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Protonation of Azines and Purines as a Model for the Electrophilic Aromatic Substitution – Rationalization by Triadic Formula

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Dedicated to Professor Dušan Hadži on the occasion of his 90th birthday

Abstract

First gas-phase carbon proton affinities of eleven azines and purines (pyrrole, pyrazole, imidazole, pyridine, pyridazine, pyrimidine, pyrazine, bicyclic purine, pyridine–*N*–oxide, 2-aminopyrimidine and uracil) were calculated by a composite G3B3 methodology and used to probe their susceptibility to undergo electrophilic aromatic substitution (EAS), taking benzene as a reference molecule. The results revealed excellent agreement with the available experimental data and were interpreted using the triadic approach. We found out that pyrroles, which are more reactive towards EAS reaction than benzene, are stronger carbon bases than the latter compound, whereas pyridines exhibit lower carbon basicity, being at the same time less reactive toward substitution by electrophiles than benzene. In all of the investigated molecules the frontier orbital describing the corresponding π–electron density at the carbon atom to be protonated is HOMO as calculated by the HF/G3large//B3LYP/6–31G(d) level of theory. Our results are in a disagreement with the work by D'Auria (M. D'Auria, *Tetrahedron Lett.* **2005**, *46*, 6333–6336; *Lett. Org. Chem.* **2005**, *2*, 659–661), who at B3LYP/6–311+G(d,p) level found out that in some of systems investigated here the HOMO orbital is not of π–symmetry, which was used to rationalize the lower reactivity of these systems towards EAS. It turned out that energies of HOMO orbitals alone correlate very poorly with carbon proton affinities, unlike the difference in proton affinities between the most basic carbon atom and thermodynamically the most favourable site of protonation, which performs much better. Triadic analysis demonstrated the importance of considering a complete picture of the protonation process and all three terms appearing in the triadic scheme individually when discussing trends in basicity/nucleophilicity of closely related molecules.

Keywords: Pyrroles, pyridines, protonation, triadic analysis, electrophilic aromatic substitutions

1. Introduction

Azines and purines are class of mono- and fused bicyclic organic compounds, respectively, in which one or more carbon atoms are replaced by a nitrogen atom within the ring(s). These structural features are an essential constituting motif of several biologically important natural products[1] and many synthetic drugs. Classical examples of such purines include adenosine, caffeine, uric acid, and two bases adenine and guanine, which are components of DNA and RNA. Along the same line, there is a large class of pharmacologically important pyrimidine derivatives that act as compounds with anti-HIV,[2,3] anti-adenovirus[4] and anti-HBV activities,[5] regulators of pain sensitivity and persistence,[6] antidepressants[7] and inhibitors of cyclin-dependent kinase as a potential drug candidate for cancer therapy.[8,9] Heterocyclic amines, on the other hand, constitute a large family of chemical carcinogens,[10] while macrocyclic compounds containing nitrogen heterocycles attracted interest as complexing agents toward neutral molecules[11] and metal cations,[12] and served as potent superbases.[13,14]

It is outside the scope of the present manuscript to account for all of the existing areas where nitrogen containing heterocycles were recognized as promising systems, but it is beyond doubt that their biological relevance indu-

ced extensive research toward the understanding of their structure–activity relationship.[15,16] This class of compounds is just one of many fields where Professor Hadži, together with his co-workers, made numerous significant contributions. His research interests involved determination of the structure, conformational, tautomeric and acid–base properties of such molecules,[17–19] insight into their interactions with solvent molecules[20,21] as well as with other important systems,[22–24] and their ability to participate in the proton transfer reactions.[25]

Incorporation of the nitrogen atom into the homocyclic aromatic moiety can easily change its chemical reactivity extensively, although, for example, its aromaticity remains fairly unchanged. For the case of pyridine versus benzene the latter was revealed by Wiberg[26] and Bird[27] and their co-workers employing calculated resonance energies, and through the inspection of the relevant homodesmotic reactions by Schleyer and Pühlhofer,[28] in contrast to Mosquera et al.[29] who concluded that "the insertion of N atoms decreases the aromaticity" of pyridine substantially compared to benzene. However, very recently Schleyer and co-workers convincingly demonstrated[30] that all possible azabenzenes, up to the hexazine N_6, are basically equally aromatic as benzene as evaluated through the nucleus-independent chemical shift index [$NICS(0)_{\pi zz}$] and the block localized wave function (BLW) based extra cyclic resonance energies (ECREs). In other words, sequential hetero–*N* substitution has little effect on the aromaticity of benzene. Still, it is well known that such aromatic compounds on reaction with electrophilic reagents undergo electrophilic aromatic substitution (EAS), unlike their open chain unsaturated counterparts, where addition reaction takes place. The former type of reactions is one of the fundamental processes of organic chemistry, which enables preparation of substituted derivatives of aromatic compounds. The mechanism of EAS involves two stages:[31,32] in the first and the rate-limiting step an electrophile accepts an electron pair from the π–system of the involved aromatics to form a resonance stabilized carbocation (σ–complex, or Ingold–Hughes arenium ion). Once formed, it rapidly loses a proton in the second step, restoring the aromaticity of the ring and giving the product of the EAS reaction. In the case of heterocyclic aromatic compounds, the great variety of available structural types causes this class of compounds to range from exceedingly reactive to practically inert toward EAS. For example, since nitrogen atom is more electronegative than CH group in benzene, and it holds electrons more tightly, pyridines are far less reactive toward substitution by electrophilic reagents than benzene.[33] On the other hand pyrroles are extremely reactive toward electrophilic aromatic substitution.[33] Like benzene they possess six π–electrons, but they are delocalized over five atoms, not six, and are not held as strongly as those of benzene.

