

# Ring Strain and Other Factors Governing the Basicity of Nitrogen Heterocycles – An Interpretation by Triadic Analysis<sup>†</sup>

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**Abstract.** M06–2X/6–311++G(2df,2pd)//M06–2X/6–31+G(d) computations were employed to investigate the intrinsic gas phase basicity of strained nitrogen heterocycles involving aziridine, azetidene, pyrrolidine and piperidine, together with their *N*-methyl and *N*-phenyl derivatives, NR(CH<sub>2</sub>)<sub>*n*</sub> (*n* = 2–5; R = H, Me and Ph). Basicity constants were compared with the corresponding acyclic counterparts, NR(CH<sub>3</sub>)<sub>2</sub> (R = H, Me and Ph), and were, based on triadic analysis, resolved into contributions mirroring features of both initial base and the final protonated form as well as their interplay, thus offering quantitative insight into the obtained results. In general, the *N*-methyl derivatives provided strongest bases investigated here, and, within each group of molecules, the basicity increased on going from three- to six-membered rings, consistent with a decrease in ring strain, with four-membered systems already surpassing or coming close to the basicity of the acyclic gauge molecule. Calculated basicities were found in a very good agreement with available experimental data, except for *N*-methylazetidene, where a remarkable discrepancy was revealed, suggesting that this system should be experimentally reassessed and its gas-phase basicity parameters revised. Triadic analysis showed different behaviour of individual contributions governing basicities, both among and within distinct families of molecules. It also convincingly demonstrated that, if a proper and a quantitatively accurate interpretation of observed basicity trends is desired, one should not rely only on concepts such as localized reactive hybrid orbitals (RHO) or thus derived nitrogen electron-donating ability (T. Ohwada *et al.*, *J. Org. Chem.* **69** (2004) 7486), which take into account only properties of the initial base in question, but rather consider protonation reaction in its entirety. (doi: [10.5562/cca2121](https://doi.org/10.5562/cca2121))

**Keywords:** Baeyer ring strain, protonation, substituent effect, superbases, triadic formula

## INTRODUCTION

Ever since Baeyer first introduced the concept of ring strain, when he studied the deviation of normal tetrahedral bond angles in cyclic alkanes in the 1880's,<sup>1</sup> the chemistry of strained organic molecules has been investigated extensively because such structures present challenges for the existing synthetic methodologies and may lead to new compounds with unusual and even unprecedented chemical behaviours.<sup>2–10</sup> Features like bonding, property, reactivity, and synthetic accessibility have been the constant subject of research activities in this area. Cyclopropane is the paradigmatic strained carbocycle, having ring strain energy  $E_{\text{strain}} = 27.5 \text{ kcal mol}^{-1}$ ,<sup>11</sup> and it has played a unique role in the study of ring strain, being a reference molecule to which other strained systems are typically compared.<sup>12–14</sup> In cyclopropane, the concept of ring strain is supported by the high electron density in the

interior of the three-member ring,<sup>15–17</sup> the relatively short C–C and C–H bond distances,<sup>15,16</sup> and the upfield shifts of its proton<sup>18</sup> and <sup>13</sup>C NMR signals.<sup>19</sup> In most cases, ring strain energy cannot be determined experimentally; it is relative rather than absolute quantity that must be defined and assessed by comparison with arbitrary reference species considered by convention to be "strain free". Nevertheless, since the former is often invoked to explain the enhanced reactivity of transformations involving small ring compounds,<sup>20–22</sup> numerous computational methods and attempts to quantify these energetic values have appeared in the literature, remaining a hotly debated topic. The latter include isodesmic,<sup>23</sup> homodesmotic,<sup>24</sup> hyperhomodesmotic<sup>25,26</sup> and group equivalent schemes.<sup>27</sup>

As part of our continuing studies concerned with the identification of electronic and geometric effects responsible for the high basicity of organic compounds,<sup>28–33</sup> we report here the effect that ring strain

