

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/230614647>

# ChemInform Abstract: Advances in Determining the Absolute Proton Affinities of Neutral Organic Molecules in the Gas Phase and Their Interpretation: A Theoretical Account

ARTICLE *in* CHEMICAL REVIEWS · AUGUST 2012

Impact Factor: 46.57 · DOI: 10.1021/cr100458v · Source: PubMed

---

CITATIONS

49

---

READS

19

## 3 AUTHORS, INCLUDING:



Boris Kovacevic

Ruđer Bošković Institute

51 PUBLICATIONS 1,287 CITATIONS

[SEE PROFILE](#)



Robert Vianello

Ruđer Bošković Institute

64 PUBLICATIONS 855 CITATIONS

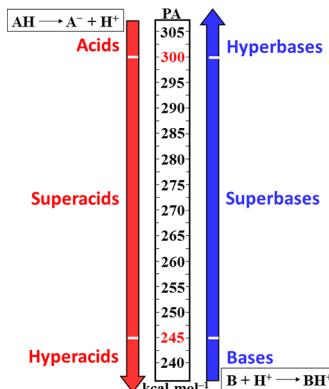
[SEE PROFILE](#)

## Advances in Determining the Absolute Proton Affinities of Neutral Organic Molecules in the Gas Phase and Their Interpretation: A Theoretical Account

Zvonimir B. Maksić,<sup>†</sup> Borislav Kovačević,\* and Robert Vianello\*

Quantum Organic Chemistry Group, Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička 54, HR-10000 Zagreb, Croatia

### Supporting Information



### CONTENTS

1. Introduction	5240
2. Theoretical Framework	5241
3. The Protonation of Neutral Molecules – Basicity	5242
3.1. Rigorous Proton Affinity Calculations – Quantitative Approach	5243
3.2. The Absolute Proton Affinity Scale in the Gas Phase – Benchmark Computations	5245
3.3. Protonation and Anti-/Aromaticity – Benzene and Cyclobutadiene	5246
3.4. Ring versus Substituent Basicity – The Phenol and Aniline Dilemma	5247
3.5. The Proton as a Probe of the Electronic Structure – Semiquantitative Approach	5248
3.5.1. A Simple Semiquantitative Scaled Hartree–Fock Model	5248
3.5.2. The Additivity of Proton Affinity in Polysubstituted Aromatic Systems	5249
3.5.3. The Electrophilic Substitution Reactivity of Angularly Perturbed Annulated Benzenes – The Mills Nixon Effect	5251
3.6. The Linear Relation between Proton and Methyl Cation Affinities	5252
3.7. The Linear Relationship between Proton and Metal Cation Affinities	5252
3.8. Proton Affinities and ESCA Shifts	5253
3.9. Proton Affinities and Ionization Energies	5253
3.10. Gas-Phase versus Solution-Phase Basicity	5254
3.11. Interpretation of Proton Affinities – Triadic Analysis	5254
4. Computer-Aided Design of Neutral Organic Superbases	5257
4.1. The Aufbau Strategy in Constructing a Ladder of Superbases	5258
4.1.1. The Imino Group as a Basicity Warhead	5258
4.1.2. The Powerful Phosphazeno and Phosphino Groups	5258
4.1.3. Proton Sponges – The Role of the Intramolecular Hydrogen Bond(s)	5259
4.1.4. Supramolecular Scaffolds for Hyperstrong Bases	5261
4.2. Theoretical versus Experimental Gas-Phase Proton Affinity/Basicity in the Superbasic Region	5261
4.3. The Ladder Scale of Neutral Organic Bases	5262
4.4. Spontaneous Proton Transfer in the Gas Phase	5262
5. Concluding Remarks	5264
Associated Content	5264
Supporting Information	5264
Author Information	5264
Corresponding Author	5264
Notes	5264
Biographies	5264
Acknowledgments	5265
References	5265

### 1. INTRODUCTION

The proton is the smallest and the lightest atomic nucleus and is the most abundant in the universe. Notwithstanding its minute size, it plays gargantuan roles in chemistry, biochemistry, and molecular biology.<sup>1–4</sup> It is pivotal in the proton transfer reactions between Brønsted acids and bases, which are among the most fundamental processes in chemistry. The proton is also ubiquitous in living matter, particularly as a partner in coupled electron–proton transfer reactions.<sup>5</sup> It comes as no surprise that the proton has been the protagonist in a myriad of both experimental and theoretical research papers describing the acid/base properties of molecules, ranging from diatomics to enzymes. They require and merit an encyclopedic effort and scope, which unfortunately exceeds

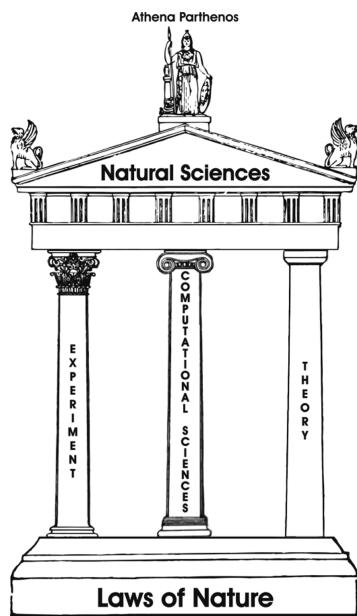
Received: December 31, 2010

Published: August 3, 2012



the boundaries of this Review. Instead, we shall try to shed light on some of the main achievements and recent advances in theoretical and computational studies of proton affinities, avoiding a taxonomic account of the literature. In particular, we shall focus on the results obtained by computational chemistry in studying the gas-phase (GP) acid/base facets of predominantly organic compounds in their ground states (GS). The period of time encompassed by this account is from the early 1990s to the present days. However, to place these results in a proper time frame, some earlier landmark papers will also be mentioned and described to provide a comprehensive account of the continuous flow of research and advances in this field, in terms of both scope and quality. A brief overview of early experimental work will be presented, which lies at the very root of the scientific investigations in gas-phase acid–base chemistry. Having said that, it should be strongly emphasized that computational chemistry is one of the main avenues of research in computational natural science nowadays. Tremendous progress has been made in the latter during the past two decades due to advances in powerful computer hardware and the development of new methods of quantum mechanics for tackling many-body problems, implemented as efficient algorithms in versatile software. Computational natural sciences tore down the borders dividing the traditional disciplines of physics, chemistry, and molecular biology, providing an important link between rigorous theory and experiment. They are rightfully termed the third pillar of the modern natural sciences (Chart 1). This is a very fortunate situation for

**Chart 1. Temple of Natural Sciences**



chemistry in general and for the proton in chemistry in particular. One can use a wide variety of ab initio computational tools in studying acid/base properties in concert with modern experimental techniques. Theoretical methods can provide information, which is not easily retrieved by experimental research, thus fulfilling an important complementary task in modern science. For example, highly accurate ab initio calculations<sup>6</sup> are invaluable for yielding the anchor bases with benchmark accuracy necessary for establishing the absolute basicity scale, which is very difficult to achieve by common

experimental techniques alone,<sup>7</sup> be they thermodynamic equilibrium,<sup>8</sup> kinetic,<sup>9,10</sup> or thermokinetic,<sup>11,12</sup> unless very careful additional spectroscopic measurements have been performed.<sup>13,14</sup> Furthermore, computational chemistry methods treat all protonation positions in polyfunctional bases on an equal footing,<sup>15</sup> whereas measurements can identify only the most basic site as a rule. Although not all aspects of gas-phase proton chemistry will be covered in this Review, for the sake of completeness we shall mention some typical problems where computational methods are indispensable. These include proton affinity in the excited states<sup>16,17</sup> and proton transfer (PT) processes in the ground and excited states,<sup>18–21</sup> as well as detailed descriptions of GS transition structures. One should also emphasize the theoretical investigation of the proton tunneling effect and its influence on enzyme catalysis.<sup>22–25</sup> Moreover, computational quantum chemistry procedures are useful in investigating the relationships between proton affinities and hydrogen-bond strength.<sup>26</sup> They are also helpful in rationalizing the close analogy between proton affinity and ESCA shifts.<sup>27–29</sup> It is important to stress that modern computational quantum chemistry methods have a pronounced predictive power, which has found useful applications in directing and accelerating experimental work. Thus, in this account, considerable emphasis will be placed on the design of strong and hyperstrong organic bases in silico, at both molecular and supramolecular levels. It will be documented that the proton is not only a quintessential chemical species, but also a probe of the electronic structure of molecules. Because the proton is an electrophilic agent par excellence, protonation offers interesting insight into electrophilic substitution reactivity.<sup>30</sup> Hence, basicity, as reflected in the corresponding protonation energies, faithfully mirrors some important intrinsic features of the initial bases. By the same token, it reveals characteristics of the corresponding final products as well, the conjugate acids produced by protonation reactions. Computational information on the spatial and electronic structures of elusive cations is particularly valuable. Consequently, considerable attention will be devoted here to the dissection of protonation energies into several contributions, to provide an interpretation of proton affinities in a physically sound and intuitively appealing way.<sup>31–33</sup> The relevance of the rationalization and understanding of both experimental and theoretical proton affinities cannot be overestimated. The interpretation of the underlying reason(s), which explains not only what but also why something happens or how molecules behave, belongs to one of the most fundamental problems in molecular science.

Although proton affinities of organic molecules in the gaseous state are the focus of this Review, analogies between proton, methyl, and several metal cation affinities, together with similarities with inner-core ionization energies, will be briefly commented upon to provide a bigger picture. Last but not least, it will be shown by a number of examples that strong overlapping and coupling of experimental and theoretical research have synergistic effects and, therefore, are highly desirable and beneficial, representing a conditio sine qua non for rapid progress in chemistry during the 21st century.

## 2. THEORETICAL FRAMEWORK

Proton affinity (PA) is one of the most fundamental properties of chemical substances, expressing the ability of a molecule to accept a proton in a chemical reaction. It is defined for a gas-

phase reaction, where a protonated conjugate acid ( $\text{BH}^+$ ) dissociates into gaseous base ( $\text{B}$ ) and the free proton ( $\text{H}^+$ ):



Proton affinity corresponds to an enthalpy change of reaction 1, whereas the matching free energy term denotes the gas basicity (GB). The proton affinity of a molecule in the ideal gas can be expressed:

$$\text{PA}(\text{B}) = \Delta H = \Delta E + RT \quad (2)$$

where  $\Delta E$  represents the difference in the total energies of the products and a reactant of reaction 1,  $T$  is the absolute temperature, and  $R$  is the ideal gas constant. It must be emphasized that experimental PA values are measured relative to a reference base, whereas computations provide absolute PAs and can treat all possible protonation sites identically, which even led some authors to propose three kinds of PA values.<sup>34</sup> An excellent and detailed overview of the background of experimental and theoretical methods for determining gas-phase basicities, proton affinities, and protonation entropies is presented in tutorial form in two reviews by Bouchoux and co-workers.<sup>35,36</sup> Only a brief account of these techniques will be provided here.

The total energy of a polyatomic molecule  $E$  can be expressed as

$$E = E_{\text{ele}} + E_{\text{ZPV}} + E_{\text{vib}} + E_{\text{rot}} + E_{\text{trans}} \quad (3)$$

where  $E_{\text{ele}}$  stands for the electronic energy,  $E_{\text{ZPV}}$  is the zero point vibrational energy of normal vibrational modes at a temperature of  $T = 0$ , and  $E_{\text{trans}}$  and  $E_{\text{rot}}$  are translational and rotational contributions to the total energy, respectively. Furthermore,  $E_{\text{vib}}$  is a vibrational energy change from 0 to 298.15 K. Employing statistical mechanics, one obtains that the contributions of the  $E_{\text{rot}}$  and  $E_{\text{trans}}$  energies for a nonlinear molecule are equal,  $(3/2)RT$  each. The energies  $E_{\text{ZPV}}$  and  $E_{\text{vib}}$  are given by eq 4:

$$E_{\text{ZPV}} = \frac{1}{2} \sum_{i=1}^{3n-6} h\omega_i \text{ and } E_{\text{vib}} = \sum_{i=1}^{3n-6} h\omega_i / (e^{h\omega_i/RT} - 1) \quad (4)$$

where  $n$  is the number of atoms in a molecule.<sup>37</sup> Combining eqs 2 and 3 and taking into account that proton ( $\text{H}^+$ ) possesses only translational energy,  $(3/2)RT$ , it follows that the PA of the base  $\text{B}$  can be calculated by using the following equation:

$$\begin{aligned} \text{PA}(\text{B}) &= [E_{\text{ele}}(\text{B}) - E_{\text{ele}}(\text{BH}^+)] \\ &+ [E_{\text{ZPV}}(\text{B}) - E_{\text{ZPV}}(\text{BH}^+)] \\ &+ [E_{\text{vib}}(\text{B}) - E_{\text{vib}}(\text{BH}^+)] + (5/2)RT \end{aligned} \quad (5)$$

Analogously, gas basicity (GB) is defined as the Gibbs energy change associated with reaction 1 in the gas phase:

$$\text{GB}(\text{B}) = \Delta G = \Delta H - T\Delta S \quad (6)$$

From eqs 3 and 6, it follows that GB can be calculated using the expression:

$$\begin{aligned} \text{GB}(\text{B}) &= [E_{\text{ele}}(\text{B}) - E_{\text{ele}}(\text{BH}^+)] \\ &+ [E_{\text{ZPV}}(\text{B}) - E_{\text{ZPV}}(\text{BH}^+)] \\ &+ [E_{\text{vib}}(\text{B}) - E_{\text{vib}}(\text{BH}^+)] + (5/2)RT \\ &- T[S(\text{B}) + S(\text{H}^+) - S(\text{BH}^+)] \end{aligned} \quad (7)$$

where  $S$  is the entropy of the species. The entropy can be expressed as the contribution of four terms:

$$S = S_{\text{el}} + S_{\text{vib}} + S_{\text{rot}} + S_{\text{trans}} \quad (8)$$

electronic, vibrational, rotational, and translational, respectively. The proton is specific in this respect, because it has only  $S_{\text{trans}}$ . The translational entropy of 1 mol of protons, considered as an ideal monatomic gas, at a temperature  $T$  may be estimated from statistical thermodynamic using the Sackur–Tetrode equation<sup>37</sup>  $S_{\text{trans}}(\text{H}^+) = 20.786 \cdot \ln(T) - 9.685 \text{ J mol}^{-1} \text{ K}^{-1}$ . At 298 K, this relationship gives  $S_{\text{trans}}(\text{H}^+) = 108.7 \text{ J mol}^{-1} \text{ K}^{-1}$ . Let us consider the protonation entropy change between base and its protonated form,  $\Delta S = S(\text{BH}^+) - S(\text{B})$ , for reaction 1. The electronic contribution ( $\Delta S_{\text{el}}$ ) is zero if we deal with zero-spin species, and the process does not involve electronic excitations. The protonation of a molecule results in one additional bond formed between the proton and neutral base. Consequently, the vibrational contribution to entropy ( $\Delta S_{\text{vib}}$ ) comes from the difference between the number of frequencies of the vibrational mode in the neutral and protonated molecules. The entropy contribution in this particular case is not large, because the additional vibration has a high frequency. The formation or destruction of hydrogen bond(s) in some particular cases can lead to a significant entropy change, because it results in the appearance or disappearance of some low frequencies. The translational contribution ( $\Delta S_{\text{trans}}$ ) is small, particularly in molecules with a mass much higher than the mass of the proton. The rotational contribution to entropy ( $\Delta S_{\text{rot}}$ ) is associated with changes in the moment of inertia, the symmetry of the molecule, and internal rotation upon protonation.<sup>38</sup> The change in the moment of inertia is negligible, except for very light molecules. Rotational entropy due to a change in symmetry can be calculated in the following way:

$$S_{\text{rot}} = -R \ln[\sigma(\text{B})/\sigma(\text{BH}^+)] \quad (9)$$

where  $\sigma$  is the symmetry number of the species in parentheses defined as the total number of independent permutations of identical atoms in a molecule that can be attained by simple rigid rotations of the entire molecule. Typical examples are  $\text{H}_2\text{O}$  ( $\sigma = 2$ ),  $\text{NH}_3$  ( $\sigma = 3$ ),  $\text{CH}_4$ , and benzene ( $\sigma = 12$ ). Change in internal rotations is usually associated with one or more free rotating groups in a molecule that become “frozen” upon protonation, due to a significant increase in the rotational barrier. In some specific cases, change in internal rotation is associated with the formation or destruction of the hydrogen bond(s). It should be pointed out that we use a  $\text{kcal mol}^{-1}$  energy unit, if not stated otherwise.

### 3. THE PROTONATION OF NEUTRAL MOLECULES – BASICITY

The purpose of this large section is to show how computational methods can serve chemistry in revealing the secrets of the basicity of neutral molecules and resolving certain controversial dilemmas. We shall commence with highly accurate calculations of the proton affinities of small molecules, which have cast firm anchors in the absolute proton affinity scale. We shall then proceed to the protonation of some paradigmatic organic molecules and to the problem of ring versus substituent basicity in several  $\pi$ -systems. Subsequently, a proton will be used as a probe of the electronic structure in polysubstituted aromatics, and an additivity rule of thumb governing their proton affinities will be elaborated. Furthermore, proton attachment offers

useful insight into the electrophilic reactivity of organic compounds. The relationships of proton affinity with some closely related intrinsic properties of neutral bases are briefly discussed. Whereas highly accurate calculations convincingly show that the physics of proton affinity in the gas phase is well understood in small molecules containing first-row atoms, the trichotomy approach will help clarify the protonation process in general, providing an interpretation of intrinsic basicity using physically sound concepts in a more intuitively appealing way.

### 3.1. Rigorous Proton Affinity Calculations – Quantitative Approach

In the 1960s and early 1970s, semiempirical all-valence-electron methods have been very popular because they have been applicable in large molecules. Unfortunately, they involved many empirical parameters, some of which were without any physical justification. Not surprisingly, even the best AM1<sup>39</sup> and PM3<sup>40,41</sup> methods were sometimes erratic, yielding unsatisfactory calculated heats of formation<sup>37,42</sup> and the accompanying proton affinities. Overcoming the imperfections in estimating PAs has been attempted by introducing the AM1<sub>sc</sub> approach,<sup>43</sup> although the results were semiquantitative at best (see later). The quantitative ab initio treatment of the thermochemistry of small and medium molecules was started by Pople et al.<sup>44</sup> with the introduction of the Møller–Plesset perturbation theory in addressing the electron correlation problem. The target accuracy for energies was values within the error bars of  $\pm 2$  or  $\pm 3$  kcal mol<sup>-1</sup> for molecules composed of atoms belonging to the first and second rows of the system of elements, respectively. A comparison between the PAs obtained by the MP2<sup>44</sup> and MP4<sup>45,46</sup> methods has been provided by Smith and Radom.<sup>47</sup> Twenty small organic and inorganic molecules were examined by using MP2/6-31G(d) optimized geometries, whereas the  $E_{ZPV}$  as well as enthalpy temperature corrections were calculated using the HF/6-31G(d) model. The final single point MP2/6-311G(d,p) and MP4/6-311G(d,p) PAs were computed with mean absolute errors (MAE) of 2.8 and 4.0 kcal mol<sup>-1</sup> against the experimental data of Szulejko and McMahon,<sup>48</sup> respectively. The corresponding largest errors, 7.2 and 8.2 kcal mol<sup>-1</sup>, were found in the H<sub>2</sub>O molecule. This result seemed surprising at first, because a more rigorous MP4 theory yielded worse results. However, each level of theory requires a corresponding quality of the basis set necessary for the balanced description of the electronic energy change upon protonation. This assertion was confirmed by the use of a more flexible 6-311+G(3df,2p) basis set. In that case, the MAE dropped to 1.9 and 0.8 kcal mol<sup>-1</sup> for the MP2 and MP4 methods, respectively, which were quite satisfactory for that period of time. This was consistent with an earlier study by DeFrees and McLean,<sup>49</sup> indicating that the use of a flexible basis set in the MP4 theory was crucial, as is well-known today. Their MP4/6-311++G(3df,3pd) calculations employing an extended Pople's 6-311++G(3df,3pd) set reproduced the experimental PA values of O, O<sub>2</sub>, CO, HF, N<sub>2</sub>, CH<sub>4</sub>, H<sub>2</sub>O, HCN, and NH<sub>3</sub> with a mean absolute error (MAE) of 1.0 kcal mol<sup>-1</sup>. It should be noted in passing that the scaled Hartree–Fock model HF<sub>SC</sub><sup>43</sup> was put forward as a pragmatic alternative to the MP2 method for studies of heavily substituted large aromatics to reveal the general trends of changes in their basicity and provide a semiquantitative description of the substituent effects at low cost (see section 3.5.1). The next attempt to achieve the chemical accuracy of 1 kcal mol<sup>-1</sup> in the ab initio calculations of the energetic properties of medium and

large molecules was the development of composite G(*n*) *n* = 1, 2, 3 methods.<sup>50–53</sup> However, before a brief description of the G(*n*) methods is given, a digression is necessary, which is related to progress in the theory and implementation of coupled cluster methods (CC). The CCSD(T) method is based on all connected single and double excitations, with a quasiperturbative estimate of the effect of connected triple excitations.<sup>54,55</sup> It is known that this approach yields results very close to exact ones provided large basis sets are used, tacitly assuming that the single reference wave function is strongly dominated by dynamic electron correlation.<sup>56</sup> This is why CCSD(T) was termed the “gold standard” in theoretical thermochemistry. However, CCSD(T) method employing very large basis sets with possible extensions to the complete set were only applicable to small molecules with just a few heavy atoms. One should just add that the quadratic QCISD(T) method was introduced to correct the size-consistency error.<sup>57</sup> The G(*n*) schemes were developed as general predictive procedures, applicable to any molecular system including sizable ones, which are able to reproduce experimental thermochemical data with known accuracy, thereby providing such information for other species where the measured values are either uncertain or nonexistent. The G2 methodology is based on the MP2/6-31G(d) geometries and starting total energies at single-point MP4/6-311G(d,p) calculations. The latter are subsequently corrected by additional basis set diffuse functions, additional d-functions on heavy atoms and p-functions on hydrogens, higher polarization functions on atoms other than hydrogens, and higher level corrections (HLC). The computational protocol approximately corresponded to the QCISD(T)/6-311+G(3df,2p)//MP2/6-31G(d) scheme. The trick was that the actual QCISD(T) calculations were performed by using a modest 6-311G(d,p) set because the G2 method would not be feasible in medium and large(r) molecules otherwise. Because the protonation reaction 1 is isogyrlic, meaning that the number of the coupled electron pairs is preserved, the empirical HLC terms cancel. Consequently, the G2 scheme<sup>58</sup> is a purely ab initio method as far as PAs are concerned. It was utilized by East et al.<sup>59</sup> in establishing the first theoretical self-consistent absolute scale of proton affinities for a total of 31 molecules with a proton affinity range of 100–230 kcal mol<sup>-1</sup>. There is a general consensus that the G2 theory gives PAs with an accuracy of  $\pm 2$  kcal mol<sup>-1</sup> or better.<sup>47,50,58,59</sup> A simplified variant of the G2 theory, using a lower order MP2 perturbation method termed G2(MP2), was proposed by Curtiss et al.<sup>60</sup> for handling large molecules. It turned out that G2(MP2) had a performance similar to that of the parent G2 method.<sup>61</sup> An even more simplified G2(MP2,SVP) scheme seems to have accuracy similar to that of G2(MP2) and is computationally considerably less demanding.<sup>62,63</sup> Further reconsideration of the G2 protocol led to the generation of G3,<sup>64</sup> G3(MP2),<sup>65</sup> and G3(B3LYP)<sup>66</sup> theoretical chemistries. The G3 generation exhibits some improvements over the preceding G2 generation in reproducing the enthalpies of formation.<sup>58</sup> Along these lines, Hammerum reported G3 calculations of the proton affinities of 29 simple organic molecules<sup>67</sup> and 23 five-membered ring heteroaromatics,<sup>68</sup> which agreed well with the experimental data. The G3(MP2) calculations helped in the revision of the measured proton affinity of furan.<sup>69</sup> Further advances include the recent development of the fourth generation G4 method<sup>70</sup> and two modifications thereof, the G4(MP2) and G4(MP3)<sup>71</sup> schemes. All three computational procedures were assessed on

the 454 experimental energies in the G3/05 test set. The average absolute deviation from the experiment showed significant improvement from 1.13 kcal mol<sup>-1</sup> (G3 theory) to 0.83, 1.04, and 1.03 kcal mol<sup>-1</sup>, respectively. However, no gas-phase proton affinity studies using the G4 methodology have been reported in the literature so far.

