{1}{RT_{eff}}; \quad \text{intercept} = \frac{\mathrm{PA}(\mathbf{A}) - \mathrm{PA}(\mathbf{B})_{avg}}{RT_{eff}} - \frac{\Delta(\Delta S)}{R} \quad (3)$$

from which two plots were generated. In the first plot, $\ln(x(\mathbf{B}_i\mathrm{H}^+)/x(\mathbf{A}\mathrm{H}^+))$ versus $[\mathrm{PA}(\mathbf{B}_i) - \mathrm{PA}(\mathbf{B})_{avg}]$, was considered, where $\mathrm{PA}(\mathbf{B}_i)$ is the proton affinity of the reference base and $\mathrm{PA}(\mathbf{B}_i)$ is the mean proton affinity of the set of the reference bases. As mentioned earlier, the term $[\mathrm{PA}(\mathbf{B}_i) - \mathrm{PA}(\mathbf{B})_{avg}]$

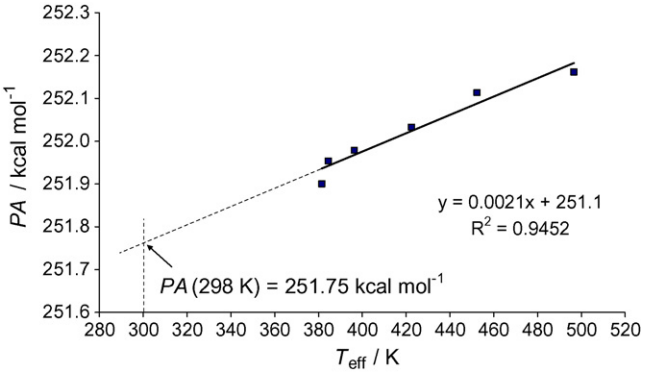



Fig. 4. Plot of the PAs of guanidine **1** obtained at different $T_{eff}$ extrapolated to 298 K.

Table 2
Proton affinities (in kcal mol$^{-1}$) of the guanidines **1**, **2**, **5**, and **6** and $T_{eff}$ for **1** as determined via the simple kinetic approach[a,b]

| $E_{lab}$ (eV) | PA(**1**) | $T_{eff}$ (K) | PA(**2**) | PA(**5**) | PA(**6**) |
|---|---|---|---|---|---|
| 1 | 251.9 | 382 | 263.4 | 257.7 | 260.2 |
| 2 | 252.0 | 385 | 262.4 | 257.7 | 260.2 |
| 3 | 252.0 | 396 | 262.5 | 257.8 | 260.2 |
| 4 | 252.0 | 422 | 264.0 | 257.6 | 260.2 |
| 5 | 252.1 | 452 | 264.8 | 257.4 | 260.1 |
| 6 | 252.2 | 497 | 264.9 | 257.8 | 260.1 |
| $PA_{avg}$ | 252.0 | | 263.7 | 257.6 | 260.2 |
| PA (298 K) | 251.8 | | 258.6 | 257.6 | 259.7 |

[a] Standard error for the determination of PAs is ±0.3 kcal mol$^{-1}$.
[b] The numbers are rounded to one significant digit.

Table 3
Proton affinities (PAs), and entropies of protonation ($\Delta S_p$) of the investigated guanidines **1–7** and the references bases **DBU**, **TBD** and **MTBD** as calculated using the DFT and MP2 (in parentheses) methods

| Bases | PA[a] (kcal mol$^-$)[1] | $PA_{exp}$ (kcal mol$^{-1}$) | $\Delta(PA)_{MP2}$ (kcal mol$^{-1}$) | $\Delta S_{p,exp}$[b] (cal K$^{-1}$ mol$^{-1}$) | $\Delta S_{p,calc}$[b] (cal K$^{-1}$ mol$^{-1}$) |
|---|---|---|---|---|---|
| **1** | 255.8 (251.5) | 251.1 | 0.4 | 4.4 | 3.5 |
| **2** | 261.3 (258.2) | 259.1 | −0.9 | 7.4 | 0.8 |
| **3** | 266.6 (264.8) | 264.0 | 0.8 | | −4.7 |
| **4** | 273.2 (276.5) | | | | −10.3 |
| **5** | 259.5 (256.1) | 257.6 | −1.5 | 3.7 | 2.4 |
| **6** | 262.6 (261.1) | 260.6 | 0.5 | −0.1 | −1.1 |
| **7** | 266.4 (268.6) | 262.9 | 5.7 | | −6.3 |
| **DBU** | 252.7 (250.2) | 250.5[c] | −0.3 | | −0.9 |
| **TBD** | 253.6 (252.1) | 252.1[c] | 0.0 | | 3.6 |
| **MTBD** | 254.8 (251.9) | 254.0[c] | −2.1 | | 4.0 |