An attempt to shed some light on differences in susceptibility toward electrophilic substitution reactions for azines and purines and to help understand this behaviour was made by D'Auria few years ago.[34] In his papers he assumed a frontier orbital control of these reactions and considered the symmetry of the corresponding HOMO orbitals in elucidating trends of reactivity of these compounds. He concluded that the low reactivity of pyridine, pyridazine, pyrazine, pyrimidine and purine to undergo electrophilic substitution could be explained with the fact that their HOMOs are not π–orbitals, but rather of σ–symmetry. On the other hand, in a more reactive pyridine–N–oxide, for example, the HOMO is π–orbital. D'Auria also reported[34] that this concept is not general, since, for example, it cannot explain a lower reactivity towards EAS of the imidazole ring compared to pyrrole, since in both cases the corresponding HOMOs are π–orbitals. Although a simple consideration of the frontier orbital symmetry could possibly reveal trends in the reactivity in the qualitative way, we do not find it sufficient for a more quantitative treatment of these phenomena. This is simply because the orbital structure of the reacting molecules is only a part of the picture of the whole reaction process. In general, reactivity of a molecule is determined both by properties of the initial molecules, but also by the features of the formed product(s), which are completely ignored in any kind of information extracted from the structure of the initial molecular orbitals. The latter statement holds even without bringing into the picture the effects of the transition state structure and the kinetic barrier height of a given chemical reaction, and particularly without proper inclusion of the solvent effect, which could have dramatic influence on polar reactions like electrophilic substitution.[35] This holds in general, although, for example Kržan and Mavri[36] recently suggested that the stability of the carbon–rich materials could be probed by just considering atomic volume of the carbon atoms through Bader's Atoms in Molecules (AIM) formalism.[37] The simplest example where orbital picture fails completely is in the case of molecules possessing several possible sites of electrophilic attack, where consideration of just frontier orbitals would predict identical reactivity trends for all such sites connected with the same reactive frontier orbital. However, in reality diverse reactivity patterns are observed for various non-equivalent sites, which is due to the features of the different products formed.

Therefore, it is the purpose of this paper to provide deeper and more complete quantitative explanation of different reactivity trends of several azines and purines concerning electrophilic substitution. In doing so, we will use methods of modern computational chemistry and consider protonation reactions, since the proton is the smallest Lewis acid and the simplest electrophile. As such, addition of a proton could be considered as the incipient step of the most fundamental electrophilic substitution reaction and a useful probe of the susceptibility toward more complex electrophiles for a family of closely related molecules. We will consider the gas-phase proton affinities of investiga-

ted systems, since they offer intrinsic properties, i.e. properties of the isolated molecules, which will be interpreted using our recently proposed triadic formula (for a review on triadic formalism see reference 38).

2. Computational Methodology

According to Brønsted, basicity is the measure of the ability of a molecule to accept a proton in a chemical reaction. Accordingly, basicity in the gas phase 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:

$$BH^+(g) \rightarrow B(g) + H^+(g);\ \Delta G^\circ = GB,\ \Delta H^\circ = PA \quad (1)$$

Here B and BH^+ denote the base in question and its protonated form, the conjugate acid, respectively. ΔG° gives intrinsic basicity of a compound not contaminated by the presence of the solvent molecules or counter-ions. The corresponding proton affinity ΔH° is related to the electronic structure of the base and its conjugate acid, and is calculated as:

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

where ΔE° represents the change in the total molecular energy in reaction (1), which includes the electronic and the zero-point energies, as well as the finite temperature (298.15 K) correction, whereas $\Delta(pV)$ denotes the pressure-volume work term. Both ΔG° and ΔH° energies are computed, provided and compared to experimentally available values, but our analysis will focus only on the proton affinities and their interpretation, because they offer a good description of basicities, being simpler for analysis at the same time.

In order to get an insight into the origin of basicity of studied molecules, we performed a triadic analysis[38] of the proton affinities, Equation (3), which enables estimation of the influence of the properties of the initial (neutral base) and final states' effects (protonated molecule), as well as their interplay, on Brønsted basicities[39] for molecules in the gas phase.

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

The physical picture behind this approach is the separation of the protonation process of a neutral base (Brønsted basicity) or a conjugate base anion[40] (reverse process governing Brønsted acidity) into the three sequential steps: (*i*) removal of an electron from the base in question to give a radical cation, (*ii*) attachment of the ejected electron to the incoming proton to form the hydrogen atom, and (*iii*) creation of the chemical bond between two newly formed radicals. 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 Deakyne.[41] Triadic analysis also proved useful in explaining substituent effects in carboxylic acids[42a] and phenols[42b] as well as Lewis acidity of borane (BH_3) derivatives[43] and some unsaturated organic molecules[44] towards the hydride ion H^-. This resolution of the protonation process into three consecutive steps has a high cognitive value, enabling classification of studied molecules into three categories depending on whether the initial, intermediate or final state effect is predominant, as described below. Initial state effects on gas-phase basicities of neutral bases are reflected in Koopmans' ionisation energies,[45] $IE(B)_n^{Koop}$, 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 1st). The $IE(B)_n^{Koop}$ values reflect the price to be paid for taking an electron from the neutral molecule in a 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 neutral base under scrutiny, they reflect genuine properties of the initial state. The geometric and electronic reorganisation effects following electron ejection are given by the relaxation energy $E(ei)^n_{rex}$, defined by Equation (4),

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

where $IE(B)_1^{ad}$ 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^{-1},[46] whereas the bond association energy describing homolytic bond formation between created radicals is given by the $(BAE)^{\bullet+}$ term, and will be used in connection with the properties of the final state – in other words, with the protonated molecule. It is calculated as an enthalpy of the reaction in which hydrogen atom and the radical cation of the investigated base form protonated conjugate acid. Although the formation of a new X–H bond is essentially a two-body interaction between the atoms X and H, or (rather) between their almost localised valence electrons, there is some additional relaxation of the rest of the molecule. For the sake of simplicity, this final relaxation is included in the $(BAE)^{\bullet+}$ term.

Although the above procedure is a simple extension of the well known thermodynamic cycle, where the sum of $IE(B)_n^{Koop}$ and $E(ei)^n_{rex}$ is replaced by a single term $IE(B)_1^{ad}$, inclusion of the Koopmans' ionisation energies offers large interpretative advantages. The $IE(B)_n^{Koop}$ corresponds to the *n*–th ionisation energy, which is related to the specific highest MO affected most by the protonation, which is conveniently termed PRIMO (PRIncipal Molecular Orbital). It is usually the highest molecular orbital

corresponding to lone pair electrons 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.