Ochterski et al.<sup>72</sup> introduced a series of complete basis set methods (CBS) for the evaluation of the accurate energies of molecular systems based on the idea of an extrapolation procedure of the MP2 energies to the complete basis set limit. This is accomplished pair wise for coupled valence electrons by exploiting the asymptotic convergence properties of the correlation energy found in two-electron systems. Higher order correlation contributions are evaluated by a sequence of calculations using basis sets differing in size and flexibility, with some empirical adjustments. The CBS-Q is the most accurate form, whereas CBS-q and CBS-4 are the most widely applicable schemes. The largest basis set in the CBS-Q method is 6-311+G(3d2f,2df,2p), where the labels within the parentheses indicate the multiple polarization functions for the second-row, first-row elements, and the H atom, respectively. Hammerum and Sølling<sup>73</sup> found that the G2(MP2), G2(MP2,SVP), CBS-q, and CBS-Q methods yielded similar proton affinities of imines, which were in reasonable accordance with experimentally determined values. A test set of eight molecules was used in a comparative assessment of the CBS-4, CBS-Q, G2(MP2), and G2 methods in the calculation of the PAs. The mean absolute errors given within parentheses for CBS-4 (1.7), CBS-Q (1.1), G2MP2 (0.8), and G2 (1.0) reflect the accuracy of the examined methods for this particular selection of molecules. The maximum deviations from the experiments were 5.4, 2.2, 1.6, and 1.7 kcal mol<sup>-1</sup>, in the same order.<sup>61</sup>

A new approach for obtaining thermochemical magnitudes beyond the coupled cluster CCSD(T) accuracy, leading to methods termed W1, W2, W3, and W4, was put forward by Martin et al.<sup>74–77</sup> The aim was to reduce inaccuracies to  $\pm 1$  kJ mol<sup>-1</sup> for molecules involving atoms of both the first and the second rows of Mendeleev's system. The proton affinities of eight molecules, NH<sub>3</sub>, H<sub>2</sub>O, C<sub>2</sub>H<sub>2</sub>, SiH<sub>4</sub>, PH<sub>3</sub>, H<sub>2</sub>S, HCl, and H<sub>2</sub>, by W1 and W2 protocols<sup>75</sup> are close to those in experiments exhibiting the MAEs of 0.44 and 0.49 kcal mol<sup>-1</sup>, respectively, whereas the MAE of the G3 method was 1.2 kcal mol<sup>-1</sup>. If we denote the errors of the W1, W2, and G3 methods as W1(E), W2(E), and G3(E) and place them in triads (W1(E), W2(E), G3(E)), they take the forms of two "pathological" cases of PH<sub>3</sub> (0.4; 0.5; 2.3) and H<sub>2</sub>O (0.2; 0.3; 1.8), which illustrates the improvements introduced by the W1 and W2 protocols over the G3 computational scheme. However, the last is applicable to large molecular systems, whereas the W1 and W2 protocols are limited to very small molecules. Finally, the W3 and W4 protocols were developed as even more robust computational thermochemistry methods for small molecules,<sup>76,77</sup> but no proton affinities have been reported yet.

The latest advances in computational chemistry in the field of thermodynamics, which is currently experiencing a renaissance, are given by a series of improvements (not discussed here) under the term HEAT (high-accuracy extrapolated ab initio thermochemistry). It has a target of sub-kJ mol<sup>-1</sup> accuracy<sup>78–83</sup> as the new standard for benchmark calculations. A very important experimental contribution to increased precision of experimental thermodynamic data was provided by Rušić et al.<sup>84</sup> with the Active Thermochemical Tables (ATcTs). They

considerably decreased the experimental uncertainties of key species, such as HO, H<sub>2</sub>O, and a few others, and shifted the standard in measuring their thermochemical properties close to the spectroscopic range, a few tenths of kJ mol<sup>-1</sup>, or, in other words, a few tens of wave numbers. These precise experimental values have been instrumental in providing reliable gauge data for HEAT methodologies, which are able to provide benchmarks for thermochemical magnitudes. One such theoretical result was helpful in establishing very good primary anchors for the absolute proton affinity scale, thereby illustrating the synergy between experiments and computational chemistry, made possible nowadays in the best sense of the word by powerful supercomputers and grid networks. This is described in some detail in the next section.

In concluding this section, it is worth emphasizing that all of the mentioned composite computational procedures were designed to mimic the quality of high-level calculations to increase the precision of theoretically obtained thermodynamic quantities. However, even nowadays the application of such protocols is still being limited to relatively small molecules. The selection of the computational model always represents a compromise between the accuracy of results and the feasibility of calculations, and it is usually influenced by features of the investigated class of compounds. Nevertheless, in choosing the most practical level of theory, a good strategy is to compare several approaches for a family of closely related molecules and gauge them with respect to experimental values or with high-level calculations, where the latter are possible. DFT B3LYP approach turned out to be very popular low cost and highly accurate computational method to investigate the basicity trends of organic molecules. In combination with four of Pople's basis sets 6-31G\*, 6-31+G\*, 6-311+G\*\*, and 6-311+G(3df,3pd), it was first assessed in comparison with experimental GB values for the set of 32 small and diverse bases by Burk and co-workers,<sup>85</sup> who demonstrated that B3LYP/6-311+G\*\* provides very satisfactory basicity results. For oxygen protonation in several different ketones, vicinal diketones, and  $\alpha$ -keto esters, Taskinen and co-workers<sup>86</sup> determined that the B3LYP/TZVP level of theory offers reliable results. The DFT as a method of choice was confirmed by Swart and co-workers<sup>87</sup> by showing that BP86/QZ4P//BP86/TZ2P achieved a mean absolute deviation of 2.0 kcal mol<sup>-1</sup> for proton affinities with respect to experiments for 42 neutral bases across the periodic table. Protonation of isolated amino acids and amino acid side chains was also used to assess the performance of several theoretical methods. Dinadayalane et al.<sup>88</sup> employed MP2 and B3LYP functional with a range of basis sets to show that B3LYP/6-311+G(d,p) is a very good choice of technique to evaluate PAs of amino acids and their derivatives. In a recent broader study, Brás and co-workers<sup>89</sup> analyzed how well 64 different functionals describe the zero-point-exclusive proton affinity at 0 K for the ionizable side chains of Lys, His, Arg, Asp, Cys, Ser, and Tyr residues relative to very accurate CCSD(T)/CBS level. Their conclusion was that M06-2X provides the most accurate PA values with errors below 1.5 kcal mol<sup>-1</sup>, being also useful for very accurate description of proton transfer reaction between different amino acids. On the other hand, Uddin et al.<sup>90</sup> demonstrated that the B3LYP/6-31+G(d,p) method offers very accurate results for various thermochemical properties of common amino acids including PA and GB values as well as protonation entropies and enthalpies of formation, comparable to the success of several G(*n*) and CBS methods. Additionally, B3LYP/6-311+

+G(3df,2p) and B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) model chemistries were determined by York and co-workers<sup>91</sup> as reliable in calculations of PAs and GBs of molecules relevant to biochemical processes, particularly acid/base catalysis. It turns out that B3LYP functional can be safely employed to study gas-phase basicity phenomena reliably and economically, as it will be discussed in the remaining parts of this Review.

### 3.2. The Absolute Proton Affinity Scale in the Gas Phase – Benchmark Computations

A complete and internally consistent ladder of absolute gas-phase basicities and proton affinities is of immense value because it reflects trends in their changes and provides accurate intrinsic susceptibilities to the proton, which could be directly related to the spatial and electronic features of molecules without perturbations exerted either by solvents or by counterions. Because interplay among experiment, theory, and computations is a must in modern research, we present a very brief outline of the experimental techniques, which reveals some problems that require the attention of theoreticians. There are essentially two kinds of experimental methods for measuring PAs: (1) equilibrium<sup>8,92</sup> and (2) kinetic.<sup>9,10,92</sup> The majority of proton affinities is determined indirectly from measurements of equilibrium constants for gas-phase proton transfer between two bases  $B_1$  and  $B_2$ :



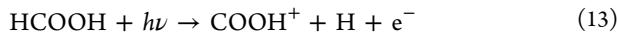
The corresponding equilibrium constant is given by  $K_{eq} = [B_1][B_2H^+]/[B_1H^+][B_2]$ . The gas-phase basicity, GB, is related to  $K_{eq}$  through the following relation:

$$-RT\ln K_{eq} = \Delta G^0 = GB(B_1) - GB(B_2) \quad (11)$$

where GB is defined by eq 6. Hence, the unknown basicity  $GB(B_1)$  can be determined by a known anchor basicity  $GB(B_2)$  deduced from independent experiments. If the equilibrium constant is measured as a function of temperature, the difference in proton affinities can be established directly (via eq 6) through the following relation:

$$\partial\ln K_{eq}/\partial(1/T) = -\Delta H^0/R = [\text{PA}(B_1) - \text{PA}(B_2)]/R \quad (12)$$

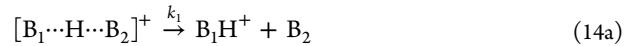
It has to be emphasized that eq 12 yields direct PA values only if experiments are conducted at several different temperatures, which allows a van't Hoff plot of  $\ln K_{eq}$  against  $1/T$  to provide  $\Delta$ PAs from the slope of the fitted line. However, in most cases, experiments are performed at the single temperature, which then give indirect PAs derived from measured gas-phase basicities employing estimated corrections for the protonation entropy term.<sup>35,36</sup> The anchor proton affinity can be identified by the direct measurement of the enthalpies of the base in question and its protonated form by using eq 1. Unfortunately, this is not possible in many cases,<sup>93</sup> and highly accurate ab initio calculations are then necessary (see below). The use of photoionization is also very helpful in this respect. Let us consider the protonation of a  $\text{CO}_2$  molecule by the photoionization of formic acid,<sup>94</sup> which has a known enthalpy of formation as well as initial base  $\text{CO}_2$ :



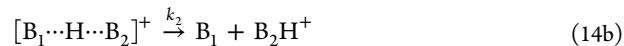
Employing eq 13, one can extract  $\Delta H_f(\text{COOH}^+)$  and utilize eq 1 in obtaining the absolute proton affinity of  $\text{CO}_2$ . This simple example illustrates the power of various experimental

techniques used in complementary ways, which can be further enhanced by highly accurate computational methods. Going back to the measurements of equilibrium constants  $K_{eq}$ , they can be performed by using high-pressure mass spectrometry techniques,<sup>95</sup> flowing afterglow experiments,<sup>96</sup> or the ion cyclotron resonance approach.<sup>97–99</sup> The earliest and most popular manner of extracting proton affinities from equilibrium measurements employed bracketing techniques,<sup>100,101</sup> where a series of proton transfer reactions 8 were carried out with known gas-phase basicities of the reference bases  $B_{refn}$  ( $n = 1, 2, 3\dots$ ). A distinction between fast exothermic and slow endothermic proton transfer then was made, leading to the bracketing of the  $\text{PA}(B)$  value of the examined base B between the closest reference bases  $B_{ref1}$  and  $B_{ref2}$ :  $\text{PA}(B_{ref1}) < \text{PA}(B) < \text{PA}(B_{ref2})$ . This has led to PAs within the limits of 2–3 kcal mol<sup>-1</sup>. Obviously, the bracketing technique leaves much room for improvement.

The kinetic approach to the estimation of gas-phase thermochemical properties includes the investigation of the fragmentation channels of weakly bound cluster ions introduced by Cooks et al.<sup>9,10,102,103</sup> Consider the proton bound complex between bases  $B_1$  and  $B_2$ :



and



The ratio of the abundances  $[B_1\text{H}^+]/[B_2\text{H}^+]$  for competitive fragmentation reactions is directly related to the thermochemical properties of bases  $B_1$  and  $B_2$  and their conjugate acids.<sup>92,102,103</sup> Specifically, the relative abundances or intensities for a spontaneous decomposition into eqs 14a and 14b channels are related to the relative free energy  $\Delta(\text{GB})$  by the following relation:

$$\Delta(\text{GB})/RT = \ln(k_1/k_2) = \ln(I_1/I_2) \quad (15)$$

where  $I_n$  signifies intensities, alias abundances. It goes without saying that basicity of base  $B_2$  has to be known to obtain basicity of the examined base  $B_1$ . A combination of bracketing and kinetic techniques was used by Bouchoux et al. in the thermokinetic method.<sup>11,12,104</sup> It is rooted in observations that the bracketing approach measures relative gas-phase basicities, rather than proton affinities,<sup>105</sup> particularly in systems possessing strong intramolecular H-bonds, where large entropy effects occur,<sup>106,107</sup> which in turn have to be properly taken into account.<sup>11,12,104</sup> An interested reader should consult the original papers because the experimental finesse and subtleties are beyond the scope of this Review.

The first experimental compendiums of GB and PA values were published by Taft et al.<sup>108</sup> and Aue and Bowers,<sup>109</sup> to be followed by a PA ladder established by Yamagdni and Kebarle.<sup>110</sup> Lias et al.<sup>111</sup> compiled a large collection of interlocked relative PAs measured in different laboratories and placed them on an internal scale, which was updated 4 years later.<sup>112</sup> Significant adjustments have been suggested at the upper end of this scale by Mautner and Sieck.<sup>113</sup> Systematic temperature-dependent investigations of the PAs in a range from *i*-butene to  $\text{NH}_3$  were undertaken by Szulejko and McMahon,<sup>48</sup> which supported the corrections introduced by Mautner and Sieck.<sup>113</sup> The proton affinity of CO was chosen as an anchor. They were also in agreement with parallel G2 calculations by Smith and Radom<sup>114</sup> for a number of

compounds. The latest NIST compilation by Lias et al.,<sup>115</sup> which spans a range of 302.4 kcal mol<sup>-1</sup> starting from the helium atom PA(He) = 42.5 kcal mol<sup>-1</sup> to cesium oxide PA(Cs<sub>2</sub>O) = 344.9 kcal mol<sup>-1</sup>, leans heavily on the equilibrium ladders of Mautner and Sieck<sup>113</sup> and of Szulejko and McMahon.<sup>48</sup> Most of the organic compounds fall within a more restricted range, extending from ca. 140 to 270 kcal mol<sup>-1</sup>. These two scales contain a sufficient number of gauge bases so that almost any new proton affinity can be measured according to Wu and McMahon.<sup>116</sup>

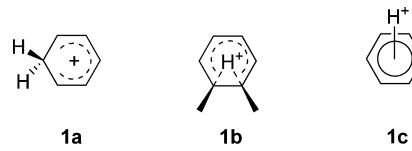
The question arises whether better accuracy than that attained in measurements could be achieved by calculations for the essential anchor molecules CO and NH<sub>3</sub>, which belong to the lower and upper parts of the basicity ladder, respectively. The answer was given by first principle computations<sup>6</sup> carried out by focal point analysis (FPA)<sup>117</sup> involving the all-electron coupled-cluster method<sup>118</sup> up to pentuple excitations with the Dunning basis set<sup>119–121</sup> aug-cc-pCVXZ, where the cardinal numbers X = D, T, Q, 5, and 6 for heavy atoms have been used, in conjunction with the corresponding aug-cc-pVXZ (X = 2–6) for hydrogen atoms. The reference wave function was determined by the restricted Hartree–Fock (RHF) method.<sup>122</sup> The corresponding HF energies were extrapolated to the complete basis set limits by two-<sup>123,124</sup> and three-parameter<sup>125</sup> fitting formulas involving the exponential cardinal number X. The coupled cluster correlation energies were extrapolated by a two-parameter polynomial formula.<sup>126</sup> Anharmonic correction to the zero-point vibrational energies was estimated by a quartic force field based on the calculated potential energy surfaces. Relativistic mass-velocity and Darwin terms<sup>127</sup> were evaluated at the first-order perturbation level by using the ACES II package.<sup>128</sup> Finally, refinement of the clamped nuclei approximation for NH<sub>3</sub> was performed using diagonal Born–Oppenheimer corrections (DBOC).<sup>129–131</sup> Because the energies are calculated with very high accuracy, they will be expressed in kJ mol<sup>-1</sup> units. It was found that the relativistic energy contributions to the absolute proton affinities are -0.14 and -0.12 kJ mol<sup>-1</sup> for NH<sub>3</sub> and CO, respectively, the latter being protonated at C atoms. The effects of computing electronic wave functions beyond the clamped nuclei formalism are -0.19 (NH<sub>3</sub>) and -0.42 (CO) in kJ mol<sup>-1</sup> as estimated by DBOC corrections. It is concluded that for a very high level of accuracy in considering proton affinities, the standard Born–Oppenheimer picture is not sufficient. The vibrational anharmonic correction to the PAs of NH<sub>3</sub> is 0.63 kJ mol<sup>-1</sup>. The largest contributions to PAs originate from the HF wave functions as expected, whereas the correlation effects are about 2%. Interestingly enough, the electron correlation diminishes the PA of NH<sub>3</sub> by 17.6 kJ mol<sup>-1</sup>, whereas it enhances the proton affinity of CO by 12.1 kJ mol<sup>-1</sup>. It follows that the electron correlation is larger in NH<sub>3</sub>, due to a lone pair and three localized N–H bonds, than in tetrahedral NH<sub>4</sub><sup>+</sup> possessing four NH bonds. In contrast, the electron correlation is stronger in protonated (HCO)<sup>+</sup>, than in the electron-rich initial base CO. The final results of Czakó et al.<sup>6</sup> for the room-temperature proton affinities are PA(NH<sub>3</sub>) = 852.6 ± 0.3 kJ mol<sup>-1</sup> and PA(CO) = 592.4 ± 0.2 kJ mol<sup>-1</sup>, which should be considered as benchmark values with sub-kJ accuracy. This means in the first place that the proton affinities of molecules, including first-row atoms, are well understood in terms of the relevant physical effects. Second, the absolute proton affinity of NH<sub>3</sub> lies between the experimental results of Szulejko and McMahon<sup>48</sup> (851.4 ± 3.3 kJ mol<sup>-1</sup>) and the recommended

853.6 kJ mol<sup>-1</sup> value of Lias.<sup>112</sup> The measured proton affinities of CO<sup>48,112</sup> are 593.7 and 594 ± 3 kJ mol<sup>-1</sup>, respectively, implying that both experimental estimates are too high by 1.3 and 1.6 kJ mol<sup>-1</sup>, respectively. In conclusion, one can say that ab initio calculations are capable of rectifying possible inconsistencies in the basicity ladder, at least for small molecules at the time being. They are also instrumental in estimating the precise proton affinities of primary and secondary local anchors on the PA scale, the latter playing an ancillary role. The theoretical framework adopted by Czakó et al.<sup>6</sup> in conjunction with Ruščić's ATcTs paradigm<sup>84</sup> provides a sign post for a broad avenue of research in the accurate thermochemistry of the 21st century by setting new standards of rigor and accuracy. This is just one example, which illustrates and corroborates the assertion that computational chemistry is one of the cornerstones of modern molecular science. We merely note in passing that the accurate calculations on the protonated CO are relevant for space chemistry, because both HCO<sup>+</sup> and COH<sup>+</sup> were observed in dense interstellar clouds.<sup>132,133</sup>

### 3.3. Protonation and Anti-/Aromaticity – Benzene and Cyclobutadiene

Benzene is the archetypal aromatic compound, which serves as a perfect model for studying the features of an important class of aromatic substances. On the other hand, the proton is the smallest electrophile, which represents a perfect model reactant in the electrophilic aromatic substitution (EAS) reaction that is so characteristic for aromatic systems.<sup>134–136</sup> There are three protonated forms, **1a**, **1b**, and **1c**, depicted in Scheme 1 corresponding to a  $\sigma$ -complex, bridged side structure, and face attached proton, respectively.

Scheme 1. Three Protonated Forms of Benzene

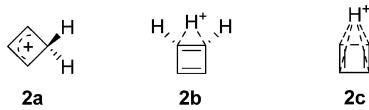


The  $\sigma$ -complex **1a** is a well-known Wheland's intermediate,<sup>137</sup> which should occur in EAS reactions.<sup>134–136</sup> Early experimental measurements, including NMR,<sup>138</sup> IR,<sup>139</sup> and X-ray<sup>140</sup> techniques, and theoretical evidence,<sup>141–143</sup> were in harmony with a general view that the most stable protonated form of benzene is **1a**, which provided a good model for a transition state in the EAS reactions. This viewpoint has been challenged by Mason et al.<sup>144</sup> on the basis of collision-induced decomposition mass spectroscopy measurements, claiming that there were two stable isomers of protonated benzene, **1a** and **1c**, the latter being more stable. This discrepancy triggered additional investigations. A comprehensive study, including MP2(fc)/6-311+G(3df,2p), MP3(fc)/6-311+G(3df,2p), and MP4/6-311G(2df,p) methods and additional G2(MP2) and G2 calculations, has convincingly shown that **1a** is the only stable conjugate acid of benzene<sup>145</sup> at each and every level of theory applied. The second protonated form, **1b**, is a transition structure (TS) for the hydrogen 1,2-bond shift. The face-protonated form, **1c**, is a double saddle with two degenerate imaginary frequencies of 1931i cm<sup>-1</sup> obtained by the MP3(fc)/6-31G(d) method. They correspond to transitions toward the apical  $\sigma$ - and edge  $\pi$ -complexes. It appears that **1b** (TS) for hydrogen scrambling is higher in energy than a Wheland's  $\sigma$ -

complex by 8.6 kcal mol<sup>-1</sup> as computed by the G2 protocol, thus being fairly low. This is compatible with a pronounced mobility of protons and the ring walk-mechanism, leading to seven equivalent protons discerned by a high temperature NMR experiment on the NMR time scale.<sup>138</sup> The experimental estimate of the barrier is roughly 9–10 kcal mol<sup>-1</sup>. An important finding was that the double-saddle structure, **1c**, is higher in energy than **1a** by 48 kcal mol<sup>-1</sup>, as obtained by G2 calculation. It followed as a corollary that there was something wrong with the experiment by Mason et al.<sup>144</sup> Subsequent IR investigations of protonated benzene noncovalently bonded to inert Ar and N<sub>2</sub> ligands confirmed this conclusion.<sup>146</sup> Incidentally, a proton placed at the very center of the benzene ring would be less stable than in the **1a** structure by 80 kcal mol<sup>-1</sup>.<sup>145</sup> An energetic property of particular importance is the proton affinity of benzene, which assumes values given within square parentheses<sup>145</sup> (in kcal mol<sup>-1</sup>), including (5/2)RT (eq 5) of 1.5 kcal mol<sup>-1</sup>: G2 [179.2], G2(MP2) [179.0], MP4/6-311G(2df,p) [179.3], MP3/6-311+G(3df,2p) [179.9], and MP2/6-311+G(3df,2p) [172.8], where MPn (*n* = 2, 3, 4) single-point calculations were carried out on the MP2/6-31G(d,p)-optimized geometries. The computed values compare well with the experimental value 179.3 kcal mol<sup>-1</sup>,<sup>115</sup> MP2 with a large 6-311+G(3df,2p) basis set being a notable exception. An important comment is appropriate here: MP2 calculation with a modest 6-31G(d) basis set yields the PA of 178.9 kcal mol<sup>-1</sup>, which is notably better than that obtained by the larger 6-311+G(3df,2p) basis set. It is necessary to reiterate that the choice of basis set must be in harmony with the theoretical framework, used in reproducing the electronic energy contribution to the PA, because misleading results could be obtained otherwise. To put it in another way, both the initial base and the final conjugate acids should be described in a balanced way. It is noteworthy that G2, G2(MP2), and MP4 proton affinity values are practically coincident with the experimental result.<sup>115</sup>

A molecule analogous to benzene is cyclobutadiene (CBD), which is a paradigm of antiaromaticity.<sup>147</sup> It is called the “Mona Lisa of organic chemistry” because of a number of peculiar and enigmatic properties.<sup>148</sup> It is intuitively expected that PA(CBD) ≫ PA(benzene), due to the alleviated antiaromaticity and significant relief of the angular strain energy upon protonation. This is, indeed, the case:<sup>143</sup> PA(CBD) = 223.1 kcal mol<sup>-1</sup> is obtained by the G2 method, which is 45.4 kcal mol<sup>-1</sup> higher than PA(benzene). It corresponds to a  $\sigma$ -complex **2a** in full analogy with benzene (Scheme 2).

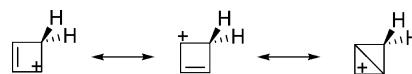
**Scheme 2.** Three Protonated Forms of Cyclobutadiene



A simple argument based on Pauling’s resonance structures shows that the protonated CBD form **2a** is stabilized by an allylic cation type of  $\pi$ -electron delocalization (cationic resonance) along the perimeter of the ring’s segments given by unprotonated carbons (Scheme 3).

The last resonance structure resembles the structure of a typical homoaromatic system, a concept put forward by Winstein some 60 years ago.<sup>149</sup> Indeed, the structure **2a** is puckered to increase the overlapping of the  $\pi$ -AOs placed at 1,3

**Scheme 3.** Resonance Structures in Protonated Cyclobutadiene



positions. This leads to a considerable shortening of the C<sub>1</sub>–C<sub>3</sub> distance by 0.22 Å as a further evidence of homoconjugative stabilization. It follows that a high PA(CBD) value is a consequence of several intermingled mechanisms, leading to the “heretical” conclusion that antiaromatic systems are even more prone to the electrophilic substitution reaction than aromatic ones. We mention that the **2b** structure is higher in G2 energy than **2a** by 43.6 kcal mol<sup>-1</sup>, which precludes ring-walk scrambling. The double-saddle critical point **2c** lies 83.7 kcal mol<sup>-1</sup> above the  $\sigma$ -complex. It has two imaginary frequencies corresponding to a descent toward either a double or a single CC bond. The experimental data on the protonated CBD are meager. There are NMR measurements of the bridgehead flipping inversion barrier<sup>150,151</sup> yielding 8.4 ± 0.5 kcal mol<sup>-1</sup> for the barrier height, which is in fair agreement with our G2 estimate of 7.8 kcal mol<sup>-1</sup>.<sup>145</sup>

#### 3.4. Ring versus Substituent Basicity – The Phenol and Aniline Dilemma

In a previous section, the proton affinity of benzene was considered in light of a number of accurate methods. An interesting question arises whether its simple derivatives phenol and aniline protonate at the heteroatom or on the ring. The problem of C versus O or N basicity in these two compounds is important, in view of their roles in chemistry and biochemistry. Experimental measurements face some problems in pinpointing the sites of protonation. A distinction in solutions between proton susceptibility of various atoms in molecules can be made by utilizing NMR and IR techniques.<sup>152,153</sup> To separate the solvent effects from genuine electronic features, investigations of conjugate acids in the gas phase or inert matrixes are required, which would facilitate the determination of the preferred sites of protonation. The gas-phase exploration of neutral species poses no problems provided they are volatile. The experimental values of PA(phenol) are 195.3 kcal mol<sup>-1</sup> according to NIST<sup>115</sup> and 196 ± 0.2 kcal mol<sup>-1</sup> provided by Bouchoux et al.<sup>154</sup> We shall adopt the latter as more accurate. Because both C and O atoms are candidates for protonation, it is instructive to compare this value with the PAs of H<sub>2</sub>O and benzene. According to NIST,<sup>115</sup> they are 165.0 and 179.3 kcal mol<sup>-1</sup>, respectively. It would be unlikely for a phenyl as a substituent to increase the PA of water by as much as 31 kcal mol<sup>-1</sup>. Hence, phenol should protonate on a benzene ring. Because the hydroxyl group is a  $\sigma$ -acceptor and  $\pi$ -donor substituent, Pauling’s resonance structures would suffice for predicting the *para*- and *ortho*-positions as preferred. This is the case, indeed, as revealed by early MP2(fc)/6-31G(d,p)//HF/6-31G(d) calculations,<sup>155</sup> which yielded PA(phenol)<sub>p</sub> = 197.0 and PA(phenol)<sub>o</sub> = 194.5 kcal mol<sup>-1</sup>, where a correction for the proton enthalpy of translation of 1.5 kcal mol<sup>-1</sup> is added. The subscripts p and o stand for the *para*- and *ortho*-positions. It appears that the simple MP2 model offers good accordance with the experimental result of Bouchoux et al.<sup>154</sup> for *para*-proton attack. The *ortho*-position has a lower PA by 2.5 kcal mol<sup>-1</sup>, whereas the PA for the *meta*-position is smaller by 15.6 kcal mol<sup>-1</sup>. It turns out that the OH substituent increases the proton affinity of benzene by 16 kcal mol<sup>-1</sup> by cationic

resonance triggered by protonation. One of the indicators of resonance is a significantly increased barrier of rotation of the OH group in protonated phenol as compared to the initial base. It is larger by 10.7 kcal mol<sup>-1</sup> according to MP2/6-31G(d) calculations.<sup>154</sup> It should be noted that the G2(MP2,SVP) method underestimates PA(phenol) by 2.4 kcal mol<sup>-1</sup>.<sup>154</sup> Protonation at oxygen yields PA(MP2) of 184.2 kcal mol<sup>-1</sup>, which is less than carbon protonation by 12.8 kcal mol<sup>-1</sup>, although phenyl substitution increases the PA of the parent water molecule by some 19 kcal mol<sup>-1</sup>. Obviously, phenol is a carbon base. It is interesting to mention the results of recent IR measurements of the protonated phenol clustered by several weakly bound argon atoms,<sup>156</sup> which in turn are known to perturb cations only slightly. It was found by vibrational analysis of the IR spectra that, under the particular conditions used in the experiment, at least two protonated isomers are present. One of them was protonated at oxygen, while the other was on the ring. It is gratifying that ab initio calculations can provide useful complementary information about all of the possible sites of protonation on an equal footing.