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exhibits on the nitrogen basicity of small heterocycles. We selected the nitrogen atom, since it represents the basic site of a large variety of strongest superbases known today.<sup>28,34,35</sup> Proper insight into the mentioned intrinsic effect is important, since strain relief on protonation can have major impact on the basicity of strained compounds. For example, this was clearly demonstrated by Abboud, Koppel and co-workers,<sup>36</sup> who employed modified G2(MP2) approach to calculate the gas-phase basicity (GB) of cubane, C<sub>8</sub>H<sub>8</sub>, to be as large as GB = 258.8 kcal mol<sup>-1</sup>, and attributed pronounced basicity to the formation of the rearrangement product, namely tetracyclo[4.2.0.0<sup>2,4</sup>.0<sup>3,8</sup>]oct-7-ylum cation, created after strain relief and the opening of the rigid framework of cubane upon protonation. However, their calculated GB value differed by about 60 kcal mol<sup>-1</sup> from that measured experimentally,<sup>37</sup> suggesting that the latter value, determined by FT-ICR mass spectrometry, does not correspond to the reversible protonation of cubane and that the proposed cation is not the final protonation product. This discrepancy was later clarified by Fokin, Schreiner and co-workers<sup>38</sup> who suggested 1,8-dihydropentalene as the final cubane protonation product along the most favourable protonation/isomerization/deprotonation downhill path at the CCSD(T)/cc-pVDZ//MP2/cc-pVDZ level, in that way tying in with experimental thermodynamics. As an even more typical example, one should mention the original paradigmatic superbasic proton sponge, namely Alder's 1,8-bis(dimethylamino)naphthalene, DMAN. Its gas-phase proton affinity was calculated at the B3LYP/6-31+G(d,p)//HF/6-31G(d,p) level by Howard<sup>39</sup> to be PA = 246.3 kcal mol<sup>-1</sup> being in perfect agreement with the experimental value of PA = 246.2 kcal mol<sup>-1</sup> measured by Kebarle and co-workers.<sup>40</sup> At the same level of theory, Howard demonstrated that DMAN is by as much as 22.4 kcal mol<sup>-1</sup> a stronger base than monosubstituted 1-(dimethylamino)naphthalene,<sup>39</sup> which is remarkable. Employing series of isodesmic reactions and model systems, Howard separated the mentioned difference in PA values into contributions from the strain-induced repulsion (SR) of both nitrogen lone pairs in the destabilized neutral molecule, DMAN, and that of the stabilizing effect due to the formation of strong intramolecular N<sup>+</sup>-H ... N hydrogen bond (HB) in the protonated form, DMANH<sup>+</sup>. He obtained values of SR = 6.4 kcal mol<sup>-1</sup> and HB = -16.0 kcal mol<sup>-1</sup>,<sup>39</sup> in that way demonstrating that strain energy largely determines the basicity of DMAN and related compounds, and that it cannot be neglected but rather employed as a useful electronic effect to promote the basicity when designing novel superbases. Furthermore, in a recent article, Alder proposed<sup>41</sup> that the key to the design of even stronger bases than either DMAN or related systems having

amino groups replaced by more basic functionalities,<sup>34</sup> is to further enhance ring strain in the initial bases by "limiting conformational freedom, especially by preventing nitrogen inversion, through the introduction of additional ring fusions."

A consistent and thorough analysis of the gas-phase basicity of simple cyclic amines, NH(CH<sub>2</sub>)<sub>n</sub> (*n* = 2–5), and their corresponding *N*-methyl and *N*-phenyl derivatives, was recently performed by Ohwada and co-workers<sup>42</sup> using CBS-Q, G3 and B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) computational methods. They observed that basicity within a family of compounds increases with the increase in the ring size *n*, but that aziridines, NR(CH<sub>2</sub>)<sub>n</sub> (*n* = 2, R = H, Me, Ph), are notably less basic than other systems with *n* = 3–5. The authors attempted to interpret calculated basicity constants by plotting the corresponding proton affinity values against the HOMO energies obtained at the HF/6-31G(d)//B3LYP/6-31G(d) level, but obtained a significant scatter of points with no correlation. They tried to improve the correlation by employing the reactive hybrid orbital (RHO) concept<sup>43</sup> and thus calculated electron-donating abilities of the nitrogen atom. The latter resulted in a better overall picture indicating a trend that an increase in RHO orbital energies leads to higher basicity. Still, for any predictive or interpretative purposes the correlation offered by Ohwada and co-workers was of very limited use. One should emphasize, that their analysis was based on considering only the properties of initial bases, namely neutral cyclic amines, thus it was very much incomplete. Specifically, no features of the protonated conjugate acids contributed to their correlation in any way, which, in principle, leads to wrong conclusions. It is quite obvious that molecular basicity is determined by features of both neutral base and its protonated form, where in some cases the properties of the latter could even prevail and should be explicitly considered. Therefore, since basicity of cyclic amines is a fundamental property in organic chemistry and for all the reasons stated above, we found it necessary to re-examine the intrinsic gas-phase basicity of simple nitrogen heterocycles investigated by Ohwada and co-workers,<sup>42</sup> and provide an insight into the calculated values employing our triadic analysis. The latter considers protonation reaction in its entirety and offers quantitative estimation of properties of both molecular forms during protonation reaction (for a review on triadic formalism see Ref. 44). In finishing this section, it is worth to note that since acid-base behaviour can be a sensitive experimental probe of various structural features including ring strain, some other properties of the strained organic molecules, such as carbon acidities<sup>45–47</sup> have been studied as well.

## COMPUTATIONAL METHODOLOGY

According to Brønsted, basicity is the measure of the capability of a molecule to accept a proton in a chemical reaction. In the gas phase, it is expressed by Equation (1), where GB is the gas phase basicity (a free-energy term) and PA is the proton affinity (an enthalpy term) for the reaction:



Here B and BH<sup>+</sup> denote the base in question and its protonated form, the conjugate acid, respectively.  $\Delta G^\circ$  gives intrinsic basicity of a compound not contaminated by the presence of the solvent molecules or counterions. The corresponding proton affinity is related to the electronic structure of the base and its conjugate acid, and has two contributions:

$$\text{PA} = \Delta H^\circ = \Delta E^\circ + \Delta(pV) \quad (2)$$

where  $\Delta E^\circ$  represents the change in the total molecular energy in reaction (1), which includes the electronic and the zero-point vibrational energies, ZPVEs, as well as the finite temperature (298.15 K) correction, while  $\Delta(pV)$  denotes the pressure-volume work term. Both GB and PA values are computed here and compared to available experimental values, but our analysis will focus only on the proton affinities, because they offer a good description of basicities, being simpler for the interpretation at the same time.