In obtaining all thermochemical data we have used a reliable and accurate G3B3 methodology,[47] which is parameterized to provide an excellent compromise between reliability (accuracy) and practicability (feasibility). It is a composite computational procedure, which uses several lower-level single-point calculations to arrive at the QCISD(T)/G3large//B3LYP/6–31G(d) level of theory. It means that all molecular geometries were optimized and thermodynamic parameters calculated by the very efficient B3LYP/6–31G(d) method. Analysis of all normal vibrational modes at the same level of theory was used to verify that all structures correspond to true minima on the electronic potential energy surface. The Koopmans' ionisation energies $(IE)_n^{Koop}$ were computed by the HF/G3large//B3LYP/6–31G(d) level of theory. Radical cations were treated with unrestricted approach. All calculations were performed using a GAUSSIAN 09 suite of programs.[48]

3. Results and Discussion

Molecules studied in this work are presented in Figure 1. They feature benzene **1** as a reference molecule; monocyclic 5-membered rings pyrrole **2**, pyrazole **3** and imidazole **4**; monocyclic 6-membered rings pyridine **5**, pyridazine **6**, pyrimidine **7** and pyrazine **8**; bicyclic purine **9**; pyridine–*N*–oxide **10**, 2-aminopyrimidine **11** and nucleic base uracil **12** in its amide tautomer. Molecules **5**–**12** were also considered in already mentioned papers by D'Auria.[34] The gas-phase basicity parameters of these compounds, dissected according to triadic analysis proposed in the Equation (3), are given in Table 1. These include both proton affinities (PAs) and gas-phase basicities (GBs).

Before any analysis of the basicity values from Table 1 is presented, let us take a look at some general observations emerging from these numbers. First of all, it should be strongly pointed out that G3B3 methodology performs amazingly well compared to experimentally determined data taken from the reference 46. This holds in particular for basicity values, where all computationally predicted quantities lie within 2 kcal mol^{-1} from experimental data, a threshold which is usually taken as the chemical accuracy. From the available data for molecules **1**–**10**, it turns out that the absolute average deviation and the largest difference between the two sets of data assume 0.8 and 1.6 kcal mol^{-1} for proton affinities, respectively, and 0.4 and 1.0 kcal mol^{-1} for the gas-phase basicities, in the same order. The situation with the ionisation energies is a bit less satisfactory, where absolute average deviation and the largest difference take values 1.3 and 2.5 kcal mol^{-1}, respectively. However, the latter is not surprising, since ionisation energies are difficult quantities to calculate more accurately, on top of the fact that experimental determinations involve rather large uncertainties in measured values in some instances. Overall, this is an excellent achievement, which lends credence to the applied computational method for the future studies of similar chemical phenomena. Therefore, for systems **9**, **11** and **12**, where some experimental data are missing, the presented calculated values could be taken as a reliable estimate of their ionisation energies and basicity constants in the gas-phase.

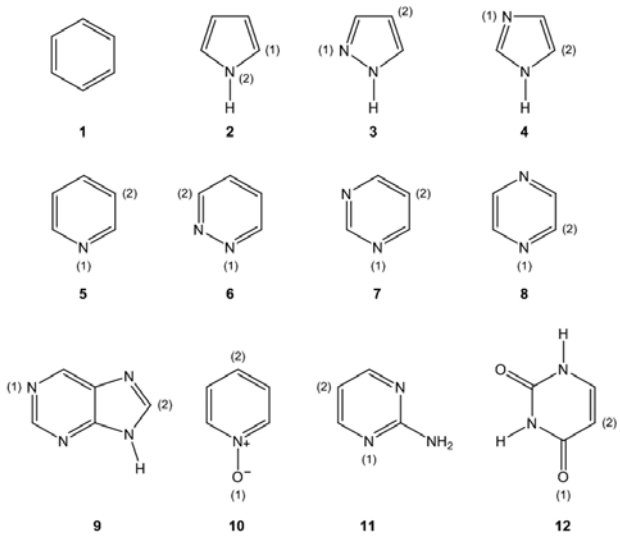

Figure 1. Schematic representation of investigated molecules. Numbering of atoms denotes two considered sites for the proton attack, which include the most basic carbon as well as the most basic heteroatom. Atom marked with number (1) is thermodynamically the most basic site in molecule.

It is evident from data in Table 1 and from the graphical representation of the relevant PRIMO orbitals depicted in Figure 2 that in all systems **1**–**12** the HOMO orbital is always of π–symmetry. This means that, within Koopmans' approximation, the price to be paid for the ionisation of all investigated neutral bases equals the negative of the energy of their HOMO orbital in the case of the proton attack to carbon atoms. This is in a disagreement with what was demonstrated by D'Auria[34] in his work using B3LYP/6–311+G(d,p) calculation. He reported that in molecules **5**–**9** HOMO orbitals are σ–orbitals, rather than π–systems. D'Auria used this observation to rationalize lower reactivity of these compounds towards electrophilic substitution reactions compared to benzene. However, it was demonstrated in the literature[49] that Hartree–Fock (HF) molecular orbital energies are closer to the experimental ionization potentials than those obtained from the DFT methods, which makes HF orbitals more suitable for our purpose. As a conclusion, it follows that the symmetry

Table 1. G3B3 proton affinities (PAs), their resolution into triadic components, and the gas-phase basicities (GBs) of selected nitrogen containing heterocycles (all values in kcal mol^{-1}).