In contrast to phenol, which is a clear-cut case of protonation on the ring, the problem of a preferential site in aniline is much more subtle. It has been unequivocally established that aniline is nitrogen protonated in an aqueous solution, because the NH<sub>3</sub><sup>+</sup> fragment is more stabilized by the solvent molecules than the protonated benzene ring.<sup>157</sup> The same conclusion was reached by Bagno and Terrier,<sup>158</sup> using computations employing the isodensity polarized continuum method (IPCM).<sup>159</sup> Bagno et al.<sup>160</sup> have also calculated the electric field gradients and magnetic nuclear shielding of protonated aniline and compared the results to NMR relaxation rates measured in a water solution. It turned out that the aniline was N-protonated, implying that experiments consistently provide conclusive evidence that aniline is a nitrogen base in solution. The gas-phase results, on the other hand, have been contradictory over a long period of time. A number of gas-phase measurements have been carried out, and the results were very much dependent on the utilized technique and experimental conditions.<sup>161</sup> We should like to single out two papers by Smith et al.<sup>162</sup> and Flammang and co-workers.<sup>163</sup> Smith et al.<sup>162</sup> performed dual-cell Fourier transform ion cyclotron resonance (FT-ICR) experiments allowing partially deuterium-labeled aniline cations to react with nitrogen bases. The results unambiguously show that nitrogen is the kinetically favored protonation position of gaseous aniline. Flammang et al.<sup>163</sup> examined the ionization of mixtures of halogenobenzenes and ammonia under chemical ionization conditions, which afforded both N and para-C protonated anilines. The N-protonated species were predominantly produced under electrospray conditions.<sup>163</sup> The theoretical results were also found to depend largely on the method employed. Very early and extremely simple HF/STO-3G calculations<sup>164</sup> accompanied by the use of isodesmic reactions<sup>165</sup> indicated that aniline is a nitrogen base and that protonation on the aromatic ring is 1–3 kcal mol<sup>-1</sup> less favorable. Hildebrand et al.<sup>166</sup> carried out MP2(fc)/6-311+G(d,p)//HF/6-31G(d) + E<sub>ZPV</sub>(HF/6-31G(d)) calculations, which reproduced the experimental proton affinities of aminoalkanes very well. The proton attack is predicted to take place at the amino NH<sub>2</sub> group, with PA(aniline)<sub>N</sub> = 211.0 kcal mol<sup>-1</sup> (1.5 kcal mol<sup>-1</sup> is added to the 0 K result to bring it to room temperature results), which was in excellent agreement with the experiment,<sup>115</sup> 210.9 kcal mol<sup>-1</sup>. The result is greatly spoiled by a very low PA value for protonated C carbon at the

para-position (204.1 kcal mol<sup>-1</sup>), thus exhibiting an excessive disparity. Generally, it was found by Russo et al.<sup>161</sup> that density functional methods and MP4 prefer C<sub>p</sub> protonation, while G2(MP2) indicates that N-protonation is more favorable. It is important to point out that G2(MP2) calculations yield a difference in the PAs of N- and C<sub>p</sub>-atoms of only 0.7 kcal mol<sup>-1</sup>. Wiberg has executed CCSD(T)/6-311++G(2df,2pd) calculations of the PAs in aniline and concluded that the anilinium ion and para-protonated aniline have essentially the same energy.<sup>167</sup> The calculated PA(aniline) = 211.4 kcal mol<sup>-1</sup> was in good agreement with the experimental<sup>115</sup> and earlier MP2 result.<sup>166</sup> Finally, Flammang et al.<sup>163</sup> performed CCSD(T)/aug-cc-pVTZ, G2, and G3 computations with the following results obtained by adding 1.5 kcal mol<sup>-1</sup> for the translational enthalpy of the proton: PA(CCSD(T))<sub>N</sub> = 211.8, PA(G2)<sub>N</sub> = 210.9, and PA(G3)<sub>N</sub> = 210.9 in kcal mol<sup>-1</sup>. The corresponding values for the C<sub>p</sub> para-positions are PA(CCSD(T))<sub>Cp</sub> = 210.8, PA(G2)<sub>Cp</sub> = 209.4, and PA(G3)<sub>Cp</sub> = 209.2 in kcal mol<sup>-1</sup>. It turns out that the nitrogen atom is preferred by roughly 1 kcal mol<sup>-1</sup>. This is, however, within the error bars of these methods, thus supporting Wiberg's conjecture about the accidental degeneracy of the gas-phase intrinsic proton affinity for N and C<sub>p</sub> atoms in aniline. It follows as a corollary that the phenyl moiety increased the proton affinity of ammonia by 6.9 kcal mol<sup>-1</sup>. On the other hand, substitution of benzene with NH<sub>2</sub> increased its proton affinity by 31.6 kcal mol<sup>-1</sup>, which is spectacular indeed. One can draw the important conclusion that the amino group is a very strong electron donor in cations leading to their substantial stabilization, which will prove very useful in designing organic superbases (vide infra). As a final observation, we should like to mention that the introduction of an additional amino group alters the aforementioned relationship between nitrogen and benzene ring protonation in a way that both 1,2- and 1,4-diaminobenzenes protonate preferentially on the nitrogen atoms, whereas the 1,3-isomer is by 10.2 kcal mol<sup>-1</sup> a stronger carbon than the nitrogen base.<sup>168</sup>

### 3.5. The Proton as a Probe of the Electronic Structure – Semiquantitative Approach

The proton is a highly electrophilic species and consequently very reactive. Attacking a neutral base, it will try to locate positions with high electron density, which makes the formation of a strong covalent bond possible. Electron density withdrawal by a positive proton triggers the redistribution of the electron density in a molecule leading to stabilization by the relaxation effect. The larger is the relaxation, the greater is the stabilization. Very efficient relaxation is easily spread in large systems with mobile π-electrons. Hence, they are good candidates for highly basic compounds. Different molecules have different electronic density distributions and abilities in dispersing positive charge. A proton is a good probe of these features. These subjects are discussed in the next subsections starting with methodology.

**3.5.1. A Simple Semiquantitative Scaled Hartree–Fock Model.** In addressing the basicity in large molecular systems, we are inevitably leaving the realm of highly accurate computational methods. There is some uncertainty in the relationship between the size (*S*) of a molecule and the accuracy (*A*) of the applied quantum many-body method:

$$\Delta S \cdot \Delta A = -|const.| \quad (16)$$

meaning that the product of complexity and accuracy is constant. If the size  $\Delta S$  increases, accuracy *A* decreases by  $-|\Delta A|$ , and vice versa. To put it another way, we have to

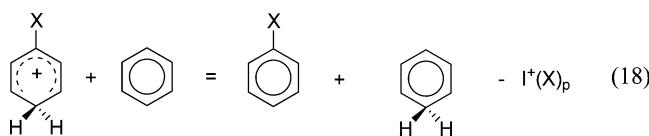
sacrifice some accuracy to increase feasibility and practicality. It must be emphasized that eq 16, as presented, implies a linear relationship between the computational cost and molecular size, which is not the case. Therefore, this equation should only be considered in a qualitative manner, because the exact relationship 16 changes with increasing computer power. We shall target the desired error margin of 2–4 kcal mol<sup>-1</sup> or better for proton affinities and basicities in large molecules. The case of benzene has shown that the MP2 method with an adequate basis set can do a very good job. Similarly, the MP2 method can reproduce the proton affinity of nitrogen in aniline within the experimental error limits very well, but fails to offer satisfactory PAs of carbon atoms of the benzene ring. Therefore, the methods of choice have to be (a) feasible in large systems, (b) designed and very carefully tested for the specific problem under scrutiny, and (c) used within the domains of their applicability. Otherwise, very unpleasant surprises are possible. Hence, one should always bear in mind that model computations have to be carried out with care and the results should be used with due caution. The same holds for the modeling process itself, which should be based on the physical picture, and on a final assessment against experimental or rigorous theoretical results. It turned out that the MP2(fc)/6-31G(d,p)//HF/6-31G(d) + E<sub>ZPV</sub>(HF/6-31G(d)) method gave results in good accordance with experiment for a wide variety of polysubstituted benzenes and naphthalenes for the ring protonation.<sup>167–173</sup> Interestingly, it was found that proton affinities calculated by this MP2 model can be reduced to the electronic energies of base B and conjugate acid B<sub>α</sub>H<sup>+</sup> obtained at the HF/6-31G(d) level, where  $\alpha$  denotes a site of protonation on the aromatic ring. The corresponding formula reads as follows:

$$\text{PA}(\text{B}_\alpha) = 0.8633 \cdot \Delta E_{\text{el}}(\text{HF}/6-31\text{G}(\text{d})) + 12.9 \text{ kcal mol}^{-1} \quad (17)$$

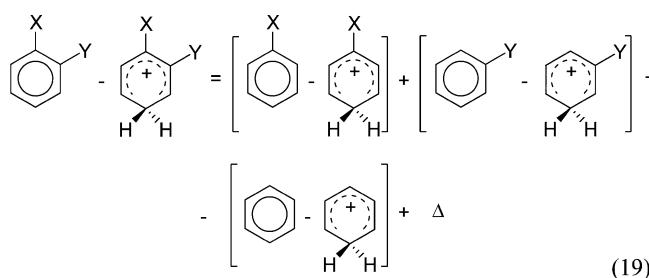
It is obtained by the least-squares fitting of the PA(MP2) values in substituted benzenes, naphthalenes, and biphenyls.<sup>43</sup> The statistical parameters of the linear correlation are very good, as evidenced by  $R^2 = 0.98$  and the mean average deviation MAD = 1.2 kcal mol<sup>-1</sup>. This simplified model for the calculation of PAs is called the scaled Hartree–Fock model (HF<sub>sc</sub>). The very good performance of the HF<sub>sc</sub> model is surprising and calls for comment. The linear relationship 17 is a consequence of the fact that  $E_{ZPV}$  does not depend on the finer details of the molecular wave function. In fact, it is atomic additive magnitude, depending only on the number of the atoms of each element in the molecule.<sup>174,175</sup> A protonated base has one more H atom and an additional covalent bond. The latter contributes to  $E_{ZPV}$  upon protonation on the aromatic ring, with a fairly constant average value of 6.4 kcal mol<sup>-1</sup> and an absolute average deviation of only 0.3 kcal mol<sup>-1</sup>. It constitutes a fraction of the free term in eq 17. Second, the electron correlation energy contribution to PAs is important but, obviously, quite successfully absorbed in the linear relation with  $\Delta E_{\text{ele}}(\text{HF})$ . This is presumably the consequence of the pronounced additivity of the correlation energy in Lewis molecules<sup>176–178</sup> but also in planar  $\pi$ -systems.<sup>179,180</sup> The scaled HF model, embodied in formula 17, was applied to calculations of the PAs of pyrene and its monofluoro-derivatives.<sup>173</sup> The most favorable site of protonation in pyrene pinpointed by the HF<sub>sc</sub> model was in agreement with an NMR study by Laali.<sup>181</sup> It is also in harmony with electrophilic substitution reactivity, such as the nitration, bromination, chlorination, and acylation

of pyrene, which occurs at the protonation preferential site.<sup>182</sup> In fluoro-derivatives of pyrene, the favorable protonation positions are in accord with the appearance of the corresponding cations in superacidic media, as confirmed by NMR measurements.<sup>183</sup> Finally, it should be mentioned that one could design a type (17) of HF<sub>sc</sub> correlation using experimental PAs. Unfortunately, they are not abundant enough for aromatic compounds. Hence, a purely theoretical relation 17 was preferred. It should also be pointed out that formula 17 can be obtained by using AM1 energies or  $\Delta H_f$  enthalpies. Their performance is considerably worse than that of the HF<sub>sc</sub> model. Moreover, they are not general enough, because separate formulas were needed for the substituted naphthalenes and biphenyls, unlike in the case of HF<sub>sc</sub> calculations. It is fair to say that density functional DFT methods did not provide reliable PAs in the early 1990s. However, the situation has dramatically changed in the meantime. Hence, DFT methods will be briefly discussed in section 4 dedicated to the tailoring of strong organic superbases, where they are heavily used.

**3.5.2. The Additivity of Proton Affinity in Polysubstituted Aromatic Systems.** Molecules are not droplets but, instead, highly structured systems. Arrangements of atoms in three dimensions lead to wonderful molecular architectures. There are a number of molecular properties that can be decomposed in atomic terms, implying that a molecule “remembers” the atoms that took part in its formation. Qualitatively speaking, molecules are ensembles of modified atoms. They leave their signatures or fingerprints in many molecular observables, either individually or in functional groups. Experimental knowledge and theoretical deliberations have led to a model of modified atoms in molecules (MAM).<sup>184–186</sup> This concept has also proved useful in rationalizing the influence of substituents on proton affinities in aromatic compounds. Let us consider the effect of substituent X on the proton affinity of benzene at the *para*-position. Making use of conceived homodesmotic reactions,<sup>187,188</sup> the following is obtained in a pictorial representation:



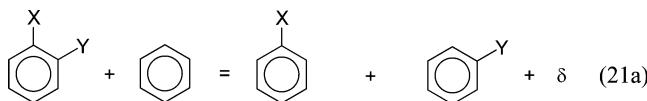
where  $I^+(\text{X})_p$  denotes the increment in the PA value caused by the  $\text{X}_p$  atom or atomic group relative to a free benzene. The increments for *ortho*- and *meta*-positions  $I^+(\text{X})_o$  and  $I^+(\text{X})_m$  are analogously defined. The proton affinity of disubstituted benzene can be similarly expressed as:



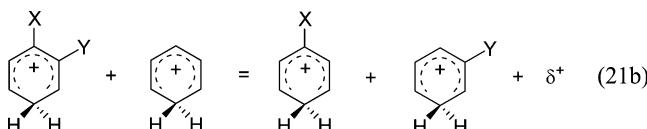
The energy expressions given in brackets are  $\text{PA}(\text{C}_6\text{H}_5\text{X}_p)$ ,  $\text{PA}(\text{C}_6\text{H}_5\text{Y}_m)$ , and  $\text{PA}(\text{benzene})$ . Adding and subtracting  $\text{PA}(\text{benzene})$  on the right side of eq 19, one obtains:

$$\text{PA}(\text{C}_6\text{H}_4\text{X}_p\text{Y}_m) = \text{PA}(\text{benzene}) + \text{I}^+(\text{X})_p + \text{I}^+(\text{Y})_m + \Delta \quad (20)$$

The effect of two substituents should be additive, if  $\Delta$  is a very small number or zero. It is easy to see that  $\Delta = \delta - \delta^+$  is the difference between two terms, which denote the interference energy between substituents X and Y in a neutral base ( $\delta$ ) and in conjugate acid ( $\delta^+$ ) according to the homodesmotic reactions 21a and 21b:



and

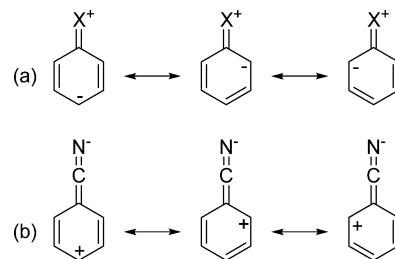


The values of interference energies  $\delta$  and  $\delta^+$  are relatively low as compared to proton affinities. Furthermore, they practically cancel making  $\Delta = \delta - \delta^+$  negligible in most cases. Hence, the effect of substituents is approximately additive as a rule, thus giving rise to an independent substituent approximation (ISA), where each substituent acts as if all of the others were nonexistent. Generalization of formula 20 yields:

$$\text{PA}(\text{substituted benzene}) = \text{PA}(\text{benzene}) + \sum_N \text{I}^+(\text{N})_{\alpha(N)} \quad (22)$$

where the summation runs over all of the substituents  $N$ , and  $\alpha(N)$  denotes the position of the substituents relative to the protonation site ( $\alpha = o, m, p, i$ ). It should be noted that ipso (i) protonation requires separate treatment,<sup>189</sup> because the perturbation of the substituent placed at the protonation site is large. The same holds for the  $\text{C}_i-\text{X}$  bond, which undergoes rehybridization from  $\text{sp}^2$  to  $\text{sp}^3$ . The increments were calculated by the MP2(fc)/6-31G(d,p)//HF/6-31G(d) +  $E_{ZPV}$ (HF/6-31G(d)) method. The additivity formula works very well for disubstituted and polysubstituted benzenes with MAD deviation from the MP2 calculated proton affinities of 1 kcal mol<sup>-1</sup>. In just a few cases were deviations of 3 kcal mol<sup>-1</sup> found.<sup>170</sup> This is a caveat emptor situation, in which some special effects take place in neutral bases or conjugate acids, requiring a special scrutiny. However, additivity works well in most cases, which shows that it can serve as a rule of thumb (see later). It also provides a simple diagnostic apparatus for special effects leading to nonadditivity. The latter should subsequently be meticulously examined, because it would shed more light on intramolecular interactions. Let us consider some useful information deduced from the increments and additivity property of the PAs in the substituted benzenes. The increments  $\text{I}^+(\text{F})_p = 1.3$ ,  $\text{I}^+(\text{OH})_p = 15.6$ , and  $\text{I}^+(\text{CH}_3)_p = 7.4$  (in kcal mol<sup>-1</sup>) are in fair agreement with the experimental  $-\Delta H_f$  values in the same order, 1.3, 13.4, and 8.4 kcal mol<sup>-1</sup>, which were measured by a series of equilibrium proton transfer reactions of F, OH, and CH<sub>3</sub> para-substituted benzenes relative to the parent molecule.<sup>190</sup> Generally speaking, the increments are in accordance with the electrophilic reactivity of various positions on the benzene ring. The  $\pi$ - or pseudo  $\pi$ -electron-donating groups or atoms, such as OH, F, and CH<sub>3</sub>, have positive *ortho* and *para* increments, thus activating these sites in the electrophilic reactions as illustrated by Scheme 4a. In

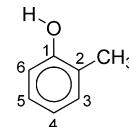
**Scheme 4.** Resonance Forms of Monosubstituted Benzenes with Either (a) Electron-Donating or (b) Electron-Withdrawing Substituents



contrast, the electron-withdrawing CN group (Scheme 4b) deactivates the *ortho*- and *para*-positions, making *meta*-carbon more susceptible to electrophilic attack than others, as borne out by the proton affinity increments.

An illuminating example is given by *o*-cresol (Scheme 5). It is known that *o*-cresol undergoes substitution mainly at positions

**Scheme 5.** Structure and Atom Numbering in *o*-Cresol



*ortho* and *para* to the OH group. This is obvious from their increments<sup>171</sup> given within parentheses in kcal mol<sup>-1</sup> ( $\text{I}^+(\text{OH})_o = 13.1$ ;  $\text{I}^+(\text{OH})_m = 0.0$ ;  $\text{I}^+(\text{OH})_p = 15.6$ ; and  $\text{I}^+(\text{CH}_3)_o = 6.3$ ;  $\text{I}^+(\text{CH}_3)_m = 3.0$ ;  $\text{I}^+(\text{CH}_3)_p = 7.4$ ). Substitutions at *ortho* and *para* to the methyl group would imply that the OH group influence is excluded, because  $\text{I}^+(\text{OH})_m = 0$ . On the other hand, position 4 would combine the increase in PA of both substituents  $\text{I}^+(\text{OH})_p$  and  $\text{I}^+(\text{CH}_3)_m$ , yielding the resulting  $\Delta\text{PA}$  relative to benzene as much as 18.6 kcal mol<sup>-1</sup>. Experimentally, it is known that *o*-cresol reacts with bromine about 5 times more rapidly than phenol, with the substitution occurring at the C4 position.<sup>191</sup> Obviously, the additivity rule of thumb can provide useful hints before full calculations and actual experiments are performed.

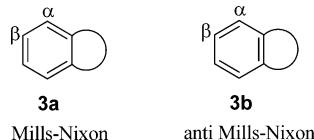
The results of the polysubstituted benzenes are given in Table S1. Perusal of the data shows good performance of the additivity formula 19 relative to the MP2 results. Importantly, the additivity rule yields results in agreement with available experimental data in all cases except one: 1,2,4,5-tetrafluorobenzene protonated at the C3 atom of the ring (Table S1). The proton affinities PA(MP2) and PA(add) are 164.2 and 164.1 kcal mol<sup>-1</sup>, respectively, which are at considerable variance with the NIST<sup>115</sup> value of 178.4 kcal mol<sup>-1</sup>. The latter should be reexamined, because the discrepancy is excessive. This brief discussion is concluded by the PA of perfluorobenzene obtained using a specific procedure (not described here) for ipso-protonation.<sup>189</sup> The PA(add) value of 152.2 kcal mol<sup>-1</sup> is in satisfactory agreement with PA(MP2) = 153.8 kcal mol<sup>-1</sup> and the experimental result of Szulejko and McMahon<sup>48</sup> of 153.8 kcal mol<sup>-1</sup>. It is fair to say that the additivity formula works well in substituted benzenes<sup>169,170</sup> as well as in substituted naphthalenes.<sup>171,172</sup> Recently, it was found that it also works for substituted pyridines.<sup>192</sup> Beyond any doubt, the additivity rule holds in other substituted aromatics, providing a useful rule of thumb. However, it is usually more than a sheer

rule of thumb because it yields semiquantitative estimates of proton affinities, using a piece of paper and elementary arithmetic. In summary, one should emphasize that various substituents perturb aromatic moieties by affecting their  $\sigma$ - and  $\pi$ -electronic structures. The extent of perturbation depends on the substituent's electron releasing or withdrawing power. The changes in the  $\pi$ -networks have strong and far-reaching consequences in influencing electrophilic substitution reactivity. Thus, proton affinity is a useful diagnostic tool for determining the electronic structure of aromatic systems and their reactivity. A lot can be learned about molecules by attaching a proton at each basic position, which can be performed by computational methods in an almost routine manner. The proton is also a useful probe for determining the changes in aromatic systems perturbed by angularly strained small rings, the subject of the next paragraph.

### 3.5.3. The Electrophilic Substitution Reactivity of Angularly Perturbed Annulated Benzenes – The Mills Nixon Effect.

**Because the proton is the smallest and most potent electrophile (Lewis acid), apart from the somewhat larger and positively doubly charged  $\alpha$ -particle, it is frequently used as an ideal model in studying electrophilic substitution reactions. There are two reasons behind the pronounced reactivity of the proton: the first is the unit positive charge combined with high electron affinity EA = 313.6 kcal mol<sup>-1</sup>. Second, the chemically very active H atom possessing unpaired electron spin, formed by electron capture, is the smallest radical in chemistry. As discussed above, proton affinity is a very useful property in examining substituent effects in aromatics and their influence on electrophilic reactivity. This is a consequence of the fact that proton attachment to the carbon atom on the aromatic ring forms a Wheland's  $\sigma$ -complex, which, according to Hammond's postulate,<sup>193</sup> provides a good approximation of the transition state for electrophilic substitution at this very position on the molecular perimeter. It appears that the fusion of small rings to aromatic moieties perturbs the latter through the substantial rehybridization of the carbon junction atoms, thus affecting their  $\sigma$ -electron structure, bond distances, and, to some extent, bond angles. The structural changes induce partial  $\pi$ -electron localization in the aromatic fragment(s). Concomitantly, the reactivity of the aromatic moieties is influenced as well. This was first observed 70 years ago by Mills and Nixon.<sup>194</sup> The properties of the Mills–Nixon systems are considered at great length in ref 195. In fact, there are two types of partial  $\pi$ -electron localization: Mills–Nixon (MN) type 3a and reversed or anti-Mills–Nixon type (AMN) 3b, as shown in Scheme 6.**

**Scheme 6. Two Different  $\pi$ -Electron Localization Patterns in Annulated Benzene**



The latter was found for the first time by Maksić et al.<sup>196</sup> in the benzoborirene and benzocyclopropenyl cation. It comes as no surprise that MN and AMN systems exhibit completely different reactivities. In the former type of compounds, electrophilic substitution will take place preferentially at  $\beta$ -positions, as experimentally shown in the early 1950s.<sup>134</sup> By

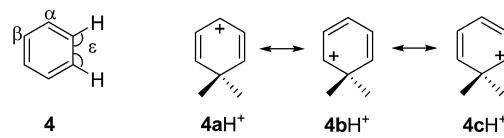
contrast, an AMN compound undergoes electrophilic substitutions predominantly at the  $\alpha$ -positions.<sup>195,197</sup> We shall discuss it in further detail below, but, in a nutshell, it is all about the matching or not of two  $\pi$ -bond localization schemes. The first is given by the ground-state  $\pi$ -electron distribution in MN and AMN systems (Scheme 6). The second  $\pi$ -bond localized pattern is given by the  $\sigma$ -complex formed by the electrophile X<sup>+</sup> attack on positions  $\alpha$  and  $\beta$  of the system under study (Scheme 7).