In order to get an insight into the origin of the basicity of studied molecules, we performed triadic separation<sup>44</sup> of proton affinities, Equation (3), which enables the estimation of the influence of the properties of the initial (neutral base) and the final state effects (protonated molecule), as well as their interplay on Brønsted basicities for molecules in the gas phase.

$$\text{PA}(\text{B}) = -\text{IE}(\text{B})_n^{\text{Koop}} + E(\text{ei})_{\text{rex}}^n + (\text{BAE})^{*+} + 313.6 \text{ kcal mol}^{-1} \quad (3)$$

It has been demonstrated that this approach has certain advantages over some other models aiming to interpret Brønsted acidities and basicities, as discussed in great detail recently by Deakye,<sup>48</sup> and it was already successfully employed in the analysis of proton affinities,<sup>49–51</sup> deprotonation enthalpies<sup>52–54</sup> and hydride affinities.<sup>55–57</sup> Initial state effects of neutral bases are reflected in Koopmans' ionisation energies,<sup>58</sup>  $\text{IE}(\text{B})_n^{\text{Koop}}$ , calculated in the frozen electron density and clamped atomic nuclei approximation (i.e., ionisation from the  $n$ -th molecular orbital, counting the HOMO as the 1<sup>st</sup>). The  $\text{IE}(\text{B})_n^{\text{Koop}}$  values reflect the price to be paid for

taking an electron from the neutral molecule in the bond association process with the incoming proton, assuming that the ionisation is a sudden process. Since Koopmans' ionisation energies depend exclusively on the electron distribution of the investigated neutral base, they reflect genuine properties of the initial state and are most affected by ring strain. The geometric and electronic reorganisation effects following electron ejection are given by the relaxation energy  $E(\text{ei})_{\text{rex}}^n$ , defined by Equation (4):

$$E(\text{ei})_{\text{rex}}^n = \text{IE}(\text{B})_n^{\text{Koop}} - \text{IE}(\text{B})_1^{\text{ad}} \quad (4)$$

where  $\text{IE}(\text{B})_1^{\text{ad}}$  is the first adiabatic ionisation energy of the base. This is the intermediate phase of the protonation process. Finally, the electron affinity of the proton is experimentally determined to be exactly 313.6 kcal mol<sup>-1</sup>,<sup>59</sup> whereas the bond association energy describing homolytic bond formation between created radicals is given by the (BAE)<sup>\*+</sup> term, and will be used in connection with the properties of the final state (protonated molecule). The latter is calculated as an enthalpy of the reaction in which hydrogen atom, H<sup>•</sup>, and the radical cation of the investigated base, B<sup>•+</sup>, combine to form protonated conjugate acid, BH<sup>+</sup>. Since we are mostly interested in trends of changes obtained by relative values against the reference molecule, it is useful to define the triad of contributions to proton affinities as:

$$\Delta \text{PA}(\text{B}) = \text{PA}(\text{B}) - \text{PA}(\text{B}_{\text{REF}}) = \left[ -\Delta(\text{IE})_n^{\text{Koop}}; \Delta E(\text{ei})_{\text{rex}}^n; \Delta(\text{BAE})^{*+} \right] \quad (5)$$

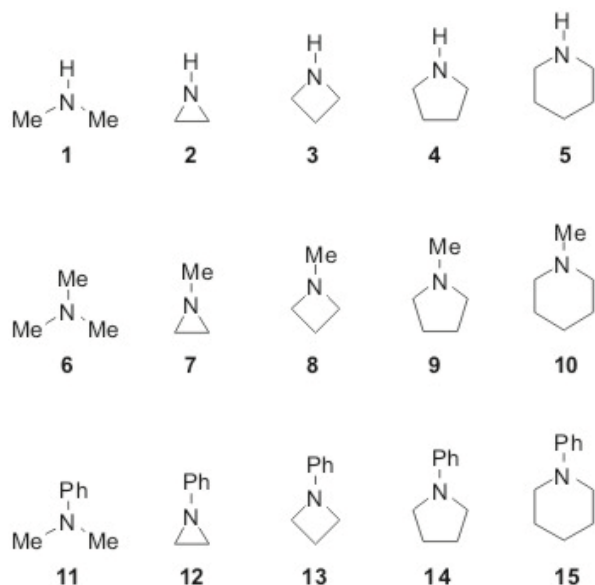
where B and B<sub>REF</sub> denote molecule in question and the reference base, respectively, whereas square brackets imply summation of the three terms within, defined as:

$$-\Delta(\text{IE})_n^{\text{Koop}} = -\text{IE}(\text{B})_n^{\text{Koop}} + \text{IE}(\text{B}_{\text{REF}})_n^{\text{Koop}} \quad (6a)$$

$$\Delta E(\text{ei})_{\text{rex}}^n = E(\text{ei})_{\text{rex}}^n(\text{B}) - E(\text{ei})_{\text{rex}}^n(\text{B}_{\text{REF}}) \quad (6b)$$

$$\Delta(\text{BAE})^{*+} = \text{BAE}(\text{B})^{*+} - \text{BAE}(\text{B}_{\text{REF}})^{*+} \quad (6c)$$