[a] PA = $H$(neutral) − $H$(protonated) + $H(H^+)$, where $H(H^+) = 2.5\,RT$ and includes the work term.
[b] $\Delta S_p = S$(protonated) − $S$(neutral); $S(H^+)$ is omitted in the calculations because it cancels out.
[c] http://www.webbook.nist.gov/chemistry.

instead of PA($\mathbf{B}_i$) was employed in order to avoid linear dependence of the calculated parameters [49]. A best-fit line of this plot gives a slope equal to $1/RT_{eff}$ and an intercept equal to $(PA(\mathbf{A}) - PA(\mathbf{B})_{avg})/RT_{eff} - \Delta(\Delta S_p)/R$. The branching ratio at each collision energy used gives a different slope and intercept. The slopes and the intercepts of the obtained linear fits correspond to $1/RT_{eff}$ and $[PA(\mathbf{A}) - PA(\mathbf{B})_{avg}]/RT_{eff}$, respectively (Eq. (3)). The resulting values are summarized in Table 3. A plot of negative of each of the intercepts versus the slopes from the first plot were then correlated which led to a new fit and supplied the term $[PA(\mathbf{A}) - PA(\mathbf{B})_{avg}]$ from the slope and $\Delta(\Delta S)/R$ from the intercept (Fig. 5). We note in passing that the errors of the PAs of the reference bases are neglected in this analysis.

From the obtained differences $PA(\mathbf{A}) - PA(\mathbf{B})_{avg}$ of $-1.11 \pm 0.12$ kcal mol$^{-1}$, a proton affinity of $251.1 \pm 0.3$ kcal mol$^{-1}$ is derived for the parent compound **1**. Similarly, from the intercept of the second plot, using the average calculated entropy of protonation for the reference bases ($\Delta S_{avg} = 2.22$ cal K$^{-1}$ mol$^{-1}$, the term $\Delta S_p(\mathbf{1})$ was determined as 4.4 cal K$^{-1}$ mol$^{-1}$. As shown further below, this value is in reasonable agreement with the result obtained from the quantum chemical calculations ($\Delta S_{p,calc}(\mathbf{1}) = 3.5$ cal K$^{-1}$ mol$^{-1}$). Likewise, the PAs and $\Delta S_p$ of the guanidine derivatives **2**, **5**, and **6** were determined and compared to the calculated values (Table 3).

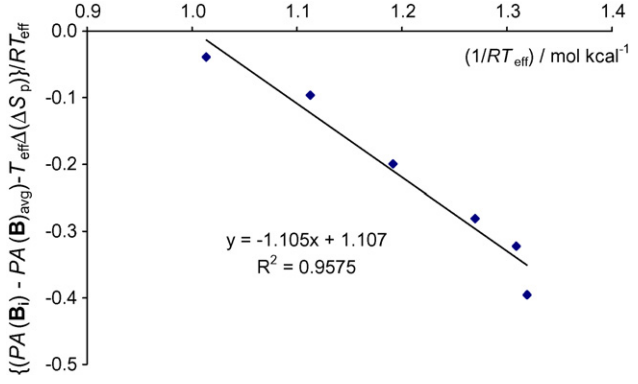



Fig. 5. Plot of $\{[PA(\mathbf{B}_i) - PA(\mathbf{B})_{avg}] - T_{eff}\Delta(\Delta S_p)\}/RT_{eff}$ vs. $1/RT_{eff}$ for some heterodimers of **1** derived from the data in Table 3.