**Scheme 7. Two Possible Routes for an Electrophilic Attack on Annulated Benzene**



One observes that  $\beta$ -electrophilic attack induces  $\pi$ -delocalization in 3aX<sup>+</sup>, which is compatible with the  $\pi$ -distribution in the MN compounds and incompatible for the AMN systems. Consequently,  $\beta$ -attack is favored in MN and disfavored in AMN compounds. The opposite is true for  $\alpha$ -electrophilic substitution (viz., Schemes 6 and 7). This qualitative conjecture is confirmed by calculations for X<sup>+</sup> = H<sup>+</sup>, CH<sub>3</sub><sup>+</sup>. Let us consider the protonation of a model system, where two vicinal CH bonds are bent toward each other, mimicking a small fused ring.<sup>198</sup> Angles  $\epsilon$  of 110° and 94° simulate five- and four-membered carbocycles, respectively, thereby representing two characteristic MN systems. It should be pointed out that benzene itself for  $\epsilon$  = 120° is a model for tetraline if the hyperconjugation with CH<sub>2</sub> groups is ignored. This ideal model is free of the "contamination" introduced by carbocyclic conjugation or hyperconjugation, thus reflecting a pure angular strain effect. Its dominating localization VB structure 4 is given in Scheme 8.

**Scheme 8. A Modeled Annulated Benzene 4 and Dominating Localization Valence–Bond Structures of Protonated Benzene**



The resonance effect in the benzenium ion is described by the structures 4aH<sup>+</sup>–4cH<sup>+</sup>. MP2(fc)/6-31G(d)//HF/6-31G(d) calculations have been carried out for proton attachment at the  $\alpha$  and  $\beta$  positions. The difference in the proton affinities between the  $\alpha$  and  $\beta$  positions for deformation angles  $\epsilon$  = 120°, 111°, and 94° yields a straight line:

$$\text{PA}_\beta - \text{PA}_\alpha = -0.166\epsilon^\circ + 19.9 \text{ in kcal mol}^{-1} \quad (23)$$

with  $R^2 = 0.999$ . A negative slope indicates that selectivity in favor of the  $\beta$  position increases as the angle of annelation decreases in the MN systems. Employing homodesmotic reactions, it can be shown that the difference, PA(E <sub>$\beta$</sub> ) – PA(E <sub>$\alpha$</sub> ), does not explicitly depend on the angular strain energy in the ground state but is instead solely the result of the (mis)matching of the GS and TS modes of  $\pi$ -bond localization.<sup>198</sup> The angular strain in the GS implicitly affects

reactivity by determining the pattern of the  $\pi$ -electron partial localization. The situation in real benzocyclopropene, benzoclobutene, and benzocyclopentene molecules is more complicated because it includes hyperconjugative interaction with methylene groups. However, the hyperconjugation effect can be estimated and delineated from the angular strain effect.<sup>30</sup> Employing the same MP2 method, the preference of the  $\beta$ -site protonation is expressed in a formula analogous to a previous one:

$$\text{PA}_\beta - \text{PA}_\alpha = -0.046e^\circ + 7.68 \text{ in kcal mol}^{-1} \quad (24)$$

Regioselectivity induced by small annelated rings in pinning down the site of the electrophilic attack on the benzene ring was confirmed in this way for the first time by theoretical means, thus vindicating the Mills–Nixon hypothesis.<sup>30</sup> It should be noted that the combined effect of the OH substituent and MN effect did not alter the general conclusion.<sup>199</sup> As a final comment, it should be pointed out that in the following three AMN systems: the edge protonated 1,2-benzene serving as a model system, benzoborirene, and benzopropenyl cation, the MP2(fc)/6-31G(d)//HF/6-31G(d) calculations have conclusively shown opposite behavior in the orientation of the proton attack on aromatic moiety as compared to MN systems.<sup>197</sup>

### 3.6. The Linear Relation between Proton and Methyl Cation Affinities

The broad similarity between the  $\text{H}^+$  and  $\text{CH}_3^+$  cations has been known for a long time.<sup>200</sup> This is of great importance because the methyl cation plays an important role in Friedel–Crafts alkylation reactions<sup>201</sup> and seems to participate in interstellar chemical synthesis<sup>202</sup> and carcinogenic processes by interacting with DNA.<sup>203</sup> However, one has to be careful because there are examples where the analogy between  $\text{CH}_3^+$  and  $\text{H}^+$  breaks down particularly in solution.<sup>204</sup> A rough linear relation between methyl cation affinity (MeCA) and proton affinity was reported independently by Bartmess<sup>205</sup> and McMahon et al.<sup>206</sup> by correlating known experimental data available at the time, although the former work emphasized significant scattering in correlation. A small experimental scale of MeCA values spanning a range of 15 kcal mol<sup>-1</sup> has been established by  $\text{CH}_3^+$  attachment to N, O, and C lone pairs for several cyanamides, ethers, and iodides by Deakyne and Mautner.<sup>207</sup> The experimental pulsed high-pressure MS data were accompanied by MP<sub>n</sub> ( $n = 2, 3, 4$ ) calculations. The best agreement was achieved by the lowest MP2 level, employing a very modest 6-31G(d) basis set in accordance with our early proton affinity computations (vide supra). A few years later, a new ladder of MeCA affinities was constructed by Glukhovtsev et al.<sup>208</sup> on the basis of variable-temperature proton-transfer equilibrium measurements and G2 calculations. A problem with the earlier data was the MeCA value of the anchor compound  $\text{N}_2$ , which had been too high. It was found by Glukhovtsev et al.<sup>208</sup> that  $\text{MeCA}(\text{N}_2) = 44.0 \text{ kcal mol}^{-1}$  leading to the revision of all of the MeCA values, which had been determined earlier relative to the  $\text{N}_2$  anchor. Prompted by the similarity between  $\text{H}^+$  and  $\text{CH}_3^+$ , which in turn has a fairly localized positive charge, or to be more precise, it has a unit positive charge delocalized over a small  $\text{CH}_3$  skeleton, we undertook a comparative study of the MeCA and PA affinities in substituted benzenes employing the MP2(fc)/6-31G(d,p)//HF/6-31G(d) +  $E_{\text{ZPV}}(\text{HF}/6-31G(\text{d}))$  method.<sup>209</sup> It was found that  $\text{MeCA}(\text{benzene})$  is 81.4 kcal mol<sup>-1</sup>, in good accordance with an experimental estimate of 81.0 kcal mol<sup>-1</sup>. It follows that the

MeCA of benzene is 99 kcal mol<sup>-1</sup> lower than PA(benzene). Furthermore, taking into account all of the calculated MCAs and PAs of the studied substituted benzenes, it turned out that methyl cation affinities are lower than proton affinities on average by some 98 kcal mol<sup>-1</sup>, thus being close to the difference between the intrinsic MeCA and PA of the parent benzene. Most importantly, there is a linear relationship between MeCA and PA:

$$\text{MeCA}(\text{MP2}) = 0.967\text{PA}(\text{MP2}) - 91.7 \text{ in kcal mol}^{-1} \quad (25)$$

This linear correlation is of high quality, with  $R^2 = 0.996$  and  $\text{MAE} = 0.7 \text{ kcal mol}^{-1}$ . It is of interest that the calculated MCAs follow a similar additivity rule, just like the proton affinities of the substituted benzenes. Its performance is good but could be improved by the least-squares fitting of the  $\text{MeCA}(\text{add})$  estimates with the MeCA results calculated by the MP2 method. The corresponding relation reads as follows:

$$\text{MeCA}(\text{MP2}) = 0.941\text{MeCA}(\text{add}) + 4.9 \text{ in kcal mol}^{-1} \quad (26)$$

with  $R^2 = 0.996$  and the standard deviation of  $\sigma = 0.9 \text{ kcal mol}^{-1}$ . It follows that the back of the envelope calculation of the additive MeCA(add) values yields quite reliable MeCA(MP2) estimates with no effort, which is remarkable. In conclusion, one can state without any exaggeration that  $\text{CH}_3^+$  and  $\text{H}^+$  cations are indeed alike, at least within the family of polysubstituted benzenes and perhaps in the families of other closely related molecules. It is noteworthy that Wei et al.<sup>210</sup> found  $\text{CH}_3^+$  to be a better model for organocatalytic transformations than the proton, because these reactions involve an initial nucleophilic attack instead of an electrophilic one. Finally, a computational study of an  $\text{CH}_3^+$  attack on some MN systems corroborated the Mills–Nixon hypothesis<sup>211</sup> just like earlier calculations using the proton as the electrophile (vide supra).

### 3.7. The Linear Relationship between Proton and Metal Cation Affinities

Although the basicity of a base in the gas phase is generally expressed as its affinity toward the proton, it can also be expressed toward a metal cation.<sup>212</sup> Metal cation affinity (MCA) and metal cation basicity (MCB) can be defined in a manner similar to that of proton affinity and basicity. For complexation reaction 27:



MCB is defined as negative free energy of reaction 27:

$$\text{MCB} = -\Delta G_{\text{M}(n)+} = -RT \ln K \quad (28)$$

whereas MCA is defined as a negative value of the enthalpy change of reaction 27:

$$\text{MCA} = -\Delta H_{\text{M}(n)+} \quad (29)$$

There has been great interest in evaluating the metal cation basicity of diverse bases to different metal cations such as  $\text{Li}^+$ ,  $\text{Al}^+$ ,  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Be}^{2+}$ ,  $\text{Ca}^{2+}$ , etc.<sup>213–220</sup> However, despite all efforts, metal cation basicity scales are more limited than the proton affinity scale. Probably the most complete and accurate MCB scales involve alkali metal cations.<sup>215–222</sup> Parallel to the experimental and theoretical determination of MCBs, there was an attempt to establish a linear correlation between MCBs and the corresponding proton affinities/basicities. The lithium

cation was one of the most thoroughly studied in that sense.<sup>222–226</sup> However, there is a significant difference between  $\text{Li}^+$  and  $\text{H}^+$  when the formation of a bond with a base is concerned. A proton adds to a base, forming a strong covalent bond, while a bond between a base and  $\text{Li}^+$  is mainly ionic. Moreover,  $\text{Li}^+$  has the ability to form bridging structures with bases possessing two or more atoms with lone pairs. Alcamí et al. have studied complexes of polydentate bases such as azoles,<sup>223</sup> methyldiazoles,<sup>224</sup> and azines<sup>225</sup> with  $\text{Li}^+$  and found that the correlation between proton affinity and metal cation basicity follows two different linear relationships, one for those cases where  $\text{Li}^+$  is singly coordinated and a different one where  $\text{Li}^+$  is doubly coordinated. Taft et al.<sup>227</sup> concluded that there is no precise general correlation between lithium cation basicity and basicity toward protons, particularly when different compounds with diverse functionalities are included in the correlation. This conclusion was re-examined by Burk et al.,<sup>222</sup> who used a very large set of 205 compounds and confirmed that a single correlation cannot give a good fit. However, satisfactory correlations were found for families with similar basicity centers. The lack of overall correlation was attributed to the widely variable sensitivities of different types of molecules to the changes in the substituents, as well as the chelating effects of some  $\text{Li}^+$  adducts.

### 3.8. Proton Affinities and ESCA Shifts

Electron spectroscopy for chemical analysis (ESCA) developed by Siegbahn and co-workers<sup>228,229</sup> has significantly contributed to the understanding of the electronic structure and properties of molecules and solids. An ejection of an inner-shell electron of a particular atom in the molecule requires characteristic ionization energy. It depends on the electronic density at the ionized atom and the electron density distribution in its immediate vicinity defined by the nearest neighbors. Finally, more distant molecular domains, including substituents,<sup>230,231</sup> affect the ionization energy by long-range Coulomb interactions. Although inner-shell electrons do not directly contribute to covalent chemical bonding, they monitor their chemical environment, which influences their orbital energies. Moreover, the molecular structure (both spatial and electronic) is reflected in the electron density redistribution effect, which occurs upon the creation of a positively charged hole.<sup>232</sup> Hence, ESCA shifts also provide a useful probe of the electronic structure. This was first observed by Martin and Shirley, suggesting that there must be a similarity between the inner core electron ionization energies and protonation at the site of the ionized host atom.<sup>233</sup> This idea generated a number of papers on linear relationships between ESCA shifts and proton affinities derived by the electrostatic potential at the nuclei of ionized atoms via the Hellman–Feynman theorem.<sup>234</sup> Although it appeared that better correlation can be obtained if different classes of compounds are correlated separately, it was observed that there is no significant decrease in the quality of correlation if different types of compounds are correlated in a single correlation.<sup>235–237</sup> Catalan and Yáñez found linear correlations between experimental proton affinities and  $\text{C}(1\text{s})^2$ ,  $\text{O}(1\text{s})^2$ , and  $\text{N}(1\text{s})^2$  inner-core orbital energies calculated at the simple Hartree–Fock level.<sup>238–240</sup> Recently, improved quality for experimental  $\text{C}(1\text{s})^2$  ionization energies rendered new correlations with PAs for polyenes,<sup>241</sup> fluorobenzenes,<sup>27</sup> methylbenzenes,<sup>28</sup> and pyridines possible.<sup>192</sup> Building on these results, Carroll et al.<sup>29</sup> were able to develop an additivity formula for core-ionization energies in fluoromethylbenzenes in

analogy with the additivities found in the PAs of the substituted benzenes discussed earlier.<sup>169,170</sup> The interfertilization of these two separated and yet closely related fields is desirable, and their combination could lead to better estimates and understanding of the relaxation effects caused by core–electron ejections and proton attachments at various atoms in molecules.

### 3.9. Proton Affinities and Ionization Energies

The first attempts to establish a correlation between proton affinity and valence-shell ionization energy appeared parallel to a work on the correlation of proton affinity with inner-core (1s) ionization energies.<sup>242,243</sup> The underlying idea starts from the simple observation that proton affinity and ionization energy (IE) both depend on the differences in energy between species, which essentially differ in charge. Moreover, to remove an electron and to add a proton are electrically analogous processes. Davis and Rebelais,<sup>234</sup> and Martin and Shirley<sup>233</sup> independently observed a linear relationship between the PA and first ionization energy within a homologous series of molecules. They proposed that such a type of correlation can be useful in the prediction of proton affinity if the ionization energy of a molecule is known. However, Benoit and Harrison<sup>235</sup> found that each class of compound requires a separate correlation. An attempt to fit all of the PA and ionization energy data to a single correlation yielded a very poor correlation coefficient of 0.87, much poorer than that obtained for the separate fits where the correlation coefficients ranged between 0.97 and 0.99. The rationalization of this phenomenon was that the major effect of substituents in the case of valence-shell ionization is due to a polarization effect on the final state, the effect of which is different for each class of compound. Staley et al.<sup>244</sup> have studied the correlation between PA and ionization energy in nitriles and concluded that caution is necessary in choosing the correct ionization energy. They found that the proton affinities of nitriles are linearly correlated not to the first  $\text{CN}_\pi$  ionization energy but rather to the N lone pair  $\sigma$  IE at higher energy. Building on these results, Yáñez et al.<sup>245</sup> applied a multivariate linear correlation and for a large set of compounds, including oxygen, nitrogen, and carbon bases, demonstrated that it is possible to express the gas-phase PA as a linear function of (1s) binding energies and first ionization energies. Some “problematic” molecules, which deviated significantly from the single correlation of PA with (1s) energies, such as *N,N*-dialkylanilines and naphthalene, fit the multivariate correlation very well. They concluded that those systems are stronger bases than expected from PA versus (1s) energy correlation due to their high polarizability, which considerably facilitates the accommodation of a highly localized positive charge, a conclusion similar to that of Benoit and Harrison.<sup>235</sup> Yáñez et al. have also rationalized several nitrile peculiarities, observed by Staley et al.,<sup>244</sup> and demonstrated that a correlation should exist using either the energy of the nitrogen lone pair or the  $\text{CN}_\pi$  orbital. The deviation that was previously observed in some halogen-substituted nitriles has been interpreted as a consequence of the interaction between halogen lone pair orbitals and  $\text{CN}_\pi$  orbitals. Correlation between proton affinity and ionization energies has been performed for some other classes of compounds, such as aminoacids,<sup>246</sup> tetrazenes,<sup>247</sup> and tetraalkylhydrazines,<sup>248</sup> with the derived general conclusion that good correlation can be obtained only for similar types of compounds.

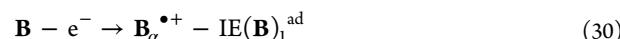
### 3.10. Gas-Phase versus Solution-Phase Basicity

Satisfactory correlations between gas-phase proton affinities or gas-phase basicities and solution  $pK_a$  values in a given solvent rarely exist. Moreover, there are some examples where there is an inversion of the basicity sequence when passing from the gas phase to the solution. The most notable example in that sense is probably the basicity of methylamines,<sup>249–251</sup> where the basicity order in the gas phase is  $(\text{CH}_3)_3\text{N} > (\text{CH}_3)_2\text{NH} > \text{CH}_3\text{NH}_2 > \text{NH}_3$ , which in a water solution changes to  $(\text{CH}_3)_2\text{NH} > \text{CH}_3\text{NH}_2 > (\text{CH}_3)_3\text{N} > \text{NH}_3$ . However, recently Hall and Bates<sup>252</sup> were able to correlate the nucleophilicity of 18 alkylamines with their water  $pK_a$  values using a correlation coefficient of 0.99. Furthermore, there are cases where the correlation of gas-phase basicity constants<sup>38a,253,254</sup> with  $pK_a$  values proved useful in predicting or rationalizing some molecular properties. To extend the gas-basicity scale with a series of phosphazene compounds, Raczynska and co-workers<sup>253,38a</sup> employed a correlation of known  $pK_a$  values in acetonitrile with GB data to determine the heretofore unknown GB values for some very basic phosphazenes. Similar studies involving several amines<sup>255</sup> and diamines  $\text{H}_2\text{N}-(\text{CH}_2)_n-\text{NH}_2$  ( $n = 2-10$ )<sup>256</sup> revealed fairly good correlation between calculated PAs and  $pK_a$  values in water solution. Recently, a very detailed analysis of the relationship between  $pK_a$  in different solvents (THF, acetonitrile, water) and gas-phase basicities has been performed by the Koppel group<sup>257</sup> to study the importance of various effects on solution basicity. Their conclusions can be summarized as follows: (a) when correlation involves molecules with large variations of molecular structure and size, the correlation coefficient is rather poor, (b) the solvent stabilization of a protonated molecule is strongly influenced by the immediate vicinity of the protonated center, and, therefore, better correlation can be obtained for the class of molecules where sterical hindrance is not present, (c) the inclusion of the molecular radius in the correlation of GB versus  $pK_a$  values significantly increases the correlation coefficient, demonstrating the importance of molecular volume/polarizability on basicity, and (d) comparison of different solvents reveals that the gas phase is a 3.2, 2.3, and 6.1 times better differentiator of basicities than THF, acetonitrile, and water, respectively.

### 3.11. Interpretation of Proton Affinities – Triadic Analysis

Rigorous theory, accurate calculations, and experimental measurements produce an immense amount of information, which has to be categorized, systematized, and understood to establish a coherent system of scientific knowledge. Providing meaning, sense, and understanding to the myriads of numbers obtained by experiments and computations is the ultimate and probably the most important step in scientific research. This can be achieved by using general theories at the fundamental level. In our case, it is quantum mechanics and simple but sound physical models at an intuitively appealing conceptual point of view. Considerable efforts and ideas have been put forward in attempts to interpret basicity and proton affinity. In the beginning, they were focused on ionization energies<sup>244,258</sup> and the frontier orbitals of the base in question<sup>259</sup> or the hybridization s-character of the lone pairs to be protonated.<sup>260</sup> More recently, density functional theory (DFT) has been utilized in the interpretation of proton affinities and identification of preferential protonation sites, based on the concepts of global and local reactivity descriptors.<sup>261–266</sup>

Interpretation of proton affinity should be based on a firm physical description of the protonation process. Let us consider a molecule and a proton in vacuo. Because quantum mechanics is a holistic theory, it embraces all of the participants in the quantum system. Consequently, the picture of protonation can be divided into three distinct sequential stages:<sup>31–33</sup> (a) a molecule is ionized by electron removal and a hydrogen atom is formed by releasing energy equal to the electron affinity of the proton  $\text{EA}(\text{H}^+) = 313.6 \text{ kcal mol}^{-1}$ , (b) a molecular radical cation is stabilized by the dispersion of the positive charge over the molecular framework, and (c) a new chemical bond is formed between the molecular radical cation of the base and the hydrogen atom. It is conceptually advantageous to dissect adiabatic ionization artificially in two steps. Let us assume that ionization is an instantaneous event at the initial  $t_0 = 0$  moment, so that both the remaining electrons and the nuclei are frozen. The ionization energy then can be conveniently calculated by using Koopmans' theorem.<sup>267</sup> This vertical ionization given in one-electron approximation reflects the genuine features of the electronic structure of the initial state of a base in question. The second step of the ionization process takes into account that ionization is not a sudden event but instead occurs in real time. Thus, both electrons and nuclei relax giving rise to stabilizing reorganization energy. The latter represents an intermediate stage of the protonation reaction. Finally, in a third stage, a covalent bond is created that leads to the bond association energy stabilization of the protonated base. This energy reflects the properties of the final state. Translating all of this into mathematical language, we obtain:



where  $\text{IE}(\mathbf{B})_1^{\text{ad}}$  signifies the first adiabatic ionization energy of a base  $\mathbf{B}$  describing the ejection of the least bound electron and the simultaneous formation of the base radical cation denoted by  $\mathbf{B}_\alpha^{\bullet+}$ . The site of protonation is denoted by subscript  $\alpha$ . The electron is captured by the incoming proton:



where  $\text{EA}(\text{H}^+)$  is the electron affinity of the proton, experimentally and theoretically determined to be 313.6 kcal  $\text{mol}^{-1}$ . Here, calculation of both the IE and the EA values assumes that the heat of the formation of the electron,  $\Delta_f H(e^-)$ , is zero at all temperatures according to the “electron convention” as opposed to the “ion convention” where in the classical Boltzmann statistics  $\Delta_f H(e^-) = 5/2 \cdot RT$ .<sup>268</sup> Nevertheless, either of the two conventions ultimately provides the same  $\text{PA}(\mathbf{B})$  values. The homolytic bond association energy (BAE) $_\alpha^{\bullet+}$  is then given by



The relaxation energy following ionization is given as the difference between Koopmans' and adiabatic ionization energies:



Combining eqs 30–33, the relation for the proton affinity obtained by trichotomy decomposition is of the following form:

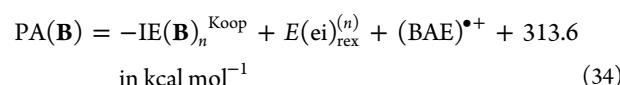


Table 1. Triadic Analysis of the Proton Affinities of Substituted Amines and Imines<sup>a</sup>

molecule B	$\text{IE}(\mathbf{B})_n^{\text{Koop}}$	$\text{IE}(\mathbf{B})_1^{\text{ad}}$	$E(\text{ei})_{\text{rex}}^{(n)}$	$(\text{BAE})_{\alpha}^{\bullet+}$	$\text{PA}(\mathbf{B})_{\text{COMP}}$	$\text{PA}(\mathbf{B})_{\text{EXP}}^c$
NH <sub>3</sub> ( <b>5</b> )	(270.3) <sub>1</sub>	228.5	41.8	120.2	205.3	204.0
NH <sub>2</sub> (CH <sub>3</sub> ) ( <b>6</b> )	(246.3) <sub>1</sub>	205.7	40.6	107.8	215.7	214.9
NH(CH <sub>3</sub> ) <sub>2</sub> ( <b>7</b> )	(231.4) <sub>1</sub>	189.9	41.5	98.9	222.6	222.2
N(CH <sub>3</sub> ) <sub>3</sub> ( <b>8</b> )	(221.2) <sub>1</sub>	180.0	41.2	93.3	226.9	226.8
<b>9</b>	(271.7) <sub>1</sub>	228.6	43.1	121.8	206.8	203.8
<b>10a</b>	(267.7) <sub>2</sub>	197.2	70.5	117.4	233.8	235.7
<b>10b</b>	(231.6) <sub>1</sub>	197.2	34.4	85.2	201.6	
<b>11</b>	(259.7) <sub>3</sub>	161.4	98.3	104.5	256.7	
<b>12</b>	(237.4) <sub>5</sub>	135.3	102.1	97.3	275.6	
<b>13</b>	(259.4) <sub>3</sub>	179.2	80.2	109.1	243.5	
<b>14</b>	(243.0) <sub>4</sub>	153.6	89.5	110.8	270.8	
<b>15</b>	(224.6) <sub>4</sub>	133.9	90.7	109.4	289.1	
<b>16</b>	(197.3) <sub>1</sub>	121.7	75.6	95.3	283.7	
<b>17</b>	(259.8) <sub>7</sub>	187.6	72.2	101.1	227.1	
<b>18</b>	(247.3) <sub>1</sub>	211.3	36.0	114.4	216.7	216.4
<b>19</b>	(232.3) <sub>1</sub>	187.4	44.9	98.3	224.5	225.5
<b>20</b>	(229.5) <sub>1</sub>	180.2	49.3	93.4	226.8	226.6
<b>21</b>	(227.7) <sub>1</sub>	180.6	47.1	94.6	227.6	228.0

<sup>a</sup>All terms are given in kcal mol<sup>-1</sup>. Radicals are treated by the unrestricted UMP2 single point calculations utilizing the same basis set. <sup>b</sup>Subscripts denote principal molecular orbitals undergoing ionization. <sup>c</sup>Experimental data are taken from ref 112.