molecule	$(IE)_n^{Koop\,a}$	$(IE)_1^{ad}$	$(IE)_1^{ad}{}_{EXP}^{b}$	$E(ei)^n{}_{rex}$	$(BAE)^{\bullet+}$	PA^c	$PA_{EXP}{}^b$	GB^c	$GB_{EXP}{}^b$
1	$(211.3)_1$	214.8	213.2	–3.5	78.9	$(177.7)_C$	179.3	$(173.0)_C$	173.4
2	$(187.1)_1$	189.9	189.3 ± 0.1	–2.8	84.5	$(208.2)_{C1}$	209.2	$(201.4)_{C1}$	201.7
	$(217.8)_2$	189.9		27.9	66.2	$(189.9)_{N2}$		$(183.2)_{N2}$	
3	$(218.2)_1$	214.4		3.8	92.5	$(191.7)_{C2}$		$(185.0)_{C2}$	
	$(289.6)_3$	214.4	213.3 ± 0.2	75.2	113.7	$(212.9)_{N1}$	213.7	$(206.3)_{N1}$	205.7
4	$(202.1)_1$	203.8		–1.7	85.4	$(195.2)_{C2}$		$(188.5)_{C2}$	
	$(275.4)_3$	203.8	203.2 ± 0.2	71.6	115.3	$(225.1)_{N1}$	225.3	$(218.2)_{N1}$	217.3
5	$(218.4)_1$	214.6		3.8	69.8	$(168.8)_{C2}$		$(163.5)_{C2}$	
	$(263.3)_3$	214.6	213.5 ± 0.2	48.8	122.5	$(221.5)_{N1}$	222.0	$(214.7)_{N1}$	214.7
6	$(241.3)_1$	202.2		39.2	39.6	$(151.0)_{C2}$		$(145.2)_{C2}$	
	$(256.3)_3$	202.2	201.6 ± 2.5	54.1	106.0	$(217.4)_{N1}$	216.8	$(210.6)_{N1}$	209.6
7	$(237.9)_1$	217.7		20.2	63.2	$(159.1)_{C2}$		$(153.7)_{C2}$	
	$(262.7)_2$	217.7	215.2 ± 1.6	45.0	115.3	$(211.2)_{N1}$	211.7	$(204.5)_{N1}$	204.5
8	$(226.1)_1$	215.4		10.7	61.4	$(159.6)_{C2}$		$(153.4)_{C2}$	
	$(259.9)_2$	215.4	214.0 ± 0.2	44.6	110.3	$(208.6)_{N1}$	209.6	$(201.8)_{N1}$	202.4
9	$(211.3)_1$	215.0		–3.8	74.8	$(173.4)_{C2}$		$(167.1)_{C2}$	
	$(260.4)_3$	215.0		45.4	121.0	$(219.5)_{N1}$	219.9	$(212.7)_{N1}$	212.3
10	$(202.6)_1$	195.1		7.5	64.4	$(182.9)_{C2}$		$(176.6)_{C2}$	
	$(202.6)_1$	195.1	193.2 ± 0.5	7.5	101.2	$(219.7)_{O1}$	220.7	$(213.6)_{O1}$	213.4
11	$(207.4)_1$	207.3		0.1	89.2	$(195.5)_{C2}$		$(189.2)_{C2}$	
	$(255.3)_2$	207.3		48.0	111.9	$(218.2)_{N1}$		$(211.5)_{N1}$	
12	$(232.3)_1$	215.8		16.5	88.6	$(186.4)_{C2}$		$(180.5)_{C2}$	
	$(283.4)_3$	215.8		67.6	106.7	$(204.5)_{O1}$		$(197.6)_{O1}$	

[a] Index *n* represents the PRIMO orbital which is ionised in the protonation process, in a way that the number 1 stands for HOMO, 2 implies HOMO–1 and so on. [b] Experimental data (EXP) for IE, PA and GB values are taken from NIST database (reference). [c] Subscripts (N), (C), (1) and (2) denote the site of the protonation in accordance with the atom numbering shown on Figure 1.

of HOMO orbitals alone cannot be used to explain different reactivity trends of azines and purines toward electrophilic aromatic substitution. It also becomes apparent from the data in Table 1 that all investigated compounds are, thermodynamically speaking, nitrogen or oxygen, rather than carbon bases. In other words, nitrogen or oxygen atoms represent preferential sites of the proton attack in these systems. The only exception, apart from the benzene **1**, because of a trivial reason, is provided by pyrrole **2**, where carbon protonation site is more basic by 18.3 kcal mol^{-1}. These observations could explain why the susceptibility towards electrophiles is diminished in some systems, possibly by the large difference in basicity between carbon atom and the other heteroatom present in the molecule, in favour of the latter. This will be examined later in the paper.

At the beginning, we will consider only carbon basicity of these compounds, exerted at the most favourable C–atom, because these values serve as an indication of the propensity of these molecules to undergo electrophilic substitution reactions. We will start our analysis with the benzene **1**, which is the simplest systems investigated here, and which should be taken as a reference molecule. Its proton affinity is 177.7 kcal mol^{-1} (Table 1), which makes it a low-basicity compound, close to the basicity of cyclopropenyl radical ($C_3H_3^{\bullet}$), formic acid (HCOOH) or elementary cobalt, whose experimentally determined proton affinities assume 176.6, 177.3 and 177.5 kcal mol^{-1}, respectively.[46] Its PRIMO orbital for the carbon protonation is doubly degenerate HOMO orbital as depicted in Figure 2.

As already mentioned, pyrroles are much more prone to electrophilic substitution than benzene,[33] which means that their basicity should be larger. In the case of molecules **2**–**4** this is nicely evidenced with the increased carbon proton affinity values relative to benzene, by 30.5, 14.0 and 17.5 kcal mol^{-1}, respectively. To determine whether differences in properties of initial bases, features of protonated conjugate acids or their interplay dominate these diversities in the proton affinity values, it is useful to define the triad of contributions to PA values as:

$$\Delta PA(\mathbf{M}) = PA(\mathbf{M}) - PA(M_{REF}) = [-\Delta(IE)_n^{Koop}; \Delta E(ei)^n{}_{rex}; \Delta(BAE)^{\bullet+}] \quad (5)$$

where **M** and M_{REF} denote molecule in question and the reference base, respectively, whereas square brackets imply summation of the three terms within, defined as:

molecule	HOMO	HOMO–1	HOMO–2
1	$(-0.33667)_{C}$	–0.33667	
2	$(-0.29814)_{C1}$	$(-0.34705)_{N1}$	
3	$(-0.34779)_{C2}$	–0.36600	$(-0.46159)_{N1}$
4	$(-0.32201)_{C2}$	–0.40146	$(-0.43890)_{N1}$
5	$(-0.34799)_{C2}$	–0.38460	$(-0.41967)_{N1}$
6	$(-0.38458)_{C2}$	–0.40558	$(-0.40846)_{N1}$
7	$(-0.37909)_{C2}$	$(-0.41862)_{N1}$	
8	$(-0.36024)_{C2}$	$(-0.41426)_{N1}$	
9	$(-0.33670)_{C2}$	–0.39038	$(-0.41503)_{N1}$
10	$(-0.32287)_{O,C}$	–0.38114	(–0.42201)
11	$(-0.33047)_{C2}$	$(-0.40681)_{N1}$	
12	$(-0.37019)_{C2}$	–0.43863	$(-0.45162)_{O1}$

$$-\Delta(\mathrm{IE})_n^{\mathrm{Koop}} = -\mathrm{IE}(\mathbf{M})_n^{\mathrm{Koop}} + \mathrm{IE}(\mathrm{M_{REF}})_n^{\mathrm{Koop}} \quad (6a)$$

$$\Delta\mathrm{E(ei)}^n_{\mathrm{rex}} = \mathrm{E(ei)}_{\mathrm{rex}}(\mathbf{M}) - \mathrm{E(ei)}_{\mathrm{rex}}(\mathrm{M_{REF}}) \quad (6b)$$

$$\Delta(\mathrm{BAE})^{\bullet+} = \mathrm{BAE}(\mathbf{M})^{\bullet+} - \mathrm{BAE}(\mathrm{M_{REF}})^{\bullet+} \quad (6c)$$