The analysis of the measured PAs obtained from application of the simple and the extended kinetic method (Tables 2 and 3) clearly indicates that the heteroalkyl-substituted guanidines **2**, **5**, and **6** are intrinsically stronger bases than **1**. This is in accordance with expectation due to the possibility of an extra stabilization resulting from the formation of IMHBs, with the effect being more pronounced in the protonated forms and hence giving rise to significantly larger PAs. The two sets of data are very similar with the exception of base **2**, for which the value obtained by the extended kinetic method is larger by 2.4 kcal mol$^{-1}$. For example, the basicities of **2** and **5** as obtained by the latter method (Table 3) are by 8.0 and 5.5 kcal mol$^{-1}$, respectively, higher than that of **1**, whereas the corresponding values obtained by the simple kinetic method (Table 2) are 10.4 and 5.6 kcal mol$^{-1}$. We also note that the increase in the number of methoxypropyl groups on going from **5** to **6** enhances the basicity by ca. 3 kcal mol$^{-1}$ (Table 3), thus indicating the operation of some attenuation effects in comparison to the difference of about 7.5 kcal mol$^{-1}$ between the PAs of the parent compound **1** and the methoxypropyl derivative **5**. It also appears that the entropy of protonation in the series of methoxypropyl derivatives decreases as the number of IMHBs increases, as intuitively expected. Surprisingly, this does not hold for the entropy of protonation of **2** which is predicted to be even larger than for **1**. This might be a consequence of the fact that for the determination of the PA of this base only two reference bases could be employed, of which one, i.e., **5** belongs to the set of the guanidines studied. Therefore, we determined the protonation entropy of **2** also by the entropy-corrected approach [50], which furnished a somewhat lower (5.6 cal mol$^{-1}$ K$^{-1}$), but still significantly larger value than for **1**. Inclusion of additional reference bases for the determination of the thermochemical properties of **2** would therefore be highly desirable, not only for the calculation of the entropy of protonation, but also to increase the reliability of the second plot within the extended kinetic method.

A similar determination of the PAs of the other guanidines under study by means of the extended kinetic method was impossible owing to the lack of suitable reference bases. However, as we were able to determine the branching ratios for the base pairs **3–6**, **6–7**, and **3–7** (Table 1, last three entries), the PAs of **3** and **7**

were calculated using the simple kinetic approach. As all three bases are structurally similar and have the same type of protonation sites, application of the simple kinetic approach seems to be justified. In performing these calculations, the effective temperatures were adopted from the measurements of **1**. In this way, proton affinities of 264.0 and 262.9 kcal mol$^{-1}$ for **3** and **7**, respectively were derived from the branching ratios of **3** and **7** versus **6**. Additionally, the branching ratio of the heterodimer [**3**·H$^+$·**7**] was determined. By applying the same procedure as above, we calculated the difference in PAs of **3** and **7** to be