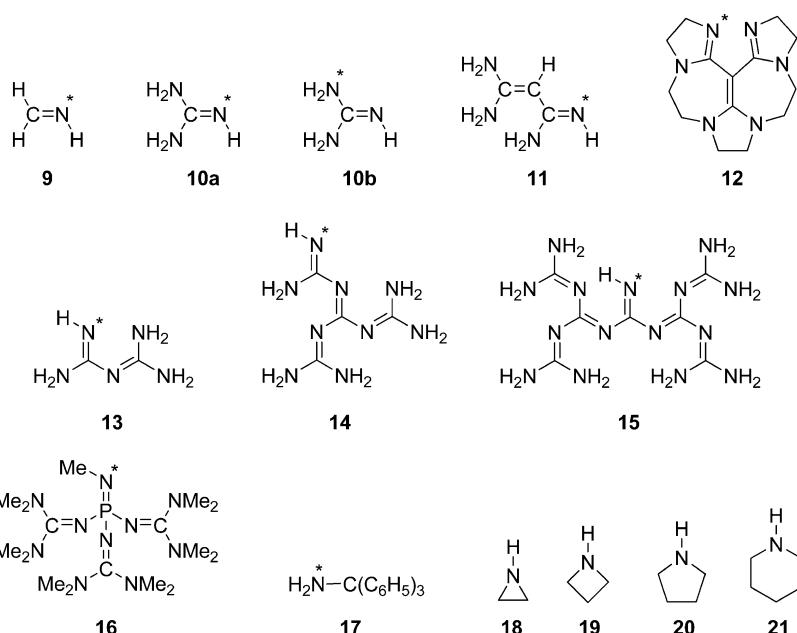


Figure 1. Graphical representation of amines and imines discussed in this work. Thermodynamically most favorable site of protonation is denoted with an asterisk.

The trend of changes relative to a reference compound is important in chemistry. For that purpose, it is practical to put the differences of the three terms appearing in eq 34, calculated relative to a standard base  $\mathbf{B}(\text{st})$ , in a triad:

$$\begin{aligned}\Delta[\text{PA}(\mathbf{B}_\alpha)] &= \text{PA}(\mathbf{B}_\alpha) - \text{PA}(\text{st}) \\ &= [-\Delta(\text{IE})_{\alpha,n}^{\text{Koop}}; \Delta E(\text{ei})_{\alpha,\text{rex}}^{(n)}; \Delta(\text{BAE})_\alpha^{\bullet+}] \quad (35)\end{aligned}$$

where

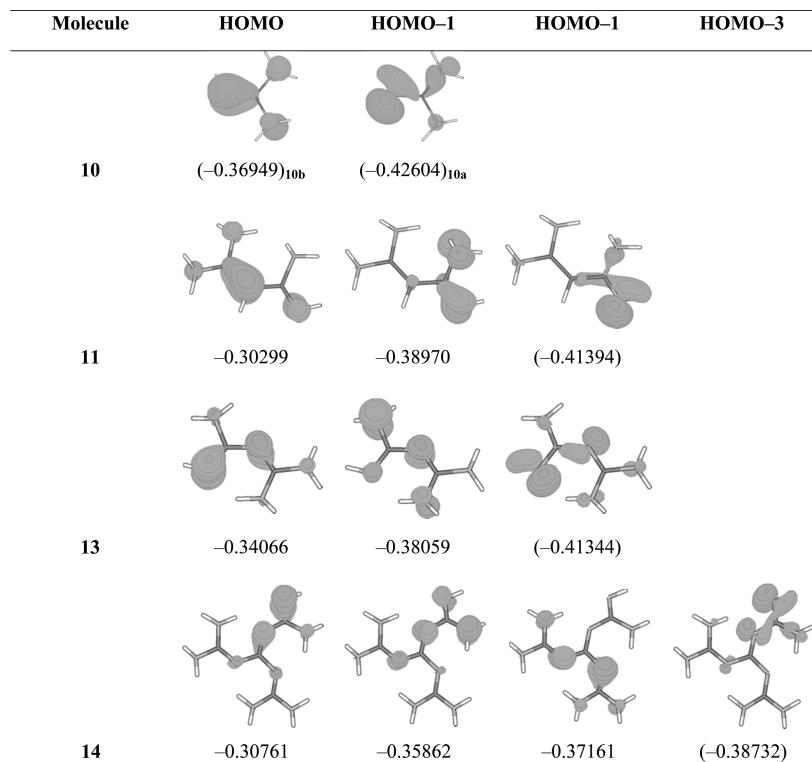
$$\Delta(\text{IE})_{\alpha,n}^{\text{Koop}} = \text{IE}(\mathbf{B})_{\alpha,n}^{\text{Koop}} - \text{IE}(\text{st})_{\beta,m}^{\text{Koop}} \quad (36a)$$

$$\Delta E(\text{ei})_{\alpha,\text{rex}}^{(n)} = E(\text{ei})(\mathbf{B})_{\alpha,\text{rex}}^{(n)} - E(\text{ei})(\text{st})_{\beta,\text{rex}}^{(n)} \quad (36b)$$

$$\Delta(\text{BAE})_\alpha^{\bullet+} = \text{BAE}(\mathbf{B})_\alpha^{\bullet+} - \text{BAE}(\text{st})_\beta^{\bullet+} \quad (36c)$$

It should be noted here that indices  $\beta$  and  $m$  could be different in principle from  $\alpha$  and  $n$ , respectively, meaning that the sites of protonation in bases  $\mathbf{B}$  and  $\mathbf{B}(\text{st})$  could differ in general. It should be emphasized that the identification of the molecular orbital, which is ionized in the protonation reaction, is a strong aspect of triadic analysis. It precisely pinpoints the molecular orbital, which most directly participates in the formation of a new bond. For that reason, it is termed the principal MO or PRIMO, which is frequently different from the highest occupied molecular orbital (HOMO).

The triadic analysis embodied in eqs 34 and 35 proved useful in rationalizing the proton affinities of neutral bases. The



**Figure 2.** Selected MOs together with their orbital energies [HF/6-311+G(2df,p)//B3LYP/6-31+G(d) results; in au] of bases discussed in the text. The orbital energies of PRIMOs are given in parentheses.

comparison of triadic analysis and the insight it offers in relation to some other approaches aiming at the same goal, like traditional Taft<sup>269</sup> separation of the effects of substituents into field/inductive, polarizability, and resonance contributions, or with methods based on global and local descriptors of reactivity advanced by Pérez and co-workers,<sup>270–276</sup> was in a very thorough and tutorial way presented by Deakyne.<sup>277</sup> There, it was emphasized that the advantages of the triadic approach are that it is general and rigorous and that it separates out initial and final state effects.<sup>277</sup> It should just be mentioned that the same triadic formula also holds for the protonation of anions.<sup>32</sup> Triadic analysis (Table 1) has been used in interpreting NH<sub>3</sub> and its methyl derivatives and a number of imino compounds, including some strong superbases and some cyclic amines (Figure 1). The method employed involves geometry optimization at the B3LYP/6-31G(d) level and single point calculations MP2(fc)/6-311+G(d,p)//B3LYP/6-31G(d) supplemented by the  $E_{ZPV}$ (B3LYP/6-31G(d)) vibrational energy.

Perusal of the data presented in Table 1 reveals very good agreement between the calculated and experimental PA values. Let us consider some examples (Figure 1) in detail. The proton affinities of methylamines NH<sub>3-m</sub>(CH<sub>3</sub>)<sub>m</sub> ( $m = 0–3$ ) increase with every methyl group attached. One observes a sharp decrease in (IE)<sub>1</sub><sup>Koop</sup> values in the same order, which implies a smaller price to be paid in terms of energy in ejecting one electron from the nitrogen unshared electron pair placed in the HOMO. This is compatible with the electron-donating property of the methyl group(s), which increases electron density at the N atom. The enhanced electron repulsion at nitrogen facilitates electron ejection from its lone pair. The relaxation energy is practically constant, whereas the bond association term decreases with the number of methyl groups. The latter feature diminishes the basicity, but Koopmans' term

prevails. Consequently, the amplified basicity along the series is a result of the initial-state effect,<sup>31</sup> in accordance with the work of Pérez and co-workers<sup>276</sup> employing local reactivity descriptors. Comparison between methanimine **9** and ammonia **5** shows that these two different types of nitrogen atoms possess almost the same intrinsic basicity (Table 1), specifically, PA(**9**) – PA(**5**) = [-1.4; 1.3; 1.6] = 1.5 kcal mol<sup>-1</sup>, suggesting that methanimine is slightly more basic as a result of the favorable contributions from the relaxation energy and the bond association energy. The latter is compatible with the hybridization model, which indicates that a hybrid orbital with a higher s-content (sp<sup>2</sup>) makes a stronger bond than one possessing a lower s-character (sp<sup>3</sup>). Interestingly, Koopmans' term predicts that **9** should be less basic than NH<sub>3</sub> if only the properties of the initial neutral molecules are taken into account. Guanidine **10a** is more basic than methanimine by PA(**10a**) – PA(**9**) = [-3.4; 27.4; -4.4] = 27.0 kcal mol<sup>-1</sup>. This large difference in basicity is solely a consequence of the higher reorganization energy in the **10a**<sup>•+</sup> radical cation. It is of interest to find a difference in PAs between the imino (**10a**) and amino (**10b**) nitrogen atoms in guanidine. The triad PA(**10a**) – PA(**10b**) = [-36.1; 36.1; 32.2] = 32.2 kcal mol<sup>-1</sup> reveals that the imino position is more basic by 32.3 kcal mol<sup>-1</sup>, which is exactly the difference between the (BAE)<sup>•+</sup> terms. The dramatically weaker N(sp<sup>3</sup>)–H<sup>+</sup> bond in **10b**H<sup>+</sup> is at first very surprising, because BAE<sup>•+</sup> bond energy is 30 kcal mol<sup>-1</sup> lower than in protonated ammonia NH<sub>4</sub><sup>+</sup> (5H<sup>+</sup>). The structure of the **10b**<sup>•+</sup> cation provides an answer. Because of strong cationic resonance, the NH<sub>2</sub> group became planar. Hence, protonation of N(sp<sup>2</sup>)H<sub>2</sub> nitrogen causes rehybridization of two sp<sup>2</sup>–sp<sup>3</sup> NH bonds and the formation of a third N(sp<sup>3</sup>)–H bond. The former is energetically costly leading to the considerably weaker basicity of the amino group versus the basicity of the imino

group in guanidine. It is noteworthy that the difference in basicity between the two basic sites in ambident compounds is always given by the difference in the bond association energies, because the first two terms should cancel out each other exactly (see eq 27). It should be noted in passing that the negative contribution arising from Koopmans' term is due to the fact that the amino nitrogen lone pair is described by HOMO, which is higher in energy than the HOMO-1 accommodating the  $\sigma$ -lone pair of imino nitrogen (Figure 2).

Let us select methaneimine **9** as a reference base in examining larger polyenes. Extension of the  $\pi$ -network in **11** leads to an appreciable increase in the relaxation energy (55.2 kcal mol<sup>-1</sup>) and proton affinity (249.9 kcal mol<sup>-1</sup>) relative to methanimine **9**,<sup>278</sup> which is in harmony with the enlarged number of cationic resonance structures. Schwesinger's vanimidine base **12** is a superbase with a proton affinity of 275.6 kcal mol<sup>-1</sup>. Comparison with methanimine reveals PA(**12**) - PA(**9**) = [34.3; 59.0; -24.5] = 68.8 kcal mol<sup>-1</sup>. Interestingly, although the PRIMO orbital in **12** is HOMO-4, the energy price for ejecting an electron from that orbital is 34.3 kcal mol<sup>-1</sup> lower than that from the HOMO of **9**. This finding, taken together with a much higher relaxation energy, makes vanimidine **12** as much as 68.8 kcal mol<sup>-1</sup> more basic than methanimine **9**. Tetraguanide **14** and heptaguanide (octopus) possessing eight amino groups **15** are more basic by 27.3 and 45.6 kcal mol<sup>-1</sup> with respect to biguanide **13**, in agreement with the extension of the  $\pi$ -system. The corresponding triads are, respectively, PA(**14**) - PA(**13**) = [16.4; 9.3; 1.7] = 27.3 kcal mol<sup>-1</sup> and PA(**15**) - PA(**13**) = [34.8; 10.5; 0.3] = 45.6 kcal mol<sup>-1</sup>. The increase in the basicity of superbases **14** and **15** is primarily a consequence of the properties of the initial state (neutral base) mirrored through Koopmans' ionization energy (Figure 2), which is supported by an intermediate stage relaxation stabilization of about 10 kcal mol<sup>-1</sup> in both cases. Interestingly, the energy of the homolytic bond formation remains practically constant and has no significant influence on the differences in basicity. Superbases **12**–**15** were also investigated by Chamorro, Pérez, and co-workers using global and local chemical reactivity descriptors defined within the conceptual DFT.<sup>274</sup> They demonstrated that there is a linear correlation between the proton affinities of these similar superbasic molecules and empirical Fukui functions, which in turn could also be interpreted by the hard–soft acid base HSAB rule derived using local DFT descriptors.

The permethylated tris(guanidino)phosphazene molecule **16** is highly basic. The reason for such enhanced basicity can be traced to the triadic formula PA(**16**) - PA(**9**) = [74.4; 32.5; -26.5] = 80.5 kcal mol<sup>-1</sup>. The relaxation and bond association energy contribute jointly to the increase of 6 kcal mol<sup>-1</sup>, whereas a dramatic influence is exerted by the initial state Koopmans' ionization energy. It is easier to eject an electron from the principal molecular orbital in **16** than that in base **9** by around 75 kcal mol<sup>-1</sup>.

Substituted trityl (triphenylmethyl) moieties have been widely used in organic synthesis as protecting groups.<sup>279</sup> Parent tritylamine **17** is more basic than both ammonia **5** and methylamine **6**.<sup>280</sup> Taking the former molecule as a reference yields PA(**17**) - PA(**5**) = [10.5; 30.4; -19.1] = 21.8 kcal mol<sup>-1</sup>, indicating a decisive effect of the relaxation energy.

The hybridization effect of the nitrogen atom and the s-character of its lone pair can greatly influence local basicity. In cyclic amines **18**–**21**, a decrease in the C–N–C angle of the ring increases the s-character in the hybrid orbitals involved in

the N–H bond and in the nitrogen lone pair. The traditional view,<sup>281,282</sup> is that the rehybridization effect of the nitrogen atom would lead to a continuous increase in basicity in going from three- to six-membered cyclic amines. However, if correct, this assumption only takes into account the properties of the initial base in determining the basicity of small ring compounds. This view was questioned by Ohwada et al.<sup>283</sup> by considering the local electron-donating abilities of nitrogen atoms in systems **18**–**21**, based on the reactive hybrid orbital (RHO) theory. It was concluded that the C–N–C bond angle (angle strain) is not the major source of the difference in the strength of the basicity in these amines. According to HF calculations by Ohwada et al.,<sup>283</sup> it is the degree of the pyramidalization of the N atom that influences the local electron-donating ability of the nitrogen the most. It is easy to see that the basicity of amines cannot be satisfactorily rationalized by considering the initial state only. Quantitative interpretation of the variation in basicity in series **18**–**21** is obtained by taking into account all of the terms in triadic analysis. Perusal of the data given in Table 1 reveals that an increase in the s-character of a hybrid describing a nitrogen lone pair leads to its stabilization with a concomitant increase in Koopmans' ionization energy. This is, however, only one of the reasons behind the decrease in the PA of the highly strained three-membered ring system **18** relative to the PA(7) of the unstrained dimethylamine **7** by 5.9 kcal mol<sup>-1</sup>, as revealed by the corresponding triad (-15.9; -5.5; 15.5) = -5.9 kcal mol<sup>-1</sup>. It appears that the rehybridization effect is canceled by the bond association term. Thus, lowering of the relaxation energy is an effectively decisive term. Similarly, in larger cyclic amine, the hybridization effect becomes even less important, whereas the relaxation effect prevails due to the larger number of C atoms leading to enhanced basicity in cyclic amines **19**–**21**. This is illustrated by the following triads: PA(**19**) - PA(7) = (-0.9; 3.4; -0.6) = 1.9, PA(**20**) - PA(7) = (1.9; 7.8; -5.5) = 4.2, and PA(**21**) - PA(7) = (3.7; 5.6; -4.3) = 5.0, in kcal mol<sup>-1</sup>. Obviously, it would be misleading to focus attention exclusively on the initial state properties. Imperfections or inadequacies in using frontier MOs for that purpose are discussed in ref 31b.

#### 4. COMPUTER-AIDED DESIGN OF NEUTRAL ORGANIC SUPERBASES

It is common wisdom that organic bases and superbases, including proton sponges, exhibit some advantageous properties, which make them more convenient than their inorganic counterparts in chemical synthesis and catalysis. The latter possess unfavorable features, such as low solubility in most organic solvents, pronounced sensitivity to moisture and CO<sub>2</sub>, and they produce hazardous waste. In contrast, organic bases require milder reaction conditions and are more user-friendly.<sup>284</sup> These and other useful characteristics have led to their wide application in organic synthesis as important auxiliary bases.<sup>285,286</sup> Moreover, organic bases and superbases are very efficient catalysts, if immobilized on appropriate surfaces acceptable in green chemistry.<sup>287–289</sup> More about the chemistry of various neutral organic bases can be found in a recent book by Ishikawa.<sup>290</sup> Consequently, the design of novel organic bases with particular emphasis on strong superbases has been the focus of interest of many experimentalists and theoreticians over several decades.<sup>290–292</sup> We shall describe below some advances in tailoring organic superbases *in silico*.

#### 4.1. The Aufbau Strategy in Constructing a Ladder of Superbases

Building on extensive exploratory computational experiments, we have developed a strategy for designing superbases<sup>292</sup> based on the Aufbau principle as summarized below:

- (1) Selection of a functional group or molecular fragment possessing high intrinsic basicity (imine, guanidine, pyridine...) based on numerical trichotomy analyses
- (2) Choice of a molecular backbone carrying a highly basic center (naphthalene, polyguanides, phosphazenes, azacalixarene)
- (3) Basicity tuning by substituent effects placed on strategic positions (alkyls, NMe<sub>2</sub>, OMe)
- (4) Special buttressing effects (strain, hydrogen bonding, corona effect)

These build-up principles in constructing a scale of organic superbases and hyperbases have led to a number of compounds exhibiting highly pronounced basicities, some of which have already been prepared in laboratories. A very important step in the computational design of a molecule exhibiting the desired properties is the choice of the theoretical model, which is reliable and yet feasible, and practical in applications involving large molecules. In the 1990s, the driving force was the MP2 theory, employing adequate basis sets for the problems under study. On the eve of the 21st century, the density functional theory methods<sup>293,294</sup> reached maturity, which makes them very efficient, cheap, and accurate enough to be convenient in thermochemistry. The most popular method on the large DFT menu was the hybrid B3LYP scheme.<sup>294</sup> Good accuracy with an error margin of  $\pm 2$  kcal mol<sup>-1</sup> or better can be achieved with the B3LYP method provided that large enough basis sets are employed, as will be seen in the following paragraph describing the tailoring of superbases classified according to proton acceptor functionalities.

**4.1.1. The Imino Group as a Basicity Warhead.** It is well-known that guanidine is a strong base in the gas phase, with PA = 235.7 kcal mol<sup>-1</sup>.<sup>115</sup> The origin of strong basicity lies in cationic resonance triggered by protonation.<sup>295–298</sup> An analysis based on homodesmotic reactions using the MP2(fc)/6-311+G(d,p)//HF/6-31G(d) + E<sub>ZPV</sub>[HF/6-31G(d)] method, henceforth MP2(I), provided estimates of conjugation in the initial neutral guanidine and a resonance effect in its protonated form of 27.8 and 51.5 kcal mol<sup>-1</sup>, respectively. It turned out that the surplus stabilization gained by protonation was 23.7 kcal mol<sup>-1</sup>, which was remarkable indeed.<sup>295</sup> Extension to linear polyguanides provided systems that exhibited even higher basicity, for the same reason. Not unexpectedly, there is a saturation effect in linear systems with a limiting value of 254 kcal mol<sup>-1</sup>. Much higher proton affinities were found in branched polyguanides, where ramification took place at the carbon atom C(b) as in tetraguanide 14 and heptaguanide 22 (Figure 3).

The most basic nitrogen in 14 is N(1), because the resonance effect is spread over two vicinal guanidino subunits placed at equal distances from the protonated center. The corresponding PA(14) = 261.8 kcal mol<sup>-1</sup>.<sup>295</sup> Generalization leads to a heptaguanidine 15 octopus (Figure 1) possessing eight amino groups with PA = 289.1 kcal mol<sup>-1</sup> computed by the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) method denoted as B3LYP(I). Introducing amino nitrogen in five-membered rings and substituting the N–H bond with methyl, one obtains superbase 22 (Figure 3) with PA = 290.0 kcal

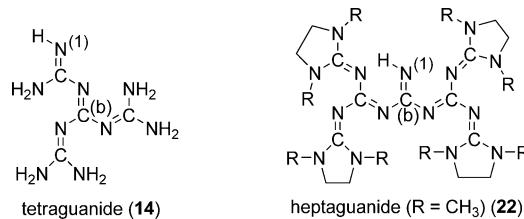


Figure 3. Two branched polyguanides with bifurcation carbon atoms denoted by C(b).

mol<sup>-1</sup> as calculated using the HF<sub>SC</sub> model.<sup>295</sup> It follows that higher branched polyguanides are very strong superbases. They have high PAs due to strong cationic resonance and the presence of a large number of imino nitrogen atoms capable of forming intramolecular hydrogen bonds (IMHBs). An analogous series of compounds is given by iminopolyenes,<sup>299</sup> where the MP2(I) method yielded PA values up to 271.9 kcal mol<sup>-1</sup>. These values can be compared to the corresponding linear polyguanides. The imino group as a basicity warhead was used in many molecular backbones (Figure 4).

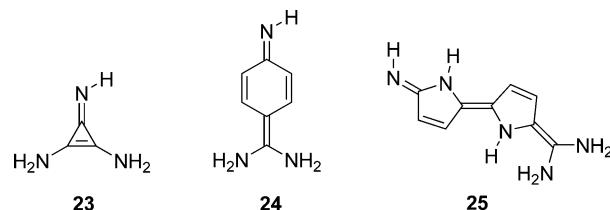


Figure 4. Some extended  $\pi$ -systems exhibiting superbasicity.

Iminocyclopropene 23 has a PA of 250.2 kcal mol<sup>-1</sup> possessing three planar amino NH<sub>2</sub> groups in the protonated form, which are attached to the cyclopropenyl cation,<sup>300</sup> suggesting that aromatization of the three-membered ring plays an important role in enhancing the basicity of this molecule. A combination of guanidine, where one of the NH<sub>2</sub> groups is replaced by 1,3-diaminocyclopropeneimine moiety, leads to an increased proton affinity of the guanidino nitrogen as high as 267.3 kcal mol<sup>-1</sup>.<sup>301</sup> The quinoimine structure 24 has a high PA = 269.2 kcal mol<sup>-1</sup> due to the aromatization of the six-membered ring induced by protonation supported by the cationic resonance involving two NH<sub>2</sub> groups.<sup>302</sup> Di-2,5-dihidropyrrolimine 25 undergoes an aromatic domino effect upon the protonation of the imino center by the sequential aromatization of both five-membered rings, the corresponding PA being 269.4 kcal mol<sup>-1</sup> as obtained by the MP2(I)<sup>303</sup> method. It should be mentioned that the aromatic domino effect contributes to a significant amplification of basicity in polyquinoimines, where the quinoid six-membered structures are aromatized by protonation and newly formed benzene moieties are rotated relative to each other by 35° to diminish mutual perturbations. The increase in PA per single quinoid ring is about 20 kcal mol<sup>-1</sup>, leading to proton affinity values up to 300 kcal mol<sup>-1</sup> or more, depending on the number of six-membered rings.<sup>304</sup>

**4.1.2. The Powerful Phosphazeno and Phosphino Groups.** The phosphazenes (Figure 5) synthesized by Schwesinger and co-workers<sup>305,306</sup> belong to the most basic organic compounds prepared in the laboratory so far. Some of them were considered by the B3LYP/6-311+G(d,p) scheme (henceforth B3LYP(II)).<sup>307</sup> Our B3LYP(I) calculations yield proton affinities for the tBu-P1, tBu-P2, tBu-P3, and tBu-P4

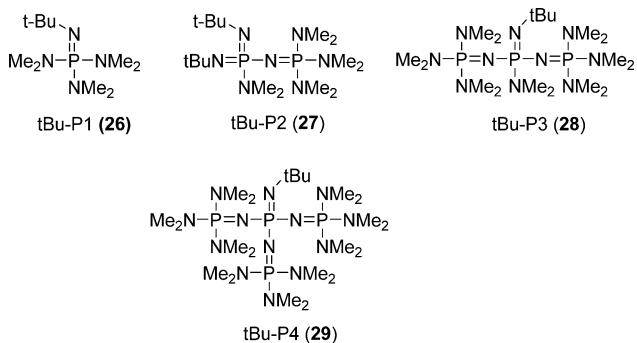


Figure 5. Schwesinger's phosphazenes  $P_n$  ( $n = 1\text{--}4$ ).