Considering data for pyrroles **2**–**4** we obtain $\mathrm{PA}(\mathbf{2})_{C1}$ – PA(**1**) = [24.2; 0.7; 5.6] = 30.5 kcal mol^{-1}; $\mathrm{PA}(\mathbf{3})_{C2}$ – PA(**1**) = [–6.9; 7.2; 13.6] = 14.0 kcal mol^{-1} and $\mathrm{PA}(\mathbf{4})_{C2}$ – PA(**1**) = [9.2; 1.8; 6.5] = 17.5 kcal mol^{-1}. As it could be seen, we obtained three different patterns of values. In this set of compounds molecule **3** is the only system, which has its HOMO orbital lower in energy than benzene by 6.9 kcal mol^{-1}. This implies that if one would consider just this contribution to the overall protonation reaction it would mean that **3** is by that amount less basic than **1**, because the price of ionising molecule **3** is higher than in benzene. However, this unfavourable contribution is compensated by advantageously larger relaxation energy upon ionisation, and it follows that the difference in PA values between molecules **3** and **1** is mostly dominated by the higher bond association energy of **3**$^{\bullet+}$, which is attributed to the properties of the final state. On the other hand, molecule **4** is slightly even more basic than **3**, which is, compared to benzene **1**, promoted by the favourable contribution from the properties of the initial molecule, mirrored through lower Koopmans' ionisation energy. Molecule **2** is by far the most basic within this set of molecules. The principal reason for that is a reduced stability of its HOMO principal molecular orbital (Figure 2), which is very exposed towards electrophiles and which contributes around 80% towards enhanced basicity of this compound with respect to benzene.

It is useful to notice that inclusion of the nitrogen atom into pyrrole system reduces its basicity primarily because this chemical modification stabilizes the HOMO of the resulting compound, making it less basic, as evidenced with the following triad: $\mathrm{PA}(\mathbf{2})_{C1}$ – $\mathrm{PA}(\mathbf{3})_{C2}$ = [31.1; –6.6; –8.0] = 16.5 kcal mol^{-1}. This unfavourable contribution from the initial state is not so much evidenced in the final PA values, since it is reduced in half jointly by larger relaxation and BAE energies. Molecule **2** is not only the strongest base among compounds **1**–**4**, it is also the only example within systems examined here, where the basicity of carbon atom outperforms the basicity of other heteroatoms, being amino nitrogen of the five-membered ring in this case. Triadic analysis $\mathrm{PA}(\mathbf{2})_{C1}$ – $\mathrm{PA}(\mathbf{2})_{N2}$ = [30.7; –30.7; 18.3] = 18.3 kcal mol^{-1} shows that the pre-

Figure 2. Schematic representation of the highest occupied molecular orbitals of systems investigated here, together with their orbital energies (in a.u.) obtained by HF/G3large//B3LYP/6–31G(d) level of theory. The orbital energies of the principal MOs participating in the protonation of molecules the most are given within parentheses with the subscript indicating an atom under the proton attack.

vailing effect is the higher exothermicity of the carbon bond association process with hydrogen atom – a final state effect, although the first two terms are larger in absolute value, but exactly cancelling each other out. It has to be said that molecule **2** is the only nitrogen containing system investigated in this work, which has no imino nitrogens in its structure. The latter moieties are usually much more basic than the corresponding amino groups,[50] which could be the reason why molecule **2** is, thermodynamically speaking, the only true carbon base studied here.

Pyridines **5**–**8** are all less potent carbon bases than benzene. This is in harmony with experimentally observed behaviour that these compounds are much less readily involved in EAS reactions.[33] It is, however, interesting to notice that the trend in magnitudes of these PA differences compared to benzene is much less pronounced in pyridines than the opposite trend in pyrroles. However, like in pyrroles, in pyridines the highest molecular orbital that is responsible for their protonation and which includes π–electron density of carbon atom to be protonated is HOMO (Figure 2), in contrast to what was reported by D'Auria.[34] To gain an insight into why these molecules are less basic than benzene, we could make use of the following triads: $PA(\mathbf{5})_{C2}$ – PA(**1**) = [–7.1; 7.3; –9.1] = –8.9 kcal mol^{-1}; $PA(\mathbf{6})_{C2}$ – PA(**1**) = [–30.0; 42.7; –39.3] = –26.7 kcal mol^{-1}; $PA(\mathbf{7})_{C2}$ – PA(**1**) = [–26.6; 23.7; –15.7] = –18.6 kcal mol^{-1} and $PA(\mathbf{8})_{C2}$ – PA(**1**) = [–14.8; 14.2; –17.5] = –18.1 kcal mol^{-1}. Although differences in the corresponding PA values do not follow any particular trend, some patterns can still be recognized. For a start, pyridines owe their reduced carbon basicity to the fact that their reactive HOMO orbitals are more stable and less exposed to nucleophiles than in benzene. However, this is not the prevailing effect which determines the overall reactivity, as this contribution is in all four cases almost completely compensated by the opposite effect of the increased relaxation energies. If only these two contributions were taken into account, pyridines would exhibit basically the same basicity and the concomitant nucleophilicity as benzene. However, what prevails in this instance is much lower bond association energy of pyridines towards hydrogen atom to form the final protonated product, which is attributed to the final state effects. We note in passing that like in pyrroles, introduction of nitrogen atoms into the structure of pyridine has the effect of further reducing basicity of **5**. The reason for that is somewhat changed from pyrroles. In the case of molecules **5** and **6** different PA values are almost exclusively due to differences in the properties of the initial bases, while other two contributions cancel each other out as $PA(\mathbf{5})_{C2}$ – $PA(\mathbf{6})_{C2}$ = [22.9; –35.4; 30.2] = 17.7 kcal mol^{-1}. Still, a notable difference is observed in the other two cases as $PA(\mathbf{5})_{C2}$ – $PA(\mathbf{7})_{C2}$ = [19.5; –16.4; 6.6] = 9.7 kcal mol^{-1} and $PA(\mathbf{5})_{C2}$ – $PA(\mathbf{8})_{C2}$ = [7.7; –6.9; 8.4] = 17.7 kcal mol^{-1}, where the situation is not so straightforward and neither terms could be denoted as dominant.