Although the above procedure is a simple extension of the well known thermodynamic cycle, where the sum of  $\text{IE}(\text{B})_n^{\text{Koop}}$  and  $E(\text{ei})_{\text{rex}}^n$  is replaced by a single term  $\text{IE}(\text{B})_1^{\text{ad}}$ , inclusion of the Koopmans' ionisation energies offers large interpretative advantages. The  $\text{IE}(\text{B})_n^{\text{Koop}}$  corresponds to the  $n$ -th ionisation energy, which is related to the specific highest MO most affected by the protonation, which is conveniently termed PRIMO (PRincipal Molecular Orbital).<sup>60</sup> It is usually the highest molecular orbital corresponding to lone pair electrons



**Figure 1.** Schematic representation of investigated cyclic and reference acyclic amines.

that get attacked by the proton in the protonation reaction. As such, it does not always have to be the HOMO; it could be one of the lower-lying molecular orbitals, which is a very important feature of the triadic analysis.

As a good compromise between the accuracy and the computational feasibility of the model, all molecular geometries were optimized by the very efficient M06-2X/6-31+G(d) method. ZPVEs and thermal corrections were extracted from the corresponding frequency calculations without the application of scaling factors. The final single-point energies were attained with a highly flexible 6-311++G(2df,2pd) basis set using M06-2X functional, which has been shown in the literature to provide very accurate thermodynamic and kinetic parameters for organic systems, being particularly successful in treating nonbonding interactions.<sup>61,62</sup> This gives rise to the M06-2X/6-311++G(2df,2pd)//M06-2X/6-31+G(d) model employed here. Koopmans' ionization energies  $(IE)_n^{Koop}$  were computed by the HF/6-311++G(2df,2pd)//M06-2X/6-31+G(d) level of theory. Radical cations were treated with unrestricted approach. All calculations were performed using the Gaussian 09<sup>63</sup> suite of programs.

## RESULTS AND DISCUSSION

Molecules studied in this work are presented in Figure 1. They include aziridine **2**, azetidine **3**, pyrrolidine **4**, and piperidine **5**, together with their *N*-methyl (**7–10**) and *N*-phenyl (**12–15**) derivatives. We also included the

**Table 1.** Calculated proton affinities (PAs), their resolution into triadic components, and gas-phase basicities (GBs) of selected nitrogen bases obtained using the M06-2X/6-311++G(2df,2pd)//M06-2X/6-31+G(d) model. Orbital energies and the corresponding Koopmans' ionization energies,  $(IE)_n^{Koop}$ , were calculated by the HF/6-311++G(2df,2pd)//M06-2X/6-31+G(d) model.<sup>(a)</sup>

molecule	$(IE)_n^{Koop}$ <sup>b</sup>	$(IE)_1^{ad}$	$(IE)_{EXP}$ <sup>c</sup>	$E(ei)_n^{rex}$	$(BAE)^{++}$	PA	$PA_{EXP}$ <sup>c</sup>	GB	$GB_{EXP}$ <sup>c</sup>
<b>1</b>	(231.0) <sub>1</sub>	192.0	191.4	39.0	98.2	219.8	222.2	212.2	214.3
<b>2</b>	(246.5) <sub>1</sub>	214.5	214.5	32.0	115.5	214.6	216.4	207.1	208.5
<b>3</b>	(233.4) <sub>1</sub>	191.7	191.4	41.7	100.7	222.6	225.5	215.4	217.2
<b>4</b>	(230.8) <sub>1</sub>	186.0	193.9	44.8	97.4	225.0	226.6	216.3	218.8
<b>5</b>	(228.7) <sub>1</sub>	184.6	185.2	44.1	97.1	226.1	228.0	218.6	220.0
<b>6</b>	(222.8) <sub>1</sub>	181.0	181.0	41.8	92.0	224.6	226.8	217.5	219.4
<b>7</b>	(234.5) <sub>1</sub>	199.2	200.6	35.3	106.4	220.8	223.4	213.5	216.1
<b>8</b>	(224.0) <sub>1</sub>	180.1	–	43.9	93.2	226.7	210.9	219.4	203.6
<b>9</b>	(221.9) <sub>1</sub>	174.2	–	47.7	88.6	228.0	230.8	221.1	223.4
<b>10</b>	(220.9) <sub>1</sub>	175.8	178.5	45.1	92.1	229.9	232.1	222.6	224.7
<b>11</b>	(176.7) <sub>1</sub>	167.4	166.0	9.3	75.8	222.0	224.9	214.4	217.3
<b>12</b>	(189.7) <sub>1</sub>	177.6	184.5	12.1	83.1	219.1	221.4	211.6	214.1
<b>13</b>	(179.3) <sub>1</sub>	165.4	163.7	13.9	72.5	220.7	223.0	213.7	215.7
<b>14</b>	(170.7) <sub>1</sub>	163.4	166.7	7.3	71.6	221.8	225.0	214.8	218.7
<b>15</b>	(185.0) <sub>1</sub>	164.4	163.7	20.6	79.0	228.2	227.7	221.0	221.4

<sup>(a)</sup> All values are in kcal mol<sup>-1</sup>. <sup>b</sup> Index *n* represents the PRIMO orbital which is ionized in the protonation process, corresponding here always to HOMO (*n* = 1). <sup>c</sup> Experimental data (EXP) for IE, PA and GB values are taken from the NIST database (Ref. 59).