(26–29) as large as 260.0, 274.4, 288.8, and 297.5 kcal mol<sup>−1</sup> in the same order, which are notably higher than the PA values of the corresponding polyguanidines having equal number of monomeric units. An interesting hybrid superbase is provided by a guanidino derivative of the P1 phosphazene **16**, depicted in Figure 1. It was introduced independently by Kolomeitsev et al.<sup>308</sup> and Kováčević and Maksić.<sup>309</sup> B3LYP(1) calculations yield the PA of **16** as large as 287.3 kcal mol<sup>−1</sup>.

Protonation of the phosphorus atom in phosphines also turned out to be beneficial for the design of novel highly basic compounds. The most studied class of such compounds is Verkade's proazaphosphatrane (cyclic azaphosphines), which are nowadays used as efficient catalysts for the many chemical transformations (Figure 6).<sup>310</sup> The parent molecule **30a** has

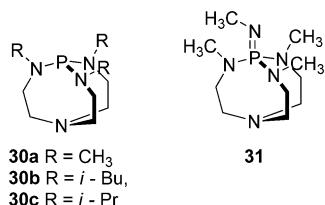


Figure 6. Verkade's proazaphosphatrane and iminophosphorane superbases.

$pK_a$  values of 26.8 and 32.9 in DMSO and acetonitrile, respectively,<sup>311</sup> and the experimental GB value of 259.0 kcal mol<sup>−1</sup>.<sup>257</sup> Calculated PA<sup>312</sup> and GB<sup>257</sup> values were determined to be PA(**30a**) = 261.0 kcal mol<sup>−1</sup> and GB(**30a**) = 255.0 kcal mol<sup>−1</sup>. Such pronounced basicity of **30a** is a consequence of the two effects, (a) high basicity of the phosphorus atom in substituted phosphines, and (b) the formation of the transannular P–N bonding that additionally stabilizes the protonated form. Replacement of N-methyl groups in **30a** with larger alkyl substituents like *i*Pr (**30b**) and *i*Bu (**30c**) led to compounds with slightly higher basicity constants.<sup>257,311,313</sup> Further development of the original Verkade's idea yielded phosphorus ylide **31** with a calculated PA value of 265.2 kcal mol<sup>−1</sup>,<sup>307</sup> being a 4.2 kcal mol<sup>−1</sup> stronger base than **30a** due to the higher degree of the delocalization of the positive charge in the protonated iminophosphoranes. Incorporation of **30a** motif into confined hemicryptophane host, synthesized recently by Raytchev and co-workers,<sup>314</sup> did not alter the strong basicity of the proazaphosphatrane, but dramatically decreased the rate of proton transfer in **31H<sup>+</sup>**, which a typical characteristic of proton sponges.

#### 4.1.3. Proton Sponges – The Role of the Intramolecular Hydrogen Bond(s).

The important role of

intramolecular hydrogen bonding was realized very early by Yamdagni and Kebarle<sup>315</sup> and independently by Aue and Bowers.<sup>316</sup> They measured the proton affinities of  $\alpha,\omega$ -diamines  $\text{NH}_2(\text{CH}_2)_n\text{NH}_2$  ( $n = 2\text{--}7$ ) and found that they were consistent with the internally hydrogen-bonded cyclic structures of the cations. Amplification of gas-phase basicity by IMHB cyclization in polyfunctional formamidines has been used by Raczynska et al.<sup>253,317</sup> in designing compounds with enhanced basicity. The cooperative effect of the multiple IMHBs was exploited in stabilizing the conjugate acids of **32a** and **32b**,<sup>318</sup> where central guanidine moiety is protonated at imino nitrogen endowed with three aminopropyl side chains (Figure 7) forming a triple corona effect. The latter structural

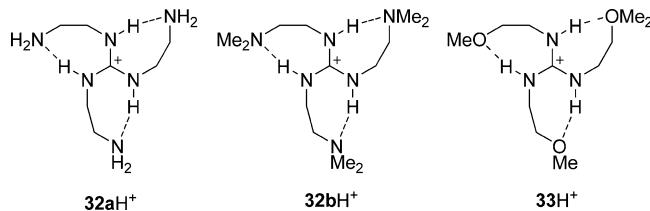
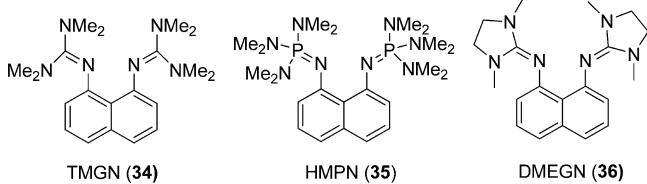


Figure 7. Triple substituted guanidines exhibiting intramolecular hydrogen bonding.

motif is given by a pseudo-seven-membered ring formed by five covalent bonds and an N–H···N bridge. It was found that the proton affinity of compounds **32a** and **32b** is significantly higher than that in the parent guanidine, 268.4 and 275.5 kcal mol<sup>−1</sup>, respectively, as obtained by the MP2(I) model. The system **32b** was synthesized,<sup>319</sup> and its X-ray crystal structure confirmed the existence of three IMHBs in protonated form. It was also experimentally and computationally corroborated that 3-(amino)propyl and 3-(dimethylamino)propyl IMHB in mono- and disubstituted guanidines significantly increased the PA of guanidine in the gas-phase.<sup>298</sup> Eckert-Maksić and co-workers were able to synthesize molecule **33**, where aminopropyl chain was replaced by the 3-methoxypropyl group,<sup>320</sup> for which the authors measured and calculated gas-phase PA values<sup>298</sup> and experimentally determined  $pK_a$  values in acetonitrile.<sup>320</sup> The results revealed that the 3-methoxypropyl group forms weaker hydrogen bonds in **33H<sup>+</sup>** than does the 3-(dimethylamino)propyl in **32bH<sup>+</sup>**, which leads to lower basicity of the former molecule. The idea of multiple IMHBs was also used by Kass,<sup>321</sup> who investigated the polyamines of up to seven amino groups. It was found that 6-(5-pentyl-1,3-diamine)undecane-1,3,6,9,11-pentaamine has a PA as high as 288.5.<sup>321</sup> Bachrach et al.<sup>322</sup> investigated 2,6-disubstituted pyridine and 2,4,7-trisubstituted quinuclidines and found that substituents capable of forming IMHB can increase PA relative to pyridine by more than 35 kcal mol<sup>−1</sup>. Obviously, the IMHB is a very fruitful motif in designing organic superbases.

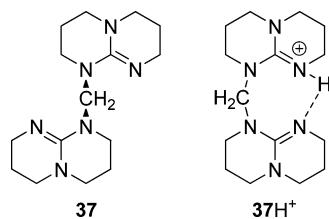
A seminal milestone paper by Alder et al.<sup>323,324</sup> in 1968 on 1,8-bis(dimethylamino)naphthalene (DMAN) triggered an outburst of interest and research in examining organic bases possessing naphthalene as a spacer.<sup>325</sup> DMAN was widely accepted as the first superbase, and its PA = 245.7<sup>111,115</sup> kcal mol<sup>−1</sup> was taken as a threshold of superbasicity. It is also the first proton sponge, a compound of high basicity and low nucleophilicity. Factors were responsible for DMAN's basicity: the steric repulsion of two lone pairs of amino groups substituted at the 1,8 positions on the naphthalene scaffold, relief of the steric strain by protonation, and the formation of a

strong IMHB. Modifications of Alder's idea went in several directions: (a) the introduction of various substituents on the naphthalene ring (buttressing effect),<sup>325</sup> (b) change of a spacer by replacing naphthalene with some aromatic and/or aliphatic moieties, (c) change of the basic amino groups by more basic functionalities, such as the guanidino fragment in TMGN<sup>326</sup> 34 and the phosphazeno group in HMPN 35 (Figure 8),<sup>327</sup> and (d) incorporation of basic fragment(s) within polycyclic and/or cage structures.



**Figure 8.** Superbasic systems possessing different guanidino and phosphazeno moieties at 1,8-positions of the naphthalene spacer.

The proton affinities for TMGN 34 and DMEGN<sup>328</sup> 36 are 257.5 and 251.4 kcal mol<sup>-1</sup>, respectively, calculated by the MP2(I) method. A very basic HMPN 35 has a proton affinity of 274.0 kcal mol<sup>-1</sup>, as estimated by the B3LYP(I) scheme. It should be stressed that TMGN, DMEGN, and HMPN were designed in combined computational and experimental efforts.<sup>326–328</sup> Among the very interesting outcomes of these computational studies are the features of the IMHBs. They are asymmetrical, meaning that the proton is directly attached to one functionality, where it causes a substantial cationic resonance effect. However, it is partially bound to a neighboring functionality, inducing about 50% of the resonance effect as compared to the first one. This is the general picture for all systems possessing H<sup>+</sup> bridges between two imino or phosphazeno functionalities. The smallest and most flexible linker between two imino groups is given by the aliphatic –CH<sub>2</sub>– group in the bis-guanidino compound 37 (Figure 9),

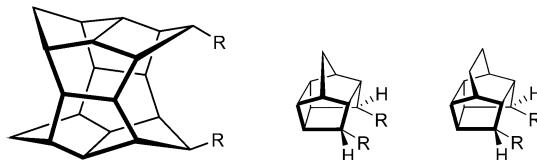


**Figure 9.** Bis-guanidino compound H<sub>2</sub>C{hpp}<sub>2</sub> in its neutral 37 and protonated form 37H<sup>+</sup>.

which was synthesized and characterized by X-ray, NMR, and computational methods.<sup>329</sup> The strength of the IMHB was estimated as 14.8 kcal mol<sup>-1</sup>, and the barrier height for intramolecular proton transfer was 2.5 kcal mol<sup>-1</sup>. However, if the *E<sub>ZPV</sub>* is explicitly included, the barrier disappears. It was concluded that the proton shuttles back and forth between two imino functionalities, thus forming a proton resonator. The calculated proton affinity is 276.0 kcal mol<sup>-1</sup>. Additionally, two more superbases should be mentioned: TMGBP with PA = 263.8 kcal mol<sup>-1</sup> by the MP2(I) method<sup>330</sup> and TMGBH possessing PA = 273.8 kcal mol<sup>-1</sup> obtained with the B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d) methods.<sup>331</sup>

Margetić and co-workers<sup>332</sup> employed much larger bis-(secododecahedrane) molecular scaffold (Scheme 9) as carriers

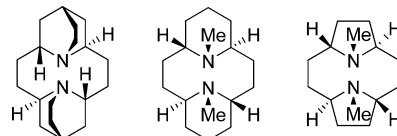
**Scheme 9.** Bis(secododecahedrane) (Left), Pentacyclo[5.4.0.0<sup>2,6</sup>.0<sup>3,10</sup>.0<sup>5,9</sup>]undecane (Middle), and Pentacyclo[6.4.0.0<sup>2,7</sup>.0<sup>3,11</sup>.0<sup>6,10</sup>]dodecane (Right) Molecular Scaffolds Used as Carriers of Basic Groups R



for the guanidino, extended guanidino, and the phosphazeno basic groups, suggesting 29 new superbases with PA values in the range of 261.6–316.3 kcal mol<sup>-1</sup>. The same approach was undertaken by Ganguly and co-workers by placing diamines and diimines on *endo,endo*-8,11-positions on the pentacyclo-[5.4.0.0<sup>2,6</sup>.0<sup>3,10</sup>.0<sup>5,9</sup>]undecane<sup>333</sup> and the pentacyclo-[6.4.0.0<sup>2,7</sup>.0<sup>3,11</sup>.0<sup>6,10</sup>]-dodecane<sup>334</sup> skeletons (Scheme 9) reaching proton affinities of up to 282.7 kcal mol<sup>-1</sup>. Along the same line, it was demonstrated that incorporation of 1,8-bisamino-naphthalene into large cyclophanes increases the basicity of the initial molecule by around 10.0 kcal mol<sup>-1</sup>.<sup>335</sup> The authors attributed basicity enhancement mainly to the structural flexibility of investigated compounds, which allows them to maximize the hydrogen-bond strength in the cation, in addition to the favorable cation–π interactions with adjacent phenyl systems of the cyclophanes. Recently, the latter has also been observed as a stabilizing effect that, when linked to 1,4-substituted benzene, promotes the basicity of 2,6-substituted pyridine by 1.0 and 1.1 pK<sub>a</sub> units in acetonitrile and water solution, respectively.<sup>336</sup> It is also worth mentioning that incorporation of two neighboring imino basic sites within large conjugated polycyclic structures<sup>337</sup> to yield croissant-like organic compounds provided super- and hyperbases with gas-phase PA and GB values of up to 322.8 and 315.0 kcal mol<sup>-1</sup>, respectively, with the corresponding pK<sub>a</sub> values in acetonitrile reaching 41.4 pK<sub>a</sub> units.

An interesting class of amine superbases is provided by polycyclic di- and polyamines. Alder<sup>338</sup> computationally designed a set of C<sub>2</sub>-chiral diamines based on 1,6-diazacyclodecane (Scheme 10) whose conjugate acids were

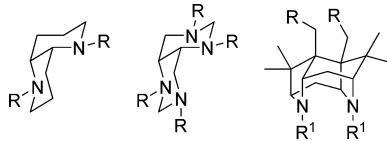
**Scheme 10.** Different 1,6-Diazacyclodecane Skeletons Employed by Alder in the Design of Novel Superbases



predicted to have PA values between 243.3 and 268.6 kcal mol<sup>-1</sup>, and pK<sub>a</sub> values of 23–26 in water and 30–33 in acetonitrile. Alder also demonstrated that the enhanced basicity of these compounds is a result of strain relief on protonation and that the key to designing even stronger bases is to limit conformational freedom, especially by preventing nitrogen inversion, through the introduction of additional ring fusions. Gogoll and co-workers<sup>339</sup> prepared a series of 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives that cover 13 pK<sub>a</sub> units in acetonitrile (8.1–21.7). However, the authors did not report gas-phase proton affinities but only PA values in acetonitrile calculated with the (PCM)/B3LYP/6-31+G(d)//

B3LYP/6-31G(d) level of theory. Ganguly et al.<sup>340</sup> investigated 1,5-diazadecaline and 1,3,5,7-tetraazadecaline derivatives (Scheme 11) and predicted that at the B3LYP/6-31+G(d,p)

**Scheme 11.** 1,5-Diazadecaline (Left), 1,3,5,7-Tetraazadecaline (Middle), and Diazatetracyclo[4.4.0.1<sup>3,10</sup>.1<sup>5,8</sup>]dodecane (Right) Skeletons Used as Carriers of Basic Moieties R



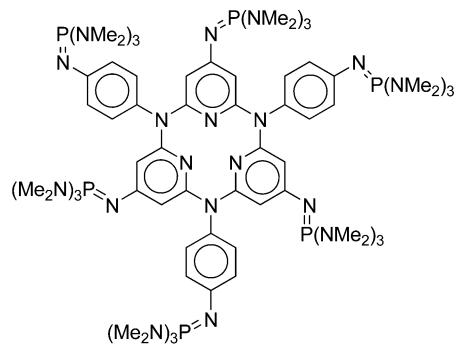
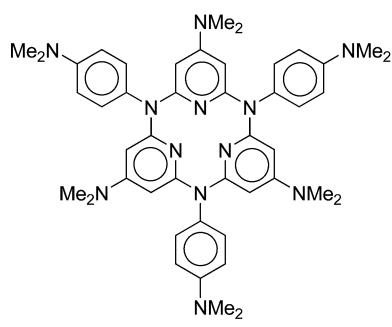
level of theory the unsubstituted *cis*-1,3,5,7-tetraazadecaline is a better proton sponge than the parent DMAN as a result of the cooperative effect of ring nitrogen atoms and the anomeric effect that occurs upon protonation. A novel class of cyclic amines was provided by 11,12-dimethyl-11,12-diaza-tetracyclo-[6.2.1.1<sup>3,6</sup>0<sup>2,7</sup>]dodecane derivatives<sup>341</sup> with PAs in the range 235.5–264.5 kcal mol<sup>-1</sup>, surpassing the basicity of DMAN by up to 18.1 kcal mol<sup>-1</sup> at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory. Analogously, Galeta and Potáček<sup>342</sup> made use of diazatetracyclo[4.4.0.1<sup>3,10</sup>.1<sup>5,8</sup>]dodecanes (Scheme 11) to provide several rungs on the basicity scale in the range between 19–22 pK<sub>a</sub> units in acetonitrile.

**4.1.4. Supramolecular Scaffolds for Hyperstrong Bases.** Recently, it was found that pyridine is a quite basic moiety, provided that it is substituted by some electron-releasing groups at active *para*-positions<sup>343</sup> and particularly if used as a building block in forming supramolecular structures.<sup>344</sup> The calculated B3LYP (I) proton affinities are within the range of 270–290 kcal mol<sup>-1</sup>, thus belonging to the upper part of the superbasicity ladder. However, even higher proton affinities are found in azacalix[3](2,6)pyridine poly-substituted by  $\text{NMe}_2$  and  $\text{N}=\text{P}(\text{NMe}_2)_3$  groups on the molecular periphery (Figure 10). The parent compound was synthesized by Kanbara et al.<sup>344</sup> The hexakis(dimethylamino) derivative (38) has PA = 296.6 kcal mol<sup>-1</sup> as estimated by the B3LYP(I) scheme,<sup>345</sup> which is very close to the proposed hyperbasicity threshold,<sup>346</sup> defined by the gas-phase proton affinity of 300 kcal mol<sup>-1</sup>, which corresponds to the PA value of the perchloric anion  $\text{ClO}_4^-$  calculated to be 299.4, 300.5, and 299.2 kcal mol<sup>-1</sup> using G2,<sup>347</sup> G2(MP2),<sup>347</sup> and G3<sup>348</sup> methodology, respectively, and measured by Kass et al.<sup>349</sup> to yield  $299.9 \pm 5.7$  kcal mol<sup>-1</sup>. The hexakis(phosphazeno)

derivative **39** (Figure 10) is a hyperbase because its PA is 314.6 kcal mol<sup>-1</sup>.<sup>350</sup> Considerable amplification of its basicity was provided by a strong bifurcated intramolecular proton bridge in conjugate acid, which in this system contributed 32 kcal mol<sup>-1</sup> to its proton affinity.

#### 4.2. Theoretical versus Experimental Gas-Phase Proton Affinity/Basicity in the Superbasic Region

The experimental determination of the gas-phase proton affinity in the superbasic region (above 245 kcal mol<sup>-1</sup>) is commonly associated with several difficulties, lack of suitable reference bases, low volatility of studied compounds, to name just a few. Therefore, it is not unusual that the gas-phase data in that region are scarce. Gal and Raczyńska<sup>233,351</sup> performed measurements of substituted amidines and guanidines in the 1990s and extended the experimental gas-phase proton affinity scale from approximately 240 kcal mol<sup>-1</sup> (which is the proton affinity of TMGN, the most basic compound with known PA at that time) to  $\sim 253$  kcal mol<sup>-1</sup>, which was measured for MTBD (Figure 11). They reported PAs of some superbasic guanidines and phosphazenes too; however, PAs were not directly measured, but obtained from the correlation between gas-phase basicities and pK<sub>a</sub> values in a way already described in section 3.10. In the last 10 years, the gas-phase basicity scale was extended up to around 264 kcal mol<sup>-1</sup> (Table 2), mainly due to a work of Koppel's group. Leito, Koppel, and their co-workers<sup>257,352</sup> performed gas-phase measurements of substituted phosphazenes and Verkade's bases; however, they reported only the gas-phase basicities and not the corresponding PA values. On the other hand, Glasovac et al.<sup>298</sup> measured the gas-phase proton affinities of guanidines substituted with heteroalkyl side chains in the range between 251 and 264 kcal mol<sup>-1</sup>. The gas-phase proton affinity ladder in the superbasic region was also supplemented by Kass and co-workers,<sup>321</sup> who have determined PA of some polyamines. The analysis of the data given in Table 2 reveals a reasonable consistency between the experimental and the computed proton affinities and gas-phase basicities, because the difference between two sets of data is less than 2 kcal mol<sup>-1</sup> in most cases. The only notable exception is provided by compounds **33** and **61**, where calculations predict that the protonated forms are stabilized by the formation of the three intramolecular hydrogen bonds (see section 4.1.3). However, under the experimental conditions due to the formation of the proton bound dimer with the reference base,<sup>298</sup> only two such hydrogen bonds are formed, resulting in around 3.5–5.0 kcal mol<sup>-1</sup> lower experimental values. We note in passing that in parallel to mentioned efforts aiming at



**Figure 10.** Supramolecular hyper-/superbases involving cyclic pyridines.

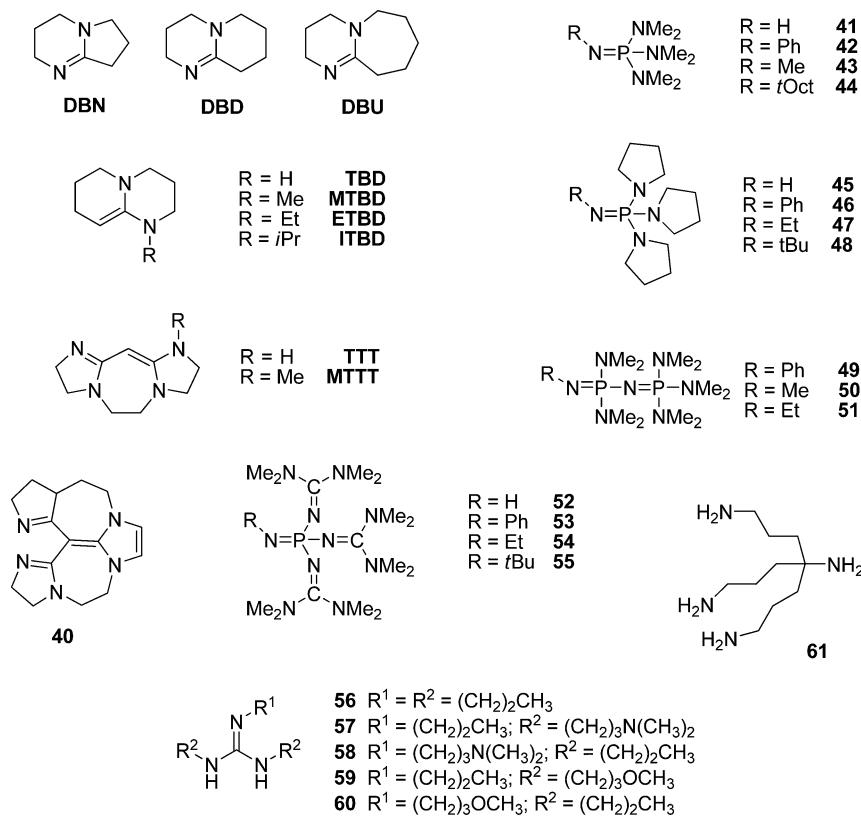


Figure 11. Some neutral organic superbases prepared in the laboratory.

extending the superbasicity ladder toward bigger PA and GB values, some recent experimental and computational work was also performed to establish consistency and accuracy in the lower regions of the basicity scale.<sup>353,354</sup>

#### 4.3. The Ladder Scale of Neutral Organic Bases

A large catalogue of organic bases obtained by computational methods following the Aufbau strategy, including systems with high superbasicity and hyperbasicity, is placed on a ladder of proton affinities in Figure 12. Two benchmarks are of importance: (a) the first is 245 kcal mol<sup>-1</sup>, which corresponds to the PA of DMAN, and (b) the second is 300 kcal mol<sup>-1</sup>, as the PA of the perchloric anion ClO<sub>4</sub><sup>-</sup>.<sup>346</sup> The domain between these values belongs to neutral organic superbases in the gas phase. The bases ascend with increasing PA, forming a one-way ladder. In contrast, acids descend in the opposite direction, where the borderline of 300 kcal mol<sup>-1</sup> signifies the threshold for superacidity.<sup>346</sup> In the same vein, 245 kcal mol<sup>-1</sup> represents the threshold for the hyperacidity in the gas phase.<sup>346</sup> The computational design of organic super and hyperacids is in progress. Once completed, a unified ladder scale of all acids and bases will be obtained.