Purine **9** is a bicyclic compound which could, in the most trivial and perhaps naive way, be considered as composed of fragments **4** and **7** annealed together. To investigate whether this simple assumption is valid, let us assume the following. Compound **4** is by 17.5 kcal mol^{-1} stronger carbon base than benzene, whereas molecule **7** is by 18.6 kcal mol^{-1} less basic at the carbon atom than reference molecule **1**. Adding these numbers together, it follows that **9** should be around 1.1 kcal mol^{-1} less susceptible towards the proton than benzene. The data in Table 1 reveal that the compound **9** is indeed less basic than benzene, but by the amount of 4.3 kcal mol^{-1}, which actually makes the very simple picture expounded above surprisingly accurate to a certain extent. It is interesting to observe that the carbon protonation of **9** occurs on the more basic subunit of the two, namely fragment **4**, but still, the overall basicity of **9** is even further lower than the sum of differences between the two constituting fragments and the benzene. This shows that the simple picture presented above could turn out to be quantitatively fairly accurate, but generally it should not be used in trying to rationalize proton affinities of fused systems, because it could lead to wrong conclusions. It also reveals, at least in a qualitative fashion, that the effect of the cationic resonance in the protonated conjugate acid, which spreads an excess positive charge all over the molecule, is operative and significant, because both fragments »feel« that the protonation occurred, although the actual protonation took place locally on the five-membered ring. Numerically, the reason for the reduced basicity of **9** compared to benzene could be tracked down to $PA(\mathbf{9})_{C2}$ – PA(**1**) = [0.0; –0.3; –4.1] = –4.4 kcal mol^{-1}. It turns out that both molecules possess energetically equal HOMO orbitals (Figure 2), which means that consideration of just energies and symmetry of the frontier orbitals would lead to the conclusion that they have identical basicity, which we demonstrated would be erroneous. The difference of 4.4 kcal mol^{-1} in basicity is purely a consequence of the final state effect evidenced through the reduced bond association energy in $\mathbf{9}^{+\bullet}$, supporting the idea that differences in cationic resonances in both conjugate acids play a significant role. As already mentioned, molecule **9** is more basic at the carbon atom than **7** because both initial and final state effects strongly promote the basicity of the former system [$PA(\mathbf{9})_{C2}$ – $PA(\mathbf{7})_{C2}$ = [26.6; –24.0; 11.6] = 14.2 kcal mol^{-1}], whereas the same compound is a weaker carbon base than **4** because of a synergy of all three terms appearing in the triadic analysis [$PA(\mathbf{9})_{C2}$ – $PA(\mathbf{4})_{C2}$ = [–9.2; –2.1; –10.6] = –21.9 kcal mol^{-1}].

Recently we demonstrated that the oxidation of the tertiary nitrogen atom into an *N*–oxide group (N^+–O^-) enhances the acidity of the vicinal C–H group by the amount of 9–17 kcal mol^{-1} in the gas-phase and around 5–11 pK_a units in DMSO.[40d] Therefore, since an *N*–oxide moiety shows acidifying effect, it could be anticipated that the carbon basicity of **10**, exerted particularly at the vicinal

ortho and the distal *para* position from an N–O group should be lower than that of benzene **1**. This is, however, not the case, as both positions are more potent carbon bases than found in the benzene. Still, *ortho* position is slightly less basic of the two, because it is closer to an N–O group. The corresponding PA and GB values for *ortho* protonation obtained with G3B3 methodology assume values 181.0 and 174.1 kcal mol^{-1}, respectively. What is in the focus of the present manuscript are the most favourable carbon basic sites, being *para* carbon atom in **10** (Table 1). This position is by 1.9 kcal mol^{-1} more basic on the PA ladder than its *ortho*-counterpart, overall being by 5.2 kcal mol^{-1} more susceptible towards the proton than benzene. The corresponding triad reads: PA(**10**)$_{C2}$ – PA(**1**) = [8.7; 11.0; –14.5] = 5.2 kcal mol^{-1}. Interestingly, effects of the initial state and of the relaxation energy promote the basicity of **10**, which is then largely reduced by the unfavourable contribution originating from the properties of the final protonated molecules. This suggests that in the neutral form molecule **10** is less aromatic and less stable than the paragidmatic aromatic molecule **1**, which makes it a better system to undergo protonation, whereas in the conjugate acid, **10H$^+$** is again less stabilized through cationic resonance effect than **1H$^+$**, which has a negative effect on the resulting basicity. On the other hand, **10** is further stronger carbon base than its counterpart pyridine **5**, exclusively due to the effect that an N–O group has on the reduced stability of the HOMO orbital of the former compound as PA(**10**)$_{C2}$ – PA(**5**)$_{C2}$ = [15.8; 3.7; –5.4] = 14.1 kcal mol^{-1}. It is interesting to observe that the carbon protonation of pyridine occurs at the *meta*-position to the nitrogen atom, whereas in **10** the proton most favourably attacks *para*-carbon atom.

The simplest way how to enhance the carbon basicity of pyridines **5**–**8** and make them more willing to undergo electrophilic aromatic substitution is to attach strong electron donating groups, like –NH$_2$ moiety to its structure. As an illustrative example, 2-aminopyrimidine **11** is already by as much as 36.4 kcal mol^{-1} more basic than pyrimidine **7** at the corresponding C5 carbon atoms, making it the strongest carbon base examined here. Such pronounced substituent effect of a single amino group could be rationalized in our triadic scheme by PA(**11**)$_{C2}$ – PA(**7**)$_{C2}$ = [30.5; –20.1; 26.0] = 36.4 kcal mol^{-1}. Amino group increases the energy of the HOMO orbital through its electron donating ability and enhances the bond association energy of the corresponding base radical cation towards the hydrogen atom. The increased exothermicity in the (BAE) term is a consequence of the enlarged cationic resonance stabilization taking place in the conjugate acid **11H$^+$**, in which –NH$_2$ group actively participates through its lone-pair electrons. This can be evidenced by the inspection of the relevant geometrical data in the protonated form as the –NH$_2$ group gets fully planar with the reduced C–N(amino) bond distance upon the protonation.