NH(CH <sub>2</sub> ) <sub>n</sub> (n = 2–5)		NMe(CH <sub>2</sub> ) <sub>n</sub> (n = 2–5)		NPh(CH <sub>2</sub> ) <sub>n</sub> (n = 2–5)	
molecule	HOMO	molecule	HOMO	molecule	HOMO
<b>2</b>	-0.39285	<b>7</b>	-0.37373	<b>12</b>	-0.30224
<b>3</b>	-0.37197	<b>8</b>	-0.35699	<b>13</b>	-0.28576
<b>4</b>	-0.36773	<b>9</b>	-0.35361	<b>14</b>	-0.27201
<b>5</b>	-0.36447	<b>10</b>	-0.35206	<b>15</b>	-0.29478

**Figure 2.** Schematic representation of HOMO orbitals for cyclic systems investigated here, together with their orbital energies (in a.u.) obtained by the HF/6–311++G(2df,2pd)//M06–2X/6–31+G(d) level of theory.

corresponding acyclic amines NR(Me)<sub>2</sub> in the analysis with R = H, Me and Ph (systems **1**, **6** and **11**, respectively), which by definition have no Baeyer strain and which will serve as reference gauge molecules in the interpretation of PA values. Calculated proton affinities (PAs), dissected according to triadic analysis, proposed in Equation (3), are given in Table 1, together with the gas-phase basicities (GBs). As a final notice, we would like to emphasize that protonation-induced changes in both the geometry and the electron distribution in these cyclic systems have already been discussed in the literature<sup>42,64</sup> and are not subject matter of the present study.

Before we start analyzing the results presented in Table 1, let us take a look at some general features emerging from these numbers. The overall agreement between M06–2X calculated and experimental data<sup>59</sup> is very good. This holds in particular for calculated PA and GB values, which are for all molecules, but two, found within 3 kcal mol<sup>–1</sup> from experimental data. Exceptions are provided by molecules **14** and **8**, where deviations assume 3.2 and 15.8 kcal mol<sup>–1</sup> for PAs, respectively, and 3.9 and 15.8 kcal mol<sup>–1</sup> for GBs, in the

same order. Particularly worrisome is the latter molecule **8**, where the discrepancy seems unusually high. For *N*-methylazetidine **8**, Ohwada and co-workers<sup>42</sup> calculated PAs of 227.3 and 227.9 kcal mol<sup>–1</sup> using high-level CBS–Q and G3 composite methodologies, thus being in close agreement with our values. Together with the overall success of M06–2X approach in reproducing experimental gas-phase basicity constants presented here, these numbers suggest that both experimental values, PA<sub>EXP</sub>(**8**) = 210.9 kcal mol<sup>–1</sup>, and GB<sub>EXP</sub>(**8**) = 203.6 kcal mol<sup>–1</sup>, quoted by the NIST database,<sup>59</sup> are probably too low, and should be re-examined and measured again. Having that in mind, if we exclude **8** from the correlation, the average absolute deviation between calculated and experimental PAs and GBs drops down to only 2.3 and 2.1 kcal mol<sup>–1</sup>, respectively, which lends credence to the results presented here.

The data in Table 1 reveal several notable trends. Molecules investigated here are all moderately strong bases spanning a range of PA values from 214.6 (**2**) to 229.9 kcal mol<sup>–1</sup> (**10**). In all systems, the reactive PRIMOs are always HOMO orbitals (Figure 2), mean-

ing that the lone pair electrons on the nitrogen atom, that gets protonated, lie in the orbital that is most exposed to the incoming proton. Relative to the parent acyclic strainless compounds, HOMO orbital energies in aziridines are increased by around  $13 \text{ kcal mol}^{-1}$ , which are then reduced back in azetidines, pyrrolidines and piperidines to values close to those found in the corresponding acyclic systems. The reason for that is the fact that upon decrease of the C–N–C bond angle, the nominally  $sp^3$ -hybridized nitrogen atom rehybridizes to increase the  $p$ -character of two orbitals directed toward carbon, which correspondingly increases the  $s$ -character of the other two hybrids, namely the orbital involved in the N–H bond and the nitrogen lone pair.<sup>65</sup> Since  $s$  electrons are closer to the nucleus, this increases the stability of the latter two orbitals. Knowing that C–N–C bond angle compression is largest in three-membered rings **2**, **7** and **12**, it follows that their PRIMOs are stabilized the most, leading to the conclusion that the price to be paid for their single-electron ionization within Koopmans' approximation is the largest. As a result, this hybridization effect of the nitrogen atom leads to a continuous increase of the basic strength on going from three- to six-membered cyclic amines. This relationship between orbital energies and PA values is evidenced in molecules investigated here (Table 1), but qualitatively at best. A notable exception to latter relation is provided with **15**, in which the energy of the HOMO is unexpectedly high, although **15** maintains pronounced basicity within the same group of molecules **11**–**15**. This offers particular evidence that the consideration of the properties of initial bases only could lead to wrong conclusions about their basicities, or other properties related to the reactivity, and that the whole protonation reaction should be considered if a quantitatively correct prediction of the trend of PA values is desired. Since, within triadic picture, Koopmans' ionization energies mirror properties of the initial state, therefore being a consequence of the magnitude of the ring strain in neutral bases, we could draw a conclusion that there is no simple relation between ring strain and the basicity, being in agreement with Ohwada and co-workers who also reached the conclusion that "angle strain in cyclic amines is not the major source of the difference in the strength of basicity".<sup>42</sup>