#### 4.4. Spontaneous Proton Transfer in the Gas Phase

The idea of a spontaneous proton transfer reaction (eq 37) in the gas phase (sometimes described as one of the “holey grails” of gas-phase ion chemistry) has been present in the literature since the early 1970s, when the first experimental measurements of proton affinities appeared.<sup>95</sup>



It was believed that spontaneous proton transfer would occur if the basicity of B is equal to or higher than the basicity of A<sup>-</sup>. Because of a lack of experimental data at the time, the gap

between the measured PAs of the strongest bases and the PAs of the strongest acids was high (>100 kcal mol<sup>-1</sup>). Accordingly, it was expected that spontaneous proton transfer could not be observed experimentally, because the gap was large enough to prevent that process. However, Legon et al.<sup>356</sup> showed by means of FT microwave spectroscopy that in the heterodimer of trimethylamine and hydrogen bromide, where the proton affinity difference is approximately 80 kcal mol<sup>-1</sup>, there is a significant degree of proton transfer. Other spectroscopic techniques, such as IR, were applied in the investigation of the interaction between some simple acids and bases.<sup>357–361</sup> Depending on the strength of the acid and the base in question, various interactions were observed, ranging from H-bonded ion pairs through proton-shared H-bonds to usual H-bonds. Mó et al.<sup>362</sup> have theoretically investigated the heterodimers of phosphonic acid. They found that spontaneous proton transfer takes place if one of the monomers has enhanced basicity and the other has enhanced acidity, even though the gap in the PA between them is high. Alkorta et al.<sup>363</sup> theoretically addressed the possibility of spontaneous proton transfer between HF, HCl, and HBr acids and various bases. According to their model, when the difference between the PA of a base and the PA of an acid is lower than 102 kcal mol<sup>-1</sup>, spontaneous proton transfer may occur in the gas phase, because the energy cost for proton transfer may be compensated for by the stabilizing interaction between both ions in the ion pair. In other words, oppositely charged products of the proton transfer equilibrium (37) undergo association into the ion pair as a final product:



Recent advances in experimental techniques for PA measurements together with the design and synthesis of new

**Table 2. Comparison of Calculated and Experimentally Determined Proton Affinities (PA) and Gas-Phase Basicities (GB) in the Superbasic Region<sup>a</sup>**

molecule	PA <sub>exp</sub>	PA <sub>calc</sub>	GB <sub>exp</sub>	GB <sub>calc</sub>
DMAN	245.7 <sup>b</sup>	245.3 <sup>j</sup>	238.0 <sup>b</sup>	237.8 <sup>l</sup>
DBN	248.2 <sup>b</sup>	250.0 <sup>l</sup>	240.2 <sup>b</sup>	242.2 <sup>l</sup>
DBD	250.1 <sup>b</sup>	251.6 <sup>l</sup>	242.4 <sup>b</sup>	243.7 <sup>l</sup>
DBU	250.5 <sup>b</sup>	252.7 [250.2] <sup>f</sup>	242.7 <sup>b</sup>	244.6 <sup>l</sup>
arginine	251.2 <sup>b</sup>	[249.3] <sup>b</sup>	240.6 <sup>b</sup>	
TBD	252.0 <sup>b</sup>	253.6 [252.1] <sup>f</sup>	244.3 <sup>b</sup>	246.9 <sup>l</sup>
MTBD	254.0 <sup>b</sup>	254.8 [251.9] <sup>f</sup>	246.2 <sup>b</sup>	248.4 <sup>l</sup> (248.0) <sup>d</sup>
ETBD	255.3 <sup>b</sup>	255.8 <sup>l</sup>	247.6 <sup>b</sup>	248.2 <sup>l</sup>
ITBD	256.1 <sup>b</sup>	257.1 <sup>l</sup>	248.4 <sup>b</sup>	249.9 <sup>l</sup> (249.1) <sup>d</sup>
TTT	>255.3 <sup>c</sup>	264.7 <sup>l</sup>	>247.1 <sup>c</sup>	257.5 <sup>l</sup>
MTTT	>257.6 <sup>c</sup>	265.5 <sup>l</sup>	>249.8 <sup>c</sup>	258.4 <sup>l</sup>
12		276.7 <sup>l</sup>		268.6 <sup>l</sup>
40		280.0 <sup>l</sup>		271.8 <sup>l</sup>
41		256.9 <sup>l</sup> (256.3) <sup>k</sup>	249.7 <sup>d</sup>	(249.6) <sup>d</sup>
42		253.0 <sup>l</sup> (252.7) <sup>k</sup>	246.2 <sup>d</sup>	(245.3) <sup>d</sup>
43		260.6 <sup>l</sup> (260.3) <sup>k</sup>	251.9 <sup>d</sup>	(252.3) <sup>d</sup>
26		260.0 <sup>e</sup>	252.9 <sup>d</sup>	(252.1) <sup>d</sup>
44			254.2 <sup>d</sup>	
45		263.1 <sup>l</sup> (262.8) <sup>k</sup>	255.2 <sup>d</sup>	(255.0) <sup>d</sup>
46		258.6 <sup>l</sup>	251.7 <sup>d</sup>	(250.9) <sup>d</sup>
47		266.3 <sup>l</sup>	259.5 <sup>d</sup>	(257.8) <sup>d</sup>
48		266.9 <sup>l</sup>	258.7 <sup>d</sup>	258.8 <sup>l</sup> (258.2) <sup>d</sup>
49		(266.9) <sup>k</sup>	261.7 <sup>d</sup>	(259.2) <sup>d</sup>
50		274.8 <sup>l</sup>		
51		274.8 <sup>l</sup>	264.6 <sup>d</sup>	(265.9) <sup>d</sup>
27		274.4 <sup>e</sup>		
28		288.8 <sup>l</sup>		282.6 <sup>l</sup>
29		297.5 <sup>l</sup>		292.4 <sup>l</sup>
30a		261.0 <sup>i</sup>	259.0 <sup>d</sup>	(255.0) <sup>d</sup>
30b			260.8 <sup>d</sup>	
31		265.2 <sup>e</sup>		
52		284.9 <sup>l</sup> (283.9) <sup>k</sup>		277.8 <sup>l</sup> (276.1) <sup>k</sup>
53		277.9 <sup>l</sup>		270.4 <sup>l</sup>
54		286.2 <sup>l</sup>		277.8 <sup>l</sup>
55		287.0 <sup>l</sup>		279.6 <sup>l</sup>
56	251.1 <sup>f</sup>	255.8 [251.5] <sup>f</sup>		
57	259.1 <sup>f</sup>	261.3 [258.2] <sup>f,h</sup>		
58	264.0 <sup>f</sup>	266.6 [264.8] <sup>f</sup>		
32b		273.2 [276.5] <sup>f</sup>		
59	257.6 <sup>f</sup>	259.5 [256.1] <sup>f</sup>		
60	260.6 <sup>f</sup>	262.6 [261.1] <sup>f,h</sup>		
33	262.9 <sup>f</sup>	266.4 [268.6] <sup>f</sup>		
61	256.2 ± 2.1 <sup>g</sup>	{261.3} <sup>g</sup>		

<sup>a</sup>Values without parentheses are calculated with the B3LYP(I) model, whereas data obtained by B3LYP(II), MP2(I), and B3LYP/aug-cc-pVTZ models are given within round, square, and curly brackets, respectively. All values are in kcal mol<sup>-1</sup>. <sup>b</sup>Reference 115. <sup>c</sup>Reference 253. <sup>d</sup>Reference 257. <sup>e</sup>Reference 307. <sup>f</sup>Reference 298. <sup>g</sup>Reference 321. <sup>h</sup>Reference 355. <sup>i</sup>Reference 312. <sup>j</sup>Reference 327. <sup>k</sup>Reference 308. <sup>l</sup>This work.

compounds with pronounced acid/base properties have significantly changed the basicity ladder picture. As described above, the organic superbases designed so far possess a proton affinity value that exceeds 300 kcal mol<sup>-1</sup>. Some inorganic compounds, such as alkali metal oxides and alkali metal hydroxides, are even more basic,<sup>364</sup> with PAs in the gas phase of up to 344.9 kcal mol<sup>-1</sup> as obtained for Cs<sub>2</sub>O.<sup>115</sup> On the other hand, the most acidic compounds fall in the range between 200 and 250 kcal mol<sup>-1</sup> on the basicity ladder, as presented in some recent papers.<sup>33,347,365–367</sup> This means that nowadays the overlap area for the basicities of neutral and anionic bases covers a range of more than 140 kcal mol<sup>-1</sup>. Therefore, a

spontaneous proton transfer reaction in the gas phase should be possible, particularly between alkali metal oxides and strong mineral acids. However, no report of such experiments has been published yet due to experimental problems with the low volatility of metal oxides. In a recent paper, Burk et al.<sup>368</sup> computationally investigated the feasibility of spontaneous proton transfer in the gas phase between several mineral acids (HClO<sub>4</sub>, HCl, HF) and K<sub>2</sub>O as a strong base. They showed that a proton transfer reaction could take place, although they also pointed out that such a reaction would not lead to charge separation. The energy needed for the separation of ions from ion pairs is energetically very high, 80 kcal mol<sup>-1</sup>, and thus the

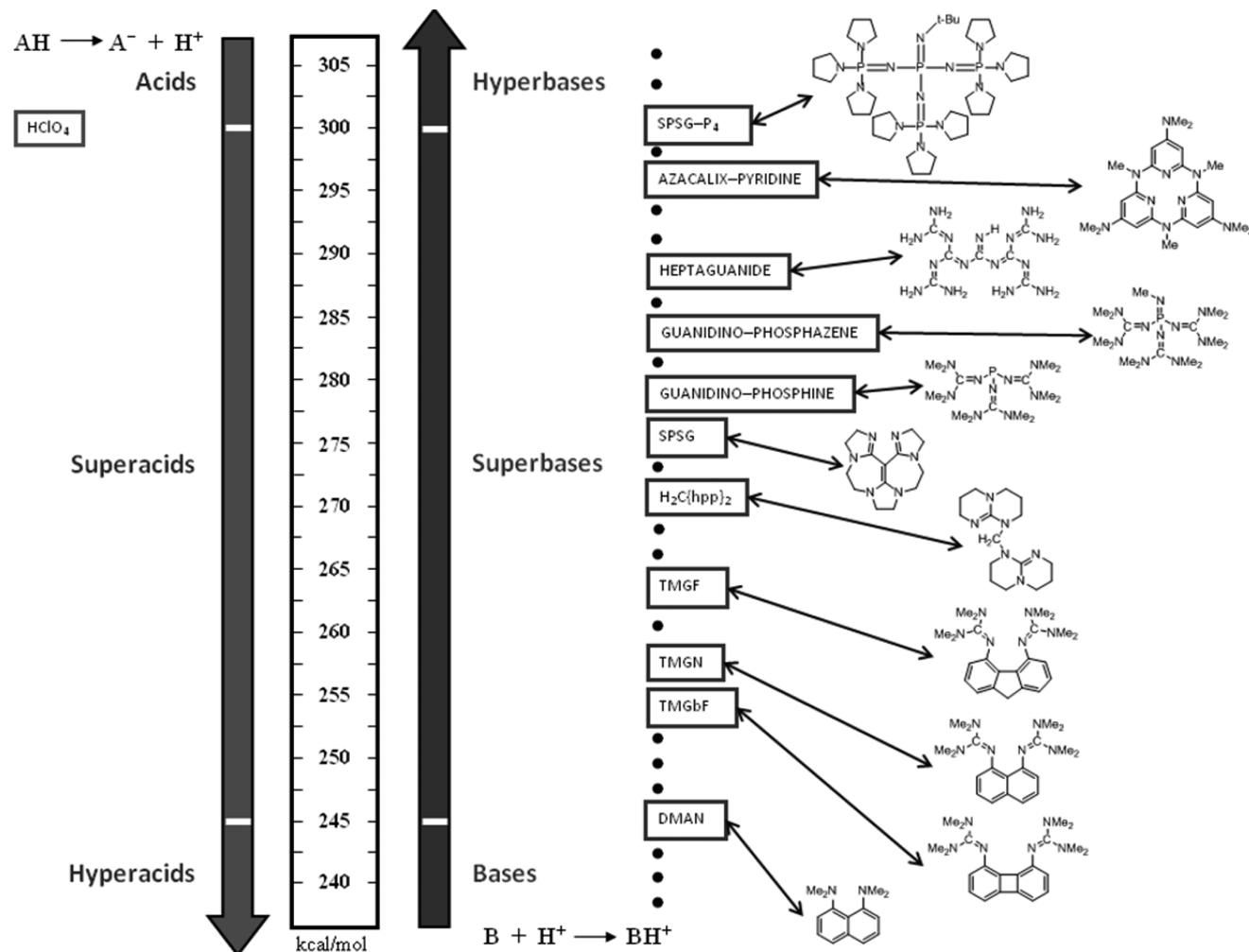


Figure 12. Ladder scale of ascending organic bases.

expected product of a proton transfer reaction would be an ion pair complex and not separated ions. More details about the feasibility of proton transfer in the gas phase can be found in an excellent review article recently published by Raczyńska et al.<sup>369</sup>

## 5. CONCLUDING REMARKS

A magnificent edifice called acid/base chemistry is rooted in a single proton, small in size but of enormous importance. The upper floors of this building are reserved for biochemistry, while the penthouse belongs to life science. The edifice will grow into a sky scraper-like in the 21st century. Evidence provided by this Review shows that the coalescence of experimental and theoretical/computational work is not only highly desirable for that purpose, but, in fact, greatly needed.

## ASSOCIATED CONTENT

### S Supporting Information

Table S1 with proton affinities of some polysubstituted benzenes obtained computationally and by the additivity rule. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*Telephone: +385-1-4561117. Fax: +385-1-4561118. E-mail: For B.K., boris@irb.hr; for R.V., vianello@irb.hr.

### Notes

The authors declare no competing financial interest.

<sup>†</sup>Deceased 3/27/2011.

### Biographies



Zvonimir Maksić earned a Ph.D. at the University of Zagreb in Theoretical Chemistry in 1968. After two postdoctoral years at the University of Tennessee, Knoxville, and the University of Texas, Austin, he returned to the Ruđer Bošković Institute (RBI) in Zagreb, where he continued his research career and teaching duties at the Faculty of Science, University of Zagreb. He retired as a full professor in 2008 but kept the position of distinguished scientist at the RBI until he suddenly passed away in March 2011.



Borislav Kovačević was born in 1970 in Sisak, Croatia. He earned a B.Sc. in Chemistry at the University of Zagreb in 1995. The same year, he joined Professor Maksić's group at the Ruđer Bošković Institute, where he obtained a Ph.D. in computational chemistry in 2001, working on the theoretical study of the basicity of organic compounds and the design of novel superbases. In 2007/08, he spent 12 months as a visiting scholar of Professor Leo Radom's group at the University of Sydney, Australia, where he began a computational study of the catalytic action of radical enzymes. He is currently a senior research associate at the Ruđer Bošković Institute.



Robert Vianello was born in Rijeka, Croatia, in 1977. He studied chemistry at the University of Zagreb, from which he graduated in 2000 and received a Ph.D. in 2003. Since 2000, he has worked at the Ruđer Bošković Institute in Zagreb, where he has held the position of a senior research associate since 2009. In 2005, he spent three months at the Institute of Organic Chemistry, University of Heidelberg, Germany, as the Alexander von Humboldt fellow. In 2010, he was awarded a prestigious individual FP7 Marie Curie Fellowship to spend 18 months at the National Institute of Chemistry in Ljubljana, Slovenia, working with Dr. Janez Mavri. Recently, he received the 2010 Promising Scientist Award from the Center of Applied Quantum Mechanics in Paris, France. His research interests include the interpretation of molecular interactions, the design of new organic materials, and computational studies of proton dynamics in hydrogen-bonded systems and enzyme biocatalysis.

## ACKNOWLEDGMENTS

This Review is dedicated to the memory of Professor Zvonimir Maksić (9/11/1938–3/27/2011), who sadly passed away during its completion. We would like to thank the Ministry of Science, Education and Sports of the Republic of Croatia for financial support through Grants 098-0982933-2932 (R.V.) and 098-0982933-2937 (B.K.). In addition, R.V. gratefully acknowledges financial support from the Unity through Knowledge Fund ([www.ukf.hr](http://www.ukf.hr)) of the Croatian Ministry of Science, Education and Sports (Grant Agreement No. 20/08), together with cofinancing provided by APO Ltd. Environmental Protection Services, Zagreb, Croatia ([www.apo.hr](http://www.apo.hr)).

## REFERENCES

- (1) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, NY, 1976.
- (2) Bamford, C. H., Tipper, C. F. H., Eds. *Comprehensive Chemical Kinetics*; Elsevier: Amsterdam, 1977; Vol. 8: Proton Transfer.
- (3) Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Chapman and Hall: London, 1973.
- (4) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: Orlando, FL, 1985.
- (5) (a) Special Issue of Proton–Coupled Electron Transfer. *Chem. Rev.* **2010**, *110*, 6937. (b) Hammes-Schiffer, S.; Stuchebrukov, A. A. *Chem. Rev.* **2010**, *110*, 6939.
- (6) Czakó, G.; Mátyus, E.; Simmonett, A. C.; Csázár, A. G.; Schaefer, H. F., III; Allen, W. D. *J. Chem. Theory Comput.* **2008**, *4*, 1220.
- (7) Erwin, K. M. *Chem. Rev.* **2001**, *101*, 391.
- (8) Bartmess, J. E. *Encyclopedia of Mass Spectrometry*; Elsevier: Amsterdam, 2003; Vol. 1, p 315 and references therein.
- (9) Cooks, R. G.; Kruger, T. L. *J. Am. Chem. Soc.* **1977**, *99*, 1279.
- (10) Cooks, R. G.; Koskinen, J. T.; Thomas, P. D. *J. Mass Spectrom.* **1999**, *34*, 85.
- (11) Bouchoux, G.; Salpin, J.-Y.; Leblanc, D. *Int. J. Mass Spectrom.* **1996**, *153*, 37.
- (12) Bouchoux, G. *J. Mass Spectrom.* **2006**, *41*, 1006.
- (13) Lossing, F. P. *J. Am. Chem. Soc.* **1977**, *99*, 7526.
- (14) McLoughlin, R. G.; Traeger, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 5791.
- (15) Alcamí, M.; Mó, O.; Yáñez, M. *J. Phys. Org. Chem.* **2002**, *15*, 174.
- (16) Antol, I.; Eckert-Maksić, M.; Lischka, H. *J. Phys. Chem. A* **2004**, *108*, 10317.
- (17) Antol, I.; Vazdar, M.; Barbati, M.; Eckert-Maksić, M. *Chem. Phys.* **2008**, *349*, 308.
- (18) Chatterjee, C.; Incarvito, C. D.; Barns, L. A.; Vaccaro, P. H. *J. Phys. Chem. A* **2010**, *114*, 6630.
- (19) Schultz, T.; Samoylova, E.; Radloff, W.; Hertl, I. V.; Soholewski, A. L.; Domcka, W. *Science* **2004**, *306*, 1765.
- (20) Aquino, A. J. A.; Plasser, F.; Barbati, M.; Lischka, H. *Croat. Chem. Acta* **2009**, *82*, 105.
- (21) Michl, J.; Bonačić-Koutecky, V. *Electronic Aspects of Organic Photochemistry*; John Wiley & Sons: New York, 1990.
- (22) More O'Ferall, R.; Guest, R. A., Eds. Special Issue of Tunneling in Chemical and Biological Reactions. *J. Phys. Org. Chem.* **2010**, *23*, 559.
- (23) Gao, J.; Ma, S.; Mayor, D. T.; Nam, K.; Pu, J.; Truhlar, D. G. *Chem. Rev.* **2006**, *106*, 3188.
- (24) Warshel, A. *Computer Modeling of Chemical Reactions in Enzymes and Solutions*; Wiley: New York, 1997.
- (25) Schreiner, P. R.; Reisenauer, H. P.; Ley, D.; Gerbig, D.; Wu, C.-H.; Allen, W. D. *Science* **2011**, *332*, 1300.
- (26) Chan, B.; Del Bene, J. E.; Radom, L. *J. Am. Chem. Soc.* **2007**, *129*, 12197.
- (27) Carroll, T. X.; Thomas, T. D.; Bergersen, H.; Børve, K. J.; Saethre, L. J. *J. Org. Chem.* **2006**, *71*, 1961.
- (28) Myrseth, V.; Saethre, L. J.; Børve, K. J.; Thomas, T. D. *J. Org. Chem.* **2007**, *72*, 5715.

- (29) Carroll, T. X.; Thomas, T. D.; Saethre, L. J.; Børve, K. J. *J. Phys. Chem. A* **2009**, *113*, 3481.
- (30) Eckert-Maksić, M.; Maksić, Z. B.; Klessinger, M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 285.
- (31) (a) Maksić, Z. B.; Vianello, R. *J. Phys. Chem. A* **2002**, *106*, 419. (b) Maksić, Z. B.; Vianello, R. *J. Phys. Chem. A* **2006**, *110*, 10651.
- (32) Maksić, Z. B.; Vianello, R. *ChemPhysChem* **2002**, *3*, 696.
- (33) Maksić, Z. B.; Vianello, R. *Pure Appl. Chem.* **2007**, *79*, 1003.
- (34) Salehzadeh, S.; Bayat, M. *Chem. Phys. Lett.* **2006**, *427*, 455.
- (35) Bouchoux, G. *Mass Spectrom. Rev.* **2007**, *26*, 775.
- (36) Bouchoux, G.; Salpin, J.-Y. *Mass Spectrom. Rev.* **2012**, *31*, 353.
- (37) Cramer, C. J. *Essentials of Computational Chemistry – Theories and Models*; John Wiley & Sons, Ltd.: Chichester, 2002; p 320.
- (38) (a) Gal, J. F.; Maria, P.-C.; Raczyńska, E. D. *J. Mass Spectrom.* **2001**, *36*, 699. (b) Bailey, W. F.; Monahan, A. S. *J. Chem. Educ.* **1978**, *55*, 489.
- (39) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
- (40) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
- (41) Stewart, J. J. P. *J. Comput. Chem.* **1991**, *12*, 320.
- (42) Lewars, E. *Computational Chemistry*; Kluwer: Boston, 2003.
- (43) Maksić, Z. B.; Kovačević, B.; Kovaček, D. *J. Phys. Chem. A* **1997**, *101*, 7446.
- (44) Binkley, J. S.; Pople, J. A. *Int. J. Quantum Chem.* **1975**, *9*, 229.
- (45) Krishnan, R.; Frisch, M. J.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 4244.
- (46) Curtiss, L. A.; Pople, J. A. *J. Phys. Chem.* **1988**, *92*, 894.
- (47) Smith, B. J.; Radom, L. *Chem. Phys. Lett.* **1994**, *231*, 345.
- (48) Szulejko, J. E.; McMahon, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 7839.
- (49) De Frees, D. J.; McLean, A. D. *J. Comput. Chem.* **1986**, *7*, 321.
- (50) Excellent expositions are given in: Curtiss, L. A.; Redfern, P. C.; Frurip, D. J. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; Wiley–VCH: New York, 2000; Vol. 15, p 147. Raghavachari, K.; Curtiss, J. In *Modern Electronic Structure Theory*, Part 4; Yarkony, D. R., Ed.; World Scientific: Singapore, 1995; p 991.
- (51) A useful overview of ab initio and DFT methods for use in mass spectroscopy gas-phase studies of the proton attachment is given by: Alcami, M.; Mó, O.; Yáñez, M. *Mass Spectrom. Rev.* **2001**, *20*, 195.
- (52) Bartlet, R. J.; Stanton, J. F. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York–Weinheim, 1994; Vol. 5, p 65.
- (53) Crawford, T. D.; Schafer, H. F., III. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D., Eds.; Wiley–VCH: New York, 2000; Vol. 14, p 33.
- (54) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479.
- (55) Wats, J. D.; Gauss, J.; Bartlet, R. J. *J. Chem. Phys.* **1993**, *98*, 8718.
- (56) Lee, T. J.; Scuseria, G. E. In *Quantum Mechanical Electronic Structural Calculations with Chemical Accuracy*; Langhoff, S. R., Ed.; Kluwer: Dordrecht, 1995; p 47.
- (57) Pople, J. A.; Head-Gordon, M.; Raghavachari, K. *J. Chem. Phys.* **1987**, *87*, 5968.
- (58) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221.
- (59) East, A. L. L.; Smith, B. J.; Radom, L. *J. Am. Chem. Soc.* **1997**, *119*, 9014.
- (60) Curtiss, L. A.; Carpenter, J. E.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1992**, *96*, 9030.
- (61) Ochterski, J. W.; Peterson, G. A.; Wiberg, K. B. *J. Am. Chem. Soc.* **1995**, *117*, 11299.
- (62) Smith, B. J.; Radom, L. *J. Phys. Chem.* **1995**, *99*, 6468.
- (63) Curtiss, L. A.; Redfern, P. C.; Smith, B. J.; Radom, L. *J. Chem. Phys.* **1996**, *104*, 5148.
- (64) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 764.
- (65) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1999**, *110*, 4703.
- (66) Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1999**, *110*, 7650.
- (67) Hammerum, S. *Chem. Phys. Lett.* **1999**, *300*, 529.
- (68) Kabli, S.; van Beelen, E. S. E.; Ingemann, S.; Henriksen, L.; Hammerum, S. *Int. J. Mass Spectrom.* **2006**, *249–250*, 370.
- (69) van Beelen, E. S. E.; Koblenz, T. A.; Ingemann, S.; Hammerum, S. *J. Phys. Chem. A* **2004**, *108*, 2787.
- (70) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **2007**, *126*, 084108.
- (71) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **2007**, *127*, 124105.
- (72) Ochterski, J. W.; Peterson, G. A.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1996**, *104*, 2598.
- (73) Hammerum, S.; Sølling, T. I. *J. Am. Chem. Soc.* **1999**, *121*, 6002.
- (74) Martin, J. M. L.; de Oliviera, G. *J. Chem. Phys.* **1999**, *111*, 1843.
- (75) Parthiban, S.; Martin, J. M. L. *J. Chem. Phys.* **2001**, *114*, 6014.
- (76) Boese, A. D.; Oren, M.; Atasoylu, O.; Martin, J. M. L. *J. Chem. Phys.* **2004**, *120*, 4129.
- (77) Karton, A.; Rabinovich, E.; Martin, J. M. L.; Ruščić, B. *J. Chem. Phys.* **2006**, *125*, 144108.
- (78) Tajti, A.; Szalay, P. G.; Császár, A. G.; Kállay, M.; Gauss, J.; Valeev, E. F.; Flowers, B. A.; Vázquez, J.; Stanton, J. F. *J. Chem. Phys.* **2004**, *121*, 11599.
- (79) Bomble, Y. J.; Vázquez, J.; Kállay, M.; Michauk, M.; Szalay, P. G.; Császár, A. G.; Gauss, J.; Stanton, J. F. *J. Chem. Phys.* **2006**, *125*, 064108.
- (80) Harding, M. E.; Vázquez, J.; Ruščić, B.; Wilson, A. K.; Gauss, J.; Stanton, J. F. *J. Chem. Phys.* **2008**, *128*, 114111.
- (81) Heckert, M.; Kállay, M.; Tew, D. P.; Klopper, W.; Gauss, J. *J. Chem. Phys.* **2006**, *125*, 044108.
- (82) Tew, D. P.; Klopper, W.; Heckart, M.; Gauss, J. *J. Phys. Chem.* **2007**, *111*, 11242.
- (83) Kállay, M.; Gauss, J. *J. Chem. Phys.* **2008**, *129*, 144101.
- (84) Ruščić, B.; Pinzon, R. E.; Morton, M. L.; von Laszewski, G.; Bittner, S. J.; Nijsure, S. G.; Amin, K. A.; Minkoff, M.; Wagner, A. F. *J. Chem. Phys.* **2004**, *108*, 9979.
- (85) Burk, P.; Koppel, I. A.; Koppel, I.; Leito, I.; Travnikova, O. *Chem. Phys. Lett.* **2000**, *323*, 482.
- (86) Taskinen, A.; Nieminen, V.; Toukoniitty, E.; Murzin, D. Yu.; Hotokka, M. *Tetrahedron* **2005**, *61*, 8109.
- (87) Swart, M.; Rösler, E.; Bickelhaupt, F. M. *J. Comput. Chem.* **2006**, *27*, 1486.
- (88) Dinadayalane, T. C.; Sastry, G. N.; Leszczynski, J. *Int. J. Quantum Chem.* **2006**, *106*, 2920.
- (89) Brás, N. F.; Perez, M. A. S.; Fernandes, P. A.; Silva, P. J.; Ramos, M. J. *J. Chem. Theory Comput.* **2011**, *7*, 3898.
- (90) Uddin, K. M.; Warburton, P. L.; Poirier, R. A. *J. Phys. Chem. B* **2012**, *116*, 3220.
- (91) Moser, A.; Range, K.; York, D. M. *J. Phys. Chem. B* **2010**, *114*, 13911.
- (92) Harrison, A. G. *Mass Spectrom. Rev.* **1997**, *16*, 201.
- (93) Dixon, D. A.; Lias, S. G. In *Molecular Structure and Energetics*; Lieberman, J. F., Greenberg, A., Eds.; VCH: Weinheim, 1987; Vol. 2, p 269.
- (94) Ruščić, B.; Berkowiz, J. *J. Chem. Phys.* **1989**, *91*, 6772.
- (95) Kebarle, P. In *Techniques for Study of Ion–Molecule Reactions*; Farrar, J. M., Saunders, W. H., Jr., Eds.; John Wiley & Sons: New York, 1988.
- (96) Schiff, M. I.; Bohme, D. K. *Int. J. Mass Spectrom. Ion Phys.* **1975**, *16*, 167.
- (97) McIver, R. T.; Eyler, J. R. *J. Am. Chem. Soc.* **1971**, *93*, 4314.
- (98) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 4726.
- (99) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311.
- (100) Beauchamp, J. L.; Butrill, S. E. *J. Chem. Phys.* **1968**, *48*, 1783.
- (101) Long, J.; Munson, B. *J. Am. Chem. Soc.* **1973**, *95*, 2427.
- (102) McLuckey, S. A.; Cameron, D.; Cooks, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 1313.