At the end we will consider biologically important purine, uracil **12**. Its carbon basicity is higher than found in benzene such that PA(**12**)$_{C2}$ – PA(**1**) = [–21.0; 20.0; 9.7] = 8.7 kcal mol^{-1}. Interestingly, taking into account only the orbital picture would in this case be completely inappropriate. The HOMO of **12** is by 21.0 kcal mol^{-1} more stable compared to **1**, which means that **12** should be much less basic than **1**. However, this contribution is outperformed by a positive contribution from the other two terms appearing in the triadic picture, leading to the overall higher carbon basicity of **12** relative to **1**. This is a *par excellence* example of how important is to consider the entire process of protonation when discussing basicity/nucleophilicity trends and not just the initial phase.

The idea that the reactivity of azines and purines towards nucleophiles could be explained just by considering the symmetry of the HOMO orbitals[34] could be challenged even further. We already demonstrated that in all systems **1**–**12** examined here the Hartree-Fock HOMO orbitals are all of π–symmetry, despite large differences and diverse trends in carbon proton affinities. Additionally, if we would try to relate the energy of these HOMO orbitals with the corresponding carbon basicities we would obtain a very poor correlativity as shown in the Figure 3 (top). The plot reveals a large scatter of points from the linear regression line and the corresponding correlativity index assumes a value as low as R^2 = 0.64. This once again demonstrates that it is very insufficient to consider just the properties of initial reactants when interpreting trends in the reactivity. Somewhat better correlativity of data for carbon PA values, that would come close to revealing the ability of such heterocyclic molecules to undergo electrophilic aromatic substitution at the carbon atom would be the difference in the proton affinities between the most favourable carbon and other heteroatom, which was, except for molecule **2**, always found to be either nitrogen or oxygen atom. This is qualitatively evidenced through a plot presented in the Figure 3 (bottom), where the correlativity index increased to R^2 = 0.84. We can conclude that the difference in PA(carbon) – PA(nitrogen/oxygen) values can serve as a good indicator of the ability of these molecules to undergo electrophilic aromatic substitution reactions. This is by no means a suggestion that the difference in PA(C) – PA(N/O) values should be used as a quantitative descriptor to interpret or predict different EAS reactivity patterns, since the correlation index between this value on one hand, and PA(C) on the other, is strongly affected by the presence of the same quantity in both correlating variables. For example, this correlation index could be made even higher and arbitrarily close to 1 by using the generalized variable [a·PA(C) – PA(N/O)] and sufficiently high value of a. The plot in Figure 3 (bottom) should be interpreted only as revealing a particular trend that the smaller the difference in PA(C) – PA(N/O) values is, the molecule would more readily like to be attacked by the electrophile at the carbon atom. If this diffe-

rence in latter basicities gets too large, the approaching electrophile will preferentially reside close to the heteroatom forming an adduct, rather than to initiate EAS reaction on the carbon centre.

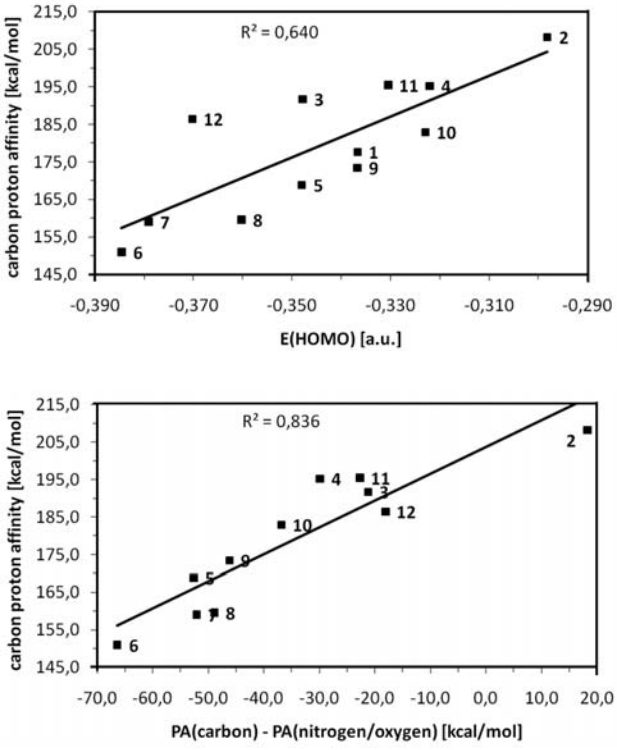

Figure 3. Correlation of the first carbon proton affinities of investigated molecules with the energy of the frontier HOMO orbitals (top) and with the difference in the proton affinities between the most favourable carbon and other heteroatom (bottom) as presented in Table 1. Molecule labels are given next to the data points.

As a final note, let us now switch our attention to thermodynamically the most favourable sites of the proton attack, which is usually not the carbon atom, being nitrogen in systems **3**–**9** and **11**, or oxygen in **10** and **12**. As already expounded, the only exception to this rule is provided by pyrrole **2**, which is a true carbon base. Still, it has to be reiterated that molecule **2** is the only compound investigated here, which possesses only amino nitrogen atom and none of the more basic imino nitrogens. Generally, it can be concluded that heteroatom protonation involves as a rule PRIMO orbital that is not HOMO, or in other words, some lower-lying orbital, which is energetically more stable and less exposed to the incoming electrophile (Figure 2). This would suggest that heteroatoms are less basic than carbons, implying again that taking into account the orbital picture of the initial molecules alone, would by no means be able to explain the observed trend in carbon/heteroatom basicities. For heteroatom protonation PRIMO orbitals represent the lone pair electrons of the σ–symmetry on the atom to be protonated, which lies in the plane of the molecule, being also the plain of the protonation process. The only exception is provided by **10H⁺**, where the proton is found at the oxygen atom of an *N*–oxide group with O–H bond perpendicular to the plane of the molecule. We note in passing that the oxygen atom of an N–O group was already identified in the literature as a very basic site through its ability to serve as a very strong intramolecular hydrogen bond acceptor.[51–54] Since the first adiabatic ionisation energy is always the same for both carbon and heteroatom protonation, it follows from the Equation (4) that terms originating from Koopmans' ionisation and from the relaxation energy cancel each other out in triadic analysis, so that their joint contribution to any differences in PA values is always zero for both basic atoms. Therefore, larger basicities of the heteroatomic sites over carbon atoms is exclusively due to the differences in the properties of the final states, i.e. protonated molecules, which is in our picture evidenced through bond association energies BAEs. In other words, it is much more exothermic to attach hydrogen atom to the ring nitrogen/oxygen heteroatom of the formed radical cation of the base, than it is to the corresponding carbon atom. This conclusion from the triadic analysis is completely logical, because the difference in the proton affinity of different basic sites within a molecule cannot depend on the properties of the initial neutral base, because it is the same molecule for any of the possible proton/electrophile site attack scenario. Although nitrogen and oxygen basicities were not the primary focus of the present study, since the approach of electrophiles to these sites would not lead to EAS reactions, it is useful to underline again the excellent agreement between theoretically predicted PA and GB values and experimentally measured data, corresponding to these thermodynamically the most favourable and experimentally accessible sites of protonation.