We will start our analysis with the smallest parent acyclic system dimethylamine **1**. Its calculated proton affinity is  $PA(\mathbf{1}) = 219.8 \text{ kcal mol}^{-1}$ , making compound **1** reasonably basic molecule with PA value similar to, for example, the imino compound 9H-purine ( $PA_{\text{EXP}} = 219.9 \text{ kcal mol}^{-1}$ ).<sup>59</sup> Relative to **1**, the basicity of cyclic molecule **2** is lower, whereas values for **3**–**5** are all higher, increasing in the same order as well. Triadic formula (5) yields:

$$PA(\mathbf{2}) - PA(\mathbf{1}) = [-15.5; -7.0; 17.3] = -5.2 \text{ kcal mol}^{-1}$$

$$PA(\mathbf{3}) - PA(\mathbf{1}) = [-2.4; 2.7; 2.5] = 2.8 \text{ kcal mol}^{-1}$$

$$PA(\mathbf{4}) - PA(\mathbf{1}) = [0.2; 5.8; -0.8] = 5.2 \text{ kcal mol}^{-1}$$

$$PA(\mathbf{5}) - PA(\mathbf{1}) = [2.3; 5.1; -1.1] = 6.3 \text{ kcal mol}^{-1}$$

It follows that **2** is by  $5.2 \text{ kcal mol}^{-1}$  a weaker base than parent compound **1**, because, on one hand, the HOMO of **2** is by  $15.5 \text{ kcal mol}^{-1}$  more stabilized than in **1** leading to lower basicity. In contrast, the bond association energy in **2** is increased by  $17.3 \text{ kcal mol}^{-1}$ . These two trends, cancelling each other out, are intuitively clear. When the lone pair is more tightly bound and the price for ionization is larger, like in **2**, then the energy gain upon formation of a new N–H bond is more beneficial. This conclusion is correct, however, qualitatively but not quantitatively as it will become obvious later. The mentioned increase of  $(BAE)^{++}$  in **2** is not enough to make it more basic than **1**, since the relaxation energy in **2** is lower as well. Taken all together, lowering of the relaxation energy, an intermediate state effect, is an effectively decisive term leading to the lower basicity of **2** relative to **1**. Similarly, in larger cyclic amines, differences in the bonding C–N–C angles and the hybridization effect of the initial state become even less important, whereas the relaxation effect prevails due to the larger number of neighbouring carbon atoms leading to enhanced basicity in cyclic amines. It is easy to see that the basicity of investigated amines cannot be satisfactorily rationalized by considering the initial state only. Along that line, if we would consider only features of the neutral base in **3**, it would predict that **3** is a weaker base than **1** by at least  $2.4 \text{ kcal mol}^{-1}$ . This is not the case, as **3** is by  $2.8 \text{ kcal mol}^{-1}$  a stronger base than **1**, as a result of a joint effect of the intermediate and final state effects. Again different trend of values is further observed for **4**. Although **4** maintains some ring strain, HOMO(**1**) and HOMO(**4**) have almost the same orbital energies, which, employing descriptors only related to initial bases, would suggest that these two molecules are equally basic. Table 1 reveals the opposite, the difference being  $5.2 \text{ kcal mol}^{-1}$  in favour of **4**, being predominantly determined by larger relaxation energy in **4**<sup>++</sup> upon electron ionization – an obvious intermediate state effect. This set of molecules, **1**–**4**, represents a clear-cut example that strongly supports the concept that ring strain is not a predominant factor, which determines the basicity of such small strained molecules. Lastly, piperidine **5** has almost no ring strain, the corresponding C–N–C angle assumes  $111.8^\circ$  at the M06-2X/6-31+G(d) level, which induces no rehybridization of the nitrogen atom and no particular stabilizing effect