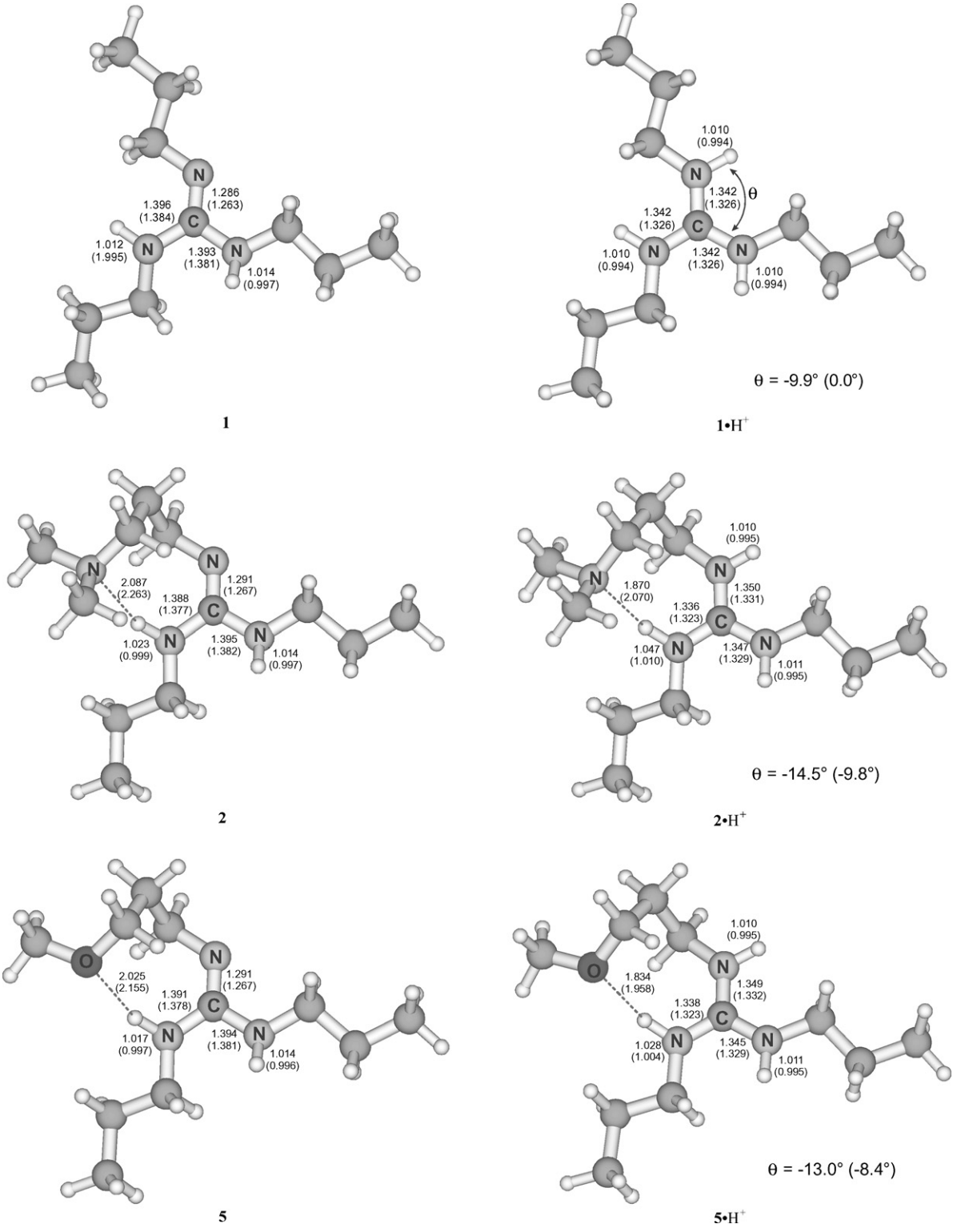



Fig. 6. The optimized structures of the most stable conformers of the guanidines **1**, **2**, and **5** and their protonated forms with selected bond lengths (in Å) and dihedral bond angles (θ) calculated at the B3LYP/6–31G(d) and HF/6–31G(d) (values in parentheses) are shown. The definition of dihedral angle (θ) is illustrated in **1**·H$^+$.

1.1 kcal mol$^{-1}$ with the guanidine **3** as the stronger base. This value is in excellent agreement with the difference in measured PAs anchored to guanidine **6**, thus corroborating the validity of the estimated PAs.

### 3.2. Calculated proton affinities

The structures and PAs of the aminopropyl congeners of bases **1–4** were previously studied by the MP2/6-311 + G(d,p)//HF/6-31G(d) method (thereafter referred to simply as MP2) [28]. This earlier study indicated that the PAs of these bases increase as the number of the 3-aminopropyl groups increases, which has been attributed to the formation of one or more IMHBs in both neutral and protonated forms. The same theoretical method was accordingly applied for the calculation of the proton affinities and entropies of the bases studied in this work. Additional computations were carried out using density functional theory, specifically, the B3LYP/6-311 + G(2df,p)//B3LYP/6-31G(d) approach (hereafter denoted as DFT), whose performance in this type of calculations was amply evidenced in earlier work [53–55]. The same methods were also used to calculate the PAs of the used reference bases. The resulting PAs of the most stable neutral and protonated forms of the studied guanidine derivatives and those of the reference bases are compared to the available experimental values in Table 3. Also included are the computational data for guanidine **4**. The calculated energy minimum structures of bases **1**, **2** and **5** and their conjugate acids are depicted in Fig. 6 as representative examples. The calculated structures of all other species studied in this work can be obtained upon request from authors.

The presented structures closely resemble the recently reported geometries of 3-aminopropyl guanidine derivatives [28] and *N*,*N*′,*N*″-*tris*-(dimethylaminopropyl)guanidine [35] and the changes induced by protonation and will be therefore not discussed here. We only point to the equalization of the C–N bonds within the guanidine moiety upon protonation and to the presence of intramolecular hydrogen bonds in the guanidines **2** and **5** and their conjugate acids. It should be noted that the proton participating in the hydrogen bond and the heteroalkyl chain(s) are linked to different nitrogen atoms within guanidine subunit, thus forming pseudo eight-membered ring(s). Further, the intramolecular hydrogen bonds in the protonated bases (**2**·H$^+$ and **5**·H$^+$) are stronger than in their neutral counterparts (**2** and **5**), as evidenced by a decrease in the N–H···X (X = N, O) contacts by 0.22 Å (for the N–H···N) and 0.19 Å (for the N–H···O). The *bis*- and *tris*-substituted systems, possessing two and three hydrogen bonds (not shown here), respectively, exhibit the same pattern of changes triggered by protonation.