4. Concluding Remarks

Triadic decomposition of the gas-phase proton affinities (PAs) of eleven azines and purines was calculated using a composite computational G3B3 methodology. Our results revealed that, except pyrrole **2**, all investigated molecules are not carbon bases, but get protonated on nitrogen or oxygen atom as thermodynamically the most favourable sites of protonation. We obtained excellent agreement between computationally obtained ionisation energies, proton affinities and the gas-phase basicities, and the available experimental data. The absolute average deviation was found to be well below chemical accuracy of 2 kcal mol^{-1}, assuming values as low as 1.3, 0.8 and 0.4 kcal mol^{-1}, respectively.

The first carbon proton affinity of all molecules served as a model for the corresponding electrophilic aroma-

tic substitution reaction, where the actual rate–limiting step involves formation of the arenium carbocation. The results were compared to benzene, taken as a gauge molecule. Our results are in a disagreement with the work by D'Auria,[34] who proposed that the reduced reactivity towards electrophilic substitution of pyridine **5**, pyridazine **6**, pyrazine **7**, pyrimidine **8** and purine **9** relative to benzene **1** could be explained by the fact that HOMOs of these molecules are not π–orbitals, as obtained by the B3LYP/6–311+G(d,p) level of theory. Our findings showed that in all of the examined systems the frontier HOMO orbital for the carbon protonation is indeed of π–symmetry, as obtained by the HF/G3large//B3LYP/6–31G(d) model. Our triadic analysis revealed that it is insufficient and conceptually inadequate to consider just the properties of the electronic distribution in the initial neutral base, as mirrored through the orbital picture, when discussing trends in reactivity. As one illustrative of many such examples found in this work, we can mention purine **12**, whose π–HOMO orbital would predict it to be by 21.0 kcal mol^{-1} less potent carbon base than benzene **1**, whereas its proton affinity value is by 8.7 kcal mol^{-1} higher.

We demonstrated that pyrroles are stronger carbon bases than benzene, therefore much more prone to electrophilic aromatic substitution, whereas the opposite occurs in pyridines. Both of these findings are in harmony with experimental observations. The reason for such behaviour is mostly because in pyrroles the frontier HOMO orbitals are higher in energy than the corresponding HOMO orbital in benzene, which makes them more exposed to the incoming electrophile and more basic, while in pyridines the HOMO orbitals are further stabilized and the price to be paid for their ionisation within Koopmans' approximation is higher, thus reducing the overall basicity/nucleophilicity. However, a simple correlation of just the HOMO orbital energies with the corresponding first carbon proton affinities revealed poor correlativity with R^2 value assuming 0.64. We found that a much better and quantitatively more accurate description of the EAS reactivity trends is offered by difference in PA values corresponding to the most basic carbon atom and thermodynamically the most favourable heteroatomic site. In that case the correlativity index increased to $R^2 = 0.84$. However, for a complete picture of the protonation process and the 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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Povzetek

Prva ogljikova protonska afiniteta enajstih azinov in purinov (pirol, pirazol, imidazol, piridin, piridazin, pirimidin, pirazin, purin, piridin-*N*-oxid, 2-aminopiridin in uracil) v plinski fazi je bila izračunana s pomočjo sestavljene G3B3 metodologije in uporabljena za raziskavo njihove dovzetnosti za elektrofilno aromatsko substitucijo (EAS), pri čemer je bil benzen vzet kot referenčna molekula. Rezultati dokazujejo zelo dobro ujemanje z eksperimentalnimi podatki in potrjujeo uporabo triadnega približka. Ugotovili smo, da piroli, ki so bolj reaktivni napram EAS reakcijam kot benzen, so močnejše ogljikove baze kot prejšnja spojina, saj piridini izkazujejo nižjo bazičnost ogljika, hkrati pa so manj reaktivni napram substitucijam z elektrofili kot benzen. S pomočjo HF/G3large//B3LYP/6–31G(d) nivoja teorije smo izračunali, da v vseh preiskovanih molekulah zunanje orbitale, ki opisujejo pripadajoco π–elektreonsko gostoto protoniranega ogljikovega atoma, so HOMO. Naši rezultati so v nasprotju z delom autorja D'Auria (M. D'Auria, Tetrahedron Lett. 2005, 46, 6333–6336; Lett. Org. Chem. 2005, 2, 659–661), ki je s pomočjo izračunov na B3LYP/6–311+G(d,p) nivoju ugotovil, da v nekaterih presikovanih sistemih HOMO orbitala uporabljena za racionalizacijo nižje reaktivnosti takšnih sistemov napram EAS, nima π simetrije. Izkazalo se je, da same energije HOMO orbital zelo slabo korelirajo z ogljikovimi protonskimi afinitetami, v nasprotju z razliko v protonski afiniteti med najbolj bazičnim ogljikovim atomom in termodinamsko najbolj ugodnim mestom protoniranja, kar se pri korelaciji odraža mnogo bolje. Triadna analiza dokazuje, da velja razmisliti o popolni sliki protonirajočega procesa in vseh treh izrazov, ki se individualno pojavljajo v triadni shemi obravnave trendov bazično/nukleofilno tesno sorodnih molekul.