to the HOMO orbital. Thus, in this case, single-electron ionization is less costly and the difference in Koopmans' ionization energies works towards the increasing basicity of **5**, which together with second largest relaxation energy of all compounds investigated here, makes this molecule the strongest base within this family of molecules (**1–5**). At the end, it is useful to emphasize that triadic analysis clearly reveals not only that the correct trend in basicity of systems **2–5** cannot be explained by considering only the features of initial bases, but also that, in all four cases, both properties of different states and their diverse relative significance are factors governing their basicities. We note in passing that, despite the fact that throughout this work, cyclic amines  $\text{NR}(\text{CH}_2)_n$ , with  $n = 3–5$  and  $\text{R} = \text{H}, \text{Me}$  and  $\text{Ph}$ , exhibit an increase in the basicity with the ring size  $n$ , and that, within family of molecules, the corresponding amplifications in PA values cover ranges between 3.2 and as much as  $7.4 \text{ kcal mol}^{-1}$ , in water solution a distinct levelling behaviour was found in aqueous  $\text{p}K_a$  values,<sup>64</sup> such that systems **3–5**, **8–10** and **13–15** possess  $\text{p}K_a$  values in a very narrow range between 11.22–11.29, 10.08–10.46 and 3.57–5.22  $\text{p}K_a$  units, respectively. This provides convincing evidence to why it is important to investigate and understand intrinsic solvent-free acid-base properties of target molecules. Nevertheless, it remains a challenge for future studies to examine the influence of ring strain on solution-phase basicity constants, such as aqueous  $\text{p}K_a$  values, in the investigated cyclic amines. For such narrowly spaced data, the difficulty lies in the selection of the appropriate computational methodology to (re)produce accurate  $\text{p}K_a$  values, since, for example, brute force calculations employing implicit continuum solvation could yield estimates easily diverging by over 4–5  $\text{p}K_a$  units.<sup>66</sup> The proper study should involve explicit solvation, to account for the specific solute-solvent interactions, accompanied with the appropriate treatment of electrostatic effects, extensive sampling and thermal averaging.<sup>67–70</sup> These are, however, associated with high computational costs and are beyond the scope of the present manuscript.

*N*-methyl derivatives **6–10** are by around 3–6  $\text{kcal mol}^{-1}$  stronger bases than the matching systems **1–5**. This is not surprising, since the methyl group is an efficient electron-donating substituent, and it helps in accommodating the positive charge produced upon protonation. In our triadic picture, the latter effect is evident in the increased relaxation energy, since the positive charge is generated during electron ionization already in the intermediate radical cation stage. For the case of parent molecule **6**, this becomes apparent as  $\text{PA}(\mathbf{6}) - \text{PA}(\mathbf{1}) = [8.2; 2.8; -6.2] = 4.8 \text{ kcal mol}^{-1}$ . Still, the predominant reason to the increased basicity of **6** is the increased Koopmans' term, which is a consequence of the C–H bond electron pair/nitrogen lone electron pair repulsion. In other words, the nitrogen lone pair in

trimethylamine **6** is placed in the HOMO orbital, which lies higher in energy (i.e., it is destabilised) than the matching orbital in dimethylamine **1** (Table 1). The  $(\text{IE})_n^{\text{Koop}}$  term for **6** is therefore lower, implying a less costly ejection of an electron in the triadic scheme. The initial favourable effect is somewhat reduced by a considerably lower homolytic bond formation energy, but the overall effect is an increase in the basicity of **6**. The same trend of values can be obtained by considering other cyclic amines **7–10** within this family of compounds. Now, the question arises: What is the effect of the ring strain on basicity within *N*-methyl derivatives **6–10**? It turns out, that most of the conclusions drawn in the previous section for systems **1–5** hold here as well. Taking **6** as the reference acyclic molecule, the triadic analysis gives:

$$\text{PA}(\mathbf{7}) - \text{PA}(\mathbf{6}) = [-11.7; -6.5; 14.4] = -3.8 \text{ kcal mol}^{-1}$$

$$\text{PA}(\mathbf{8}) - \text{PA}(\mathbf{6}) = [-1.2; 2.1; 1.2] = 2.1 \text{ kcal mol}^{-1}$$

$$\text{PA}(\mathbf{9}) - \text{PA}(\mathbf{6}) = [0.9; 5.9; -3.4] = 3.4 \text{ kcal mol}^{-1}$$

$$\text{PA}(\mathbf{10}) - \text{PA}(\mathbf{6}) = [1.9; 3.3; 0.1] = 5.3 \text{ kcal mol}^{-1}$$

One can easily notice that, compared to secondary amines **1–5**, the trend in the above values is maintained for the tertiary amines. During protonation, the predominant influence of various states governing basicity is the same as in the previous set of molecules, emphasizing once again advantages that the triadic analysis offers in the interpretation of PA values by considering the protonation reaction in its entirety. We could mention that relative triadic contributions as well as changes in proton affinities on going from three- to six-membered rings are slightly smaller here than in **1–5**. In other words, the spread of the PAs of compounds **6–10** is smaller than that in the series **1–5**.

At the end we will focus on the *N*-phenyl derivatives. The phenyl group,  $-\text{C}_6\text{H}_5$ , is a substituent that is much different from the methyl residue, as it displays its influence predominantly through the polarisation and the  $\pi$ -resonance effects of its electron-rich aromatic fragment. Still, one observes that the basicity of the *N*-phenyl derivatives is very similar to that of the corresponding *N*-methyl counterparts, being only slightly smaller as a rule (Table 1). For example, **12** is by only  $1.7 \text{ kcal mol}^{-1}$  a weaker base than **7**. Triadic analysis,  $\text{PA}(\mathbf{12}) - \text{PA}(\mathbf{7}) = [44.8; -23.2; -23.3] = -1.7 \text{ kcal mol}^{-1}$ , reveals that this is a cumulative result of an interplay between the favourable initial state effect, and destabilizing intermediate and final state effects, both large in magnitudes but opposite in signs. Data in Table 1 expose that the same trend of values is ob-

tained for the remaining molecules **13–15** relative to **8–10**.