The analysis of the data given in Table 3 shows a reasonable correlation between the experimental and the computed proton affinities (Fig. 7). Generally, it appears that DFT overestimates PAs of all bases studied with the difference being less pronounced for the reference bases. On the other hand, the MP2 method in most cases slightly underestimates the basicities of the reference bases, whereas no uniform trend seems to exist for the guanidines. Both computational methods reproduce most of the experimentally observed behavior. Thus, both computational methods predict a stronger increase in basicity in going from **1** to the 3-(*N*,*N*-dimethylamino)propyl rather than to the 3-methoxypropyl-guanidine derivatives, as observed experimentally. Specifically, replacement of the propyl group at the imino nitrogen in **1** by a 3-(*N*,*N*-dimethylamino)propyl chain, leading to base **2**, increases the PA by 5.5 and 6.7 kcal mol$^{-1}$ at the DFT and MP2 level, respectively, as compared to a value of 8.0 kcal mol$^{-1}$ obtained experimentally. Similarly, replacement of the propyl group at the imino nitrogen in **1** by 3-methoxypropyl group leads to an increase in PA by 3.7 and 4.6 kcal mol$^{-1}$ at the DFT and MP2 level of theory, respectively, as compared with an experimental value of 6.5 kcal mol$^{-1}$. The same holds true for the replacement of the propyl chains attached to the amino nitrogen atoms in **1** leading to **3** and **6**. In this case, an increase in basicity of 10.8 (DFT) and 13.3 (MP2) kcal mol$^{-1}$ for the replacement of propyl by a 3-(*N*,*N*-dimethylamino)propyl substituent and 6.9 (DFT) and 9.6 (MP2) kcal mol$^{-1}$ for the replacement of propyl by the 3-methoxypropyl group is predicted by the calculations. The relevant experimental values to be compared with are 12.9 and 9.5 kcal mol$^{-1}$. It is interesting to note that in both cases the MP2 values are in a somewhat better agreement with the experimental data than those calculated using DFT. We also note that both calculation methods significantly overestimate PA of the base **7**, which may indicate that under experimental conditions intramolecular hydrogen bonds contribute less to the stability of the protonated base than in the isolated species. Specifically, the binding proton in the dimer is shared between the analyte and the reference base, such that formation of a third intramolecular hydrogen bond in **7**·H$^+$ is kinetically less feasible compared to the calculations dealing with the protonated monomers.

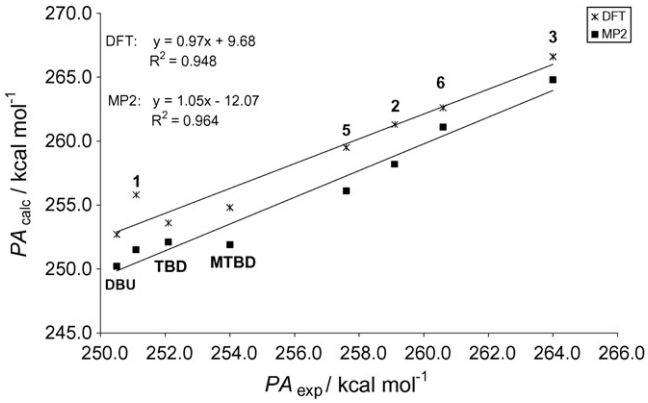



Fig. 7. Comparison of the experimental PAs with those calculated using B3LYP/6–311 + G(2df,p)//B3LYP/6–31G(d) (DFT) and MP2/6–311 + G(d,p)//HF/6–31G(d) (MP2) levels of theory. Data for base **7** are excluded from correlation.

## 4. Conclusions

The kinetic method is applied for the determination of the gas-phase proton affinities of tripropylguanidine and some of its 3-(*N*,*N*-dimethylamino)propyl and 3-methoxypropyl analogs. All heteroalkyl-substituted species were found to be very strong

bases in the gas phase due to the existence of intramolecular hydrogen bonds. In general, a reasonable correlation between experimental and computed proton affinities is found, if entropic effects are taken into consideration, which is of vital importance in the analysis of the present experimental data for the guanidines. With regard to the most basic guanidines investigated in this work, however, prior to a more detailed experimental determination of their proton affinities, new and appropriately strong reference bases need to be synthesized.

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