What is even more interesting for the present purpose is the difference in basicity between compounds **11–15** and parent molecules **1–5** to estimate the effect of the *N*-phenyl substitution. It turns out that the *N*-phenyl derivatives are characterized by (a) further less stable HOMO orbitals, thus even less costly ionization energies than those found for systems **6–10**, (b) lower relaxation energies upon electron ionization, and (c) lower homolytic bond association energies. The first effect promotes, while the other two reduce the basicity of molecules **11–15**. Consequently, **11** is, though not as much as **6**, but still slightly more basic than **1**,  $PA(\mathbf{11}) - PA(\mathbf{1}) = [54.3; -29.7; -22.4] = 2.2 \text{ kcal mol}^{-1}$ . These numbers suggest that by making *N*-phenyl substitution, one facilitates electron ionization from the nitrogen lone pair, which strongly promotes its reactivity towards protonation, the same effect already noticed with the *N*-methyl derivatives, but much more pronounced here. However, this large favourable effect is almost completely neglected by the fact that the phenyl group also strongly stabilizes the intermediate radical state through the resonance effect with the newly formed *N*-centred radical, which disfavours the subsequent  $N^+-H$  bond formation present in the protonated form. All of the three triadic contributions show regular behaviour but are varying in magnitudes. This leads to the deviating trend in the resulting PA values, in a way that molecules **11**, **12** and **15** are stronger bases than the corresponding parent molecules **1**, **2** and **5**, respectively, whereas **13** and **14** are weaker bases than **3** and **4**, in the same order.

It remains to answer the question how the cyclization affects the basicity within the *N*-phenyl derivatives? Analogously, one can select **11** as a gauge molecule and write the triadic analysis as:

$$PA(\mathbf{12}) - PA(\mathbf{11}) = [-13.0; 2.8; 7.3] = -2.9 \text{ kcal mol}^{-1}$$

$$PA(\mathbf{13}) - PA(\mathbf{11}) = [-2.6; 4.6; -3.3] = -1.3 \text{ kcal mol}^{-1}$$

$$PA(\mathbf{14}) - PA(\mathbf{11}) = [6.0; -2.0; -4.2] = -0.2 \text{ kcal mol}^{-1}$$

$$PA(\mathbf{15}) - PA(\mathbf{11}) = [-8.3; 11.3; 3.2] = 6.2 \text{ kcal mol}^{-1}$$

Interestingly, the first three molecules here, **12–14**, are weaker bases than acyclic reference **11**, which is a behaviour that is changed to what was already observed in other compounds studied here. Moreover, the trend in triadic contributions is different in all three systems. In **12**, the lower basicity is primarily determined by the initial state effect, while it is a consequence of interplays between initial and final state effects in **13**, and that of intermediate and final state contributions in **14**.

Molecule **15** is clearly a case on its own. At first sight one notices an increase in the orbital energy relative to **14**, because of a strong resonance interaction of the nitrogen lone pair electrons and the phenyl  $\pi$ -orbitals (Figure 2). Relative to **11**, this interaction stabilizes the initial system by  $8.3 \text{ kcal mol}^{-1}$  and works towards the reduction of the basicity of **15**. However, upon electron ionization, the newly formed nitrogen radical centre is in **15** significantly stabilized by the presence of the phenyl substituent, which is not so pronounced in **11**. This process overcomes the unfavourable influence of the Koopmans' term and together with a small contribution originating from the bond association energy makes **15** by  $6.2 \text{ kcal mol}^{-1}$  a stronger base than its acyclic counterpart **11**.

## CONCLUSION

Triadic decomposition of the gas-phase proton affinities (PAs) of twelve small strained nitrogen heterocycles, including aziridine, azetidine, pyrrolidine and piperidine, and their *N*-methyl and *N*-phenyl derivatives, was calculated employing the M06-2X/6-311++G(2df,2pd)//M06-2X/6-31+G(d) level of theory. We obtained excellent agreement between computationally obtained adiabatic ionisation energies, proton affinities and the gas-phase basicities (GBs), and the available experimental data, with the only exception being *N*-methylazetidine, for which a remarkable discrepancy in the calculated PA and GB values assumes  $15.8 \text{ kcal mol}^{-1}$  in both cases, suggesting that these two quantities should be experimentally revised and measured again. The results were compared with the corresponding acyclic molecules and revealed that there is no simple relationship between the resulting basicity, on one hand, and the magnitude of ring strain or any other feature depending only on the properties of initial bases, on the other. Our analysis led us to safely conclude that angular ring strain in the initial state is not the major source of the basicity trends in the investigated cyclic amines. Quite interestingly, it turned out that, if one considers a subset of closely related molecules, for example only the *N*-unsubstituted systems, in each case different triadic contributions, originating either from the properties of the initial base, final protonated form or their interplay, are predominantly responsible in determining their basicity. This emphasizes the usefulness of the triadic approach in rationalizing molecular reactivity and suggests that, for a complete picture of the protonation process and the accurate interpretation of the subtle differences in PA values one needs to consider all three terms appearing in the triadic scheme separately.

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