- (103) Cooks, R. G.; Patrick, J. S.; Kotiako, T.; McLuckey, S. A. *Mass Spectrom. Rev.* **1994**, *13*, 287.
- (104) Bouchoux, G.; Salpin, J.-Y. *J. Phys. Chem.* **1996**, *100*, 16555.
- (105) Meot-Ner (Mautner), M. *J. Phys. Chem.* **1991**, *95*, 6580.
- (106) Sieck, L. W.; Meot-Ner (Mautner), M. *J. Chem. Phys.* **1982**, *86*, 3646.
- (107) Gorman, G. S.; Amster, I. *J. Org. Mass Spectrom.* **1991**, *26*, 227.
- (108) Wolf, J. F.; Staley, R. H.; Koppel, I.; Taagepera, R. T.; McIver, J. L.; Beauchamp, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5417.
- (109) Aue, D. H.; Bowers, M. T. In *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. 2, p 2.
- (110) Yamagdni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1976**, *98*, 1320.
- (111) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695.
- (112) Hunter, E. P.; Lias, S. G. *J. Phys. Chem. Ref. Data* **1988**, *27*, 413.
- (113) Mautner, M.; Sieck, L. W. *J. Am. Chem. Soc.* **1991**, *113*, 4448.
- (114) Smith, B. J.; Radom, L. *J. Am. Chem. Soc.* **1993**, *115*, 4885.
- (115) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. In *Ion Energetics Data NIST Chemistry WebBook*, *NIST Standard Reference Database Number 69*; Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology: Gaithersburg, MD 20899, 2012, <http://webbook.nist.gov>.
- (116) Wu, R.; McMahon, T. B. *Mass Spectrom. Rev.* **2009**, *28*, 546.
- (117) Császár, A. G.; Allen, W. D.; Schafer, H. F., III. *J. Chem. Phys.* **1998**, *108*, 9751.
- (118) Čížek, J. *J. Chem. Phys.* **1966**, *45*, 4256.
- (119) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007.
- (120) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.
- (121) Woon, D. E.; Dunning, T. H., Jr. *J. Chem. Phys.* **1995**, *103*, 4572.
- (122) Hehre, W. J.; Radom, L.; Schlauer, P. v. R.; Pople, J. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
- (123) Korton, A.; Martin, J. M. L. *Theor. Chem. Acc.* **2006**, *115*, 330.
- (124) Klopper, W.; Kutzelnigg, W. *J. Mol. Struct. (THEOCHEM)* **1986**, *28*, 339.
- (125) (a) Feller, D. *J. Chem. Phys.* **1992**, *96*, 6104. (b) Feller, D. *J. Chem. Phys.* **1993**, *98*, 7059.
- (126) Helgaker, T.; Klopper, W.; Koch, H.; Noga, J. *J. Chem. Phys.* **1997**, *106*, 9639.
- (127) Cowan, R. D.; Griffin, D. C. *J. Opt. Soc. Am.* **1976**, *66*, 1010.
- (128) ACESII, <http://aces2.de>.
- (129) Handy, N. C.; Yamaguchi, Y.; Schafer, H. F., III. *J. Chem. Phys.* **1986**, *84*, 4481.
- (130) Valeev, E. F.; Sherill, C. D. *J. Chem. Phys.* **2003**, *118*, 3921.
- (131) Gauss, J.; Tajti, A.; Kállay, M.; Stauton, J. F.; Szalay, P. G. *J. Chem. Phys.* **2006**, *125*, 144111.
- (132) Dixon, D. A.; Komornicki, A.; Kraemer, W. P. *J. Chem. Phys.* **1984**, *81*, 3603.
- (133) Van der Tok, F. F. S.; Müller, H. S. P.; Harding, M. E.; Gauss, J. *Astron. Astrophys.* **2009**, *507*, 347.
- (134) Taylor, R. *Electrophilic Aromatic Substitution*; Ellis Harwood: Chichester, 1990.
- (135) Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University Press: New York, 1984.
- (136) Smith, M. B.; March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th ed.; Wiley: New York, 2001.
- (137) Wheland, G. W. *Resonance in Organic Chemistry*; Wiley: New York, 1955.
- (138) (a) Olah, G. A.; Schosberg, R. H.; Porter, R. D.; Mo, Y. K.; Kelly, D. P.; Mateescu, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 2034. (b) Olah, G. A.; Staral, J. S.; Asencio, G.; Forsyth, D. A.; Mateescu, G. D. *J. Am. Chem. Soc.* **1978**, *100*, 6299.
- (139) Reed, C. A.; Fackler, N. L. P.; Kim, K. C.; Stasko, D.; Evans, D. R.; Boyd, P. D.; Rickard, C. E. F. *J. Am. Chem. Soc.* **1999**, *121*, 6314.
- (140) Stasko, D.; Reed, C. A. *J. Am. Chem. Soc.* **2002**, *124*, 1148.
- (141) Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 6901.
- (142) Köhler, H.-J.; Lischka, H. *J. Am. Chem. Soc.* **1979**, *101*, 3479.
- (143) Howard, S. T.; Wozniak, K. *Chem. Phys. Lett.* **1993**, *212*, 1.
- (144) Mason, R. S.; Williams, C. M.; Anderson, P. D. *J. J. Chem. Soc., Chem. Commun.* **1995**, 1027.
- (145) Maksić, Z. B.; Kovačević, B.; Lesar, A. *Chem. Phys.* **2000**, *253*, 59.
- (146) (a) Solcá, N.; Dopfer, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 3628. (b) Jones, W.; Boissel, P.; Chiavarino, B.; Crestoni, M. E.; Fornarini, S.; Lemaire, J.; Maitre, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2057. (c) Doublerly, G. E.; Ricks, A. M.; Schleyer, P. v. R.; Duncan, M. A. *J. Phys. Chem. A* **2008**, *112*, 4869.
- (147) Eckert-Maksić, M.; Maksić, Z. B. In *The Chemistry of Cyclobutanes, Part 1*; Rappoport, Z., Liebman, J. F., Eds.; John Wiley & Sons: Chichester, 2005; p 17.
- (148) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *20*, 1024.
- (149) Winstein, S.; Adams, R. *J. Am. Chem. Soc.* **1948**, *70*, 838.
- (150) Olah, G. A.; Staral, J. S.; Liang, G. *J. Am. Chem. Soc.* **1974**, *96*, 6233.
- (151) Olah, G. A.; Staral, J. S.; Spear, R. J.; Liang, G. *J. Am. Chem. Soc.* **1975**, *97*, 5489.
- (152) Olah, G. A.; White, A. M.; O'Brien, D. H. O. *Chem. Rev.* **1970**, *70*, 561.
- (153) Olah, G. A.; Mo, Y. K. *J. Org. Chem.* **1973**, *38*, 353.
- (154) Bouchoux, G.; Defaye, D.; McMahon, T. B.; Likholoyot, A.; Mó, O.; Yáñez, M. *Chem.-Eur. J.* **2002**, *8*, 2900.
- (155) Eckert-Maksić, M.; Klessinger, M.; Maksić, Z. B. *Chem. Phys. Lett.* **1995**, *232*, 472.
- (156) Solcá, N.; Dopfer, O. *Chem. Phys. Lett.* **2001**, *342*, 191.
- (157) McMurry, J. *Organic Chemistry*, 4th ed.; Brooks-Cole: Pacific Grove, CA, 1996.
- (158) Bagno, A.; Terrier, F. *J. Phys. Chem. A* **2001**, *105*, 6537.
- (159) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Chem. Phys.* **1996**, *100*, 16098.
- (160) Bagno, A.; Bujnicki, B.; Bertrand, S.; Comuzzi, C.; Dorigo, F.; Janvier, P.; Scorrano, G. *Chem.-Eur. J.* **1999**, *5*, 523.
- (161) Russo, N.; Toscano, M.; Grand, A.; Mineva, T. *J. Phys. Chem. A* **2000**, *104*, 4017 and references cited therein.
- (162) Smith, R. L.; Chyall, L. J.; Beasley, B. J.; Kenttämö, H. I. *J. Am. Chem. Soc.* **1995**, *117*, 7971.
- (163) Flammang, R.; Dechamp, N.; Pascal, L.; Van Haverbeke, Y.; Gerbaux, P.; Nam, P.-C.; Nguyen, M. T. *Lett. Org. Chem.* **2004**, *1*, 23.
- (164) Pollack, S. K.; Devlin, J. L., III; Summerhays, K. D.; Taft, R. W.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4583.
- (165) Hehre, W. J.; Ditchfield, R.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4796.
- (166) Hildebrand, C.; Klessinger, M.; Eckert-Maksić, M.; Maksić, Z. B. *J. Phys. Chem.* **1996**, *100*, 9698.
- (167) Wiberg, K. B. *Collect. Czech. Chem. Commun.* **2004**, *69*, 2183.
- (168) Santos, A. F. L. O. M.; Ribeiro da Silva, M. A. V. *J. Phys. Chem. B* **2011**, *115*, 4939.
- (169) Eckert-Maksić, M.; Klessinger, M.; Maksić, Z. B. *J. Phys. Org. Chem.* **1995**, *8*, 435.
- (170) Eckert-Maksić, M.; Klessinger, M.; Maksić, Z. B. *Chem.-Eur. J.* **1996**, *2*, 1551.
- (171) Kovaček, D.; Maksić, Z. B.; Novak, I. *J. Phys. Chem.* **1997**, *101*, 1147.
- (172) Eckert-Maksić, M.; Klessinger, M.; Antol, I.; Maksić, Z. B. *J. Phys. Org. Chem.* **1997**, *10*, 415.
- (173) Eckert-Maksić, M.; Hodošek, M.; Kovaček, D.; Maksić, Z. B.; Primorac, M. *J. Mol. Struct. (THEOCHEM)* **1997**, *417*, 731.
- (174) (a) Schulman, J. M.; Disch, R. *Chem. Phys. Lett.* **1985**, *113*, 291. (b) Ibrahim, M. R.; Fataftah, Z. A. *Chem. Phys. Lett.* **1986**, *125*, 149.
- (175) Barić, D.; Maksić, Z. B.; Vianello, R. *J. Mol. Struct. (THEOCHEM)* **2004**, *672*, 201.
- (176) Barić, D.; Maksić, Z. B. *J. Phys. Chem. A* **2002**, *106*, 1612.
- (177) Barić, D.; Maksić, Z. B.; Yáñez, M. *Mol. Phys.* **2003**, *101*, 1377.
- (178) Bytautas, L.; Rudenberg, K. *Mol. Phys.* **2002**, *100*, 757.
- (179) Maksić, Z. B.; Barić, D.; Petanjek, I. *J. Phys. Chem. A* **2000**, *104*, 10873.

- (180) Maksić, Z. B.; Smith, D. M.; Barić, D. *Chem. Phys.* **2001**, *269*, 11.
- (181) Laali, K. K. *Chem. Rev.* **1996**, *96*, 1873.
- (182) Laali, K. K.; Hansen, P. E. *J. Org. Chem.* **1991**, *56*, 6795.
- (183) Laali, K. K.; Hansen, P. E. *J. Org. Chem.* **1993**, *58*, 4096.
- (184) Maksić, Z. B. *J. Mol. Struct. (THEOCHEM)* **1988**, *170*, 39.
- (185) Maksić, Z. B. In *Molecules in Physics, Chemistry and Biology*; Marnani, J., Ed.; Kluwer: Dordrecht, 1989; Vol. 3, p 49.
- (186) Kovačević, K.; Maksić, Z. B.; Moguš-Milanković, A. *Croat. Chem. Acta* **1984**, *66*, 197.
- (187) (a) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *Tetrahedron* **1976**, *32*, 313. (b) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1222.
- (188) Maksić, Z. B.; Eckert-Maksić, M. In *Theoretical Organic Chemistry*; Parkanyi, C., Ed.; *Theoretical and Computational Chemistry*; Politzer, D., Maksić, Z. B., Series Eds.; Elsevier: Amsterdam, 1998; p 203.
- (189) (a) Maksić, Z. B.; Eckert-Maksić, M.; Klessinger, M. *Chem. Phys. Lett.* **1996**, *260*, 572. (b) Eckert-Maksić, M.; Knežević, A.; Maksić, Z. B. *J. Phys. Org. Chem.* **1998**, *11*, 663.
- (190) Lau, Y. B.; Kebarle, P. *J. Am. Chem. Soc.* **1976**, *98*, 7452.
- (191) De la Mare, P. B. D. *Tetrahedron* **1959**, *5*, 107.
- (192) Ebrahimi, A.; Habibi-Khorasani, S. M.; Jahantab, M. *Comput. Theor. Chem.* **2011**, *966*, 31.
- (193) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
- (194) Mills, W. H.; Nixon, I. G. *J. Chem. Soc.* **1930**, 2510.
- (195) Maksić, Z. B.; Eckert-Maksić, M.; Mó, O.; Yáñez, M. In *Pauling's Legacy – Modern Modeling of the Chemical Bond*; Maksić, Z. B., Orville-Thomas, W. J., Eds.; Politzer, P., Maksić, Z. B., Series Eds.; Elsevier: Amsterdam, 1999; Vol. 6, Theoretical and Computational Chemistry, p 47.
- (196) Maksić, Z. B.; Eckert-Maksić, M.; Pfeifer, K. H. *J. Mol. Struct. (THEOCHEM)* **1993**, *300*, 445.
- (197) Eckert-Maksić, M.; Glasovac, Z.; Maksić, Z. B.; Zrinski, I. *J. Mol. Struct. (THEOCHEM)* **1996**, *366*, 173.
- (198) Eckert-Maksić, M.; Maksić, Z. B.; Klessinger, M. *Int. J. Quantum Chem.* **1994**, *49*, 383.
- (199) Eckert-Maksić, M.; Klessinger, M.; Kovaček; Maksić, Z. B. *J. Phys. Org. Chem.* **1996**, *9*, 269.
- (200) Hine, J.; Weimer, R. D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 3387.
- (201) Olah, G. A.; Molnar, A. *Hydrocarbon Chemistry*; J. Wiley & Sons, Inc.: New York, 1995.
- (202) Adams, N. G.; Smith, D. *Chem. Phys. Lett.* **1981**, *79*, 563.
- (203) Scribner, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 349.
- (204) Brauman, J. I.; Han, C. C. *J. Am. Chem. Soc.* **1988**, *110*, 5611.
- (205) Bartmess, J. E. *Mass Spectrom. Rev.* **1989**, *8*, 297.
- (206) McMahon, T. B.; Heine, T.; Nicol, G.; Hovey, J. K.; Kebarle, P. *J. Am. Chem. Soc.* **1988**, *110*, 7591.
- (207) Deakyne, C. A.; Meot-Ner (Mautner), M. *J. Chem. Phys.* **1990**, *94*, 232.
- (208) Glukhovtsev, M. N.; Szulejko, J. E.; McMahon, T. B.; Gould, J. W.; Scott, A. P.; Smith, B. J.; Pross, A.; Radom, L. *J. Phys. Chem.* **1994**, *98*, 13101.
- (209) Maksić, Z. B.; Eckert-Maksić, M.; Knežević, A. *J. Phys. Chem. A* **1998**, *102*, 2981.
- (210) Wei, Y.; Singer, T.; Mayr, H.; Sastry, G. N.; Zipse, H. J. *Comput. Chem.* **2008**, *29*, 291.
- (211) Eckert-Maksić, M.; Glasovac, Z.; Novak-Coumbassa, N.; Maksić, Z. B. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1091.
- (212) Laurence, C.; Graton, J.; Gal, J.-F. *J. Chem. Educ.* **2011**, *88*, 1651.
- (213) Hoyau, S.; Norrman, K.; McMahon, T. B.; Ohanessian, G. J. *Am. Chem. Soc.* **1999**, *121*, 8864.
- (214) Armentrout, P. B.; Rodgers, M. T. *J. Phys. Chem. A* **2000**, *104*, 2238.
- (215) Rodgers, M. T.; Armentrout, P. B. *Mass Spectrom. Rev.* **2000**, *19*, 215.
- (216) Fujii, T. *Mass Spectrom. Rev.* **2000**, *19*, 111.
- (217) Shankar, R.; Kolandaivel, P.; Senthilkumar, L. *J. Phys. Org. Chem.* **2011**, *24*, 553.
- (218) Petrie, S. *J. Phys. Chem. A* **2002**, *106*, 7034.
- (219) Despotović, I.; Maksić, Z. B. *Tetrahedron Lett.* **2011**, *52*, 6263.
- (220) Corral, I.; Mó, O.; Yáñez, M.; Scott, A. P.; Radom, L. *J. Phys. Chem. A* **2003**, *107*, 10456.
- (221) Gal, J.-F.; Maria, P.-C.; Massi, L.; Mayeux, C.; Burk, P.; Tamiku-Taul, J. *Int. J. Mass Spectrom.* **2007**, *267*, 7.
- (222) Burk, P.; Koppel, I. A.; Koppel, I.; Kurg, R.; Gal, J.-F.; Maria, P.-C.; Herreros, M.; Notario, R.; Abboud, J.-L. M.; Anvia, F.; Taft, R. W. *J. Phys. Chem. A* **2000**, *104*, 2824.
- (223) Alcami, M.; Mó, O.; Yáñez, M. *J. Phys. Chem.* **1989**, *93*, 3929.
- (224) Alcami, M.; Mó, O.; Yáñez, M. *J. Phys. Chem.* **1990**, *94*, 4796.
- (225) Alcami, M.; Mó, O.; de Paz, J. J. G.; Yáñez, M. *Theor. Chim. Acta* **1990**, *77*, 1.
- (226) Frash, M. V.; Hopkinson, A. C.; Bohme, D. K. *J. Am. Chem. Soc.* **2001**, *123*, 6687.
- (227) Taft, R. W.; Anvia, F.; Gal, J.-F.; Walsh, S.; Capon, M.; Holmes, M. C.; Hosn, K.; Oloumi, G.; Vasanwala, R.; Yazdani, S. *Pure Appl. Chem.* **1990**, *62*, 17.
- (228) Siegbahn, K.; Nordling, C.; Fahlman, A.; Nordberg, R.; Haurin, K.; Hedman, J.; Johansson, G.; Bergmark, T.; Karlson, S. E., Lindgren, I.; Lindberg, B. *ESCA – Atomic Molecular and Solid State Structure Studied by Means of Electron Spectroscopy*; Almqvist & Wiksell: Uppsala, 1967.
- (229) Siegbahn, K.; Nordling, C.; Johannsson, G.; Hedman, J.; Heden, P. F.; Hamrin, K.; Gelius, U.; Bergmark, T.; Werme, L. O.; Manne, R.; Baer, Y. *ESCA Applied to Free Molecules*; North Holland: Amsterdam, 1969.
- (230) Saehre, L. J.; Børvea, K. J.; Thomas, T. D. *J. Electron Spectrosc.* **2011**, *183*, 2.
- (231) Takahata, Y. *Comput. Theor. Chem.* **2011**, *978*, 77.
- (232) See, for example: Maksić, Z. B. In *Theoretical Models of Chemical Bonding, Part 3, Molecular Spectroscopy, Electronic Structure and Intramolecular Interactions*; Maksić, Z. B., Ed.; Springer Verlag: Heidelberg–Berlin, 1991; p 289.
- (233) Martin, R. L.; Shirley, D. A. *J. Am. Chem. Soc.* **1974**, *96*, 5299.
- (234) Davis, D. W.; Rabalais, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 5305.
- (235) Benoit, F. M.; Harrison, A. G. *J. Am. Chem. Soc.* **1977**, *99*, 3980.
- (236) Mills, B. E.; Martin, R. L.; Shirley, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 2380.
- (237) Smith, S. R.; Thomas, T. D. *J. Am. Chem. Soc.* **1978**, *100*, 5459.
- (238) Catalán, J.; Yáñez, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 741.
- (239) Catalán, J.; Yáñez, M. *Chem. Phys. Lett.* **1979**, *60*, 499.
- (240) Catalán, J.; Mó, O.; Pérez, P.; Yáñez, M. *J. Am. Chem. Soc.* **1979**, *101*, 6520.
- (241) Thomas, T. D.; Saethre, L. J.; Børve, K. J.; Gundersen, M.; Kukk, E. *J. Phys. Chem. A* **2005**, *109*, 5085.
- (242) (a) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 4728; (b) *J. Am. Chem. Soc.* **1975**, *97*, 4136.
- (243) Henderson, W. G.; Taagepera, D. H.; McIver, R. T.; Beauchamp, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 4729.
- (244) Staley, R. H.; Kleckner, J. E.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 2081.
- (245) Catalán, J.; Mó, O.; Pérez, P.; Yáñez. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1409.
- (246) Campbell, S.; Marzluff, E. M.; Rodgers, M. T.; Beauchamp, J. L.; Rempe, M. E.; Schwinck, K. F.; Lichtenberger, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 5251.
- (247) Kovačević, B.; Maksić, Z. B.; Rademacher, P. *Chem. Phys. Lett.* **1998**, *293*, 245.
- (248) Nelsen, S. F.; Rumack, D. T.; Sieck, W.; Meot-Ner, M. *J. Am. Chem. Soc.* **1988**, *110*, 6303.
- (249) Arnett, E. M. *Acc. Chem. Res.* **1973**, *6*, 404.
- (250) Hehre, W. J.; Pople, J. A. *Tetrahedron Lett.* **1970**, *34*, 2959.
- (251) Merrill, G. N.; Fletcher, G. D. *J. Mol. Struct. (THEOCHEM)* **2008**, *849*, 84.
- (252) Hall, H. K., Jr.; Bates, R. B. *Tetrahedron Lett.* **2012**, *53*, 1830.

- (253) Raczynska, E. D.; Maria, P.-C.; Gal, J. F.; Decouzon, M. *J. Phys. Org. Chem.* **1994**, *7*, 725.
- (254) Pankratov, A. N.; Uchaeva, I. M.; Doronin, S. Yu.; Chernova, R. K. *J. Struct. Chem.* **2001**, *42*, 739.
- (255) Gupta, M.; da Silva, E. F.; Svendsen, H. F. *J. Phys. Chem. B* **2012**, *116*, 1865.
- (256) Salehzadeh, S.; Bayat, M.; Yaghoobi, F. *J. Mol. Struct. (THEOCHEM)* **2009**, *906*, 68.
- (257) Kaljurand, I.; Koppel, I. A.; Kütt, A.; Rõõm, E.-I.; Rodima, T.; Koppel, I.; Mishima, M.; Leito, I. *J. Phys. Chem. A* **2007**, *111*, 1245.
- (258) Campbell, S.; Beauchamp, J. L.; Rempe, M.; Lichtenberger, D. L. *Int. J. Mass Spectrom. Ion Processes* **1992**, *117*, 83.
- (259) DeKock, R. L.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1979**, *101*, 6516.
- (260) Ijjali, F.; Mó, O.; Yáñez, M.; Abboud, J.-L. M. *J. Mol. Struct. (THEOCHEM)* **1995**, *338*, 225.
- (261) Baeten, A.; De Proft, F.; Geerlings, P. *Int. J. Quantum Chem.* **1996**, *60*, 931.
- (262) Marino, T.; Russo, N.; Tocci, E.; Toscano, J. *Mass Spectrom.* **2001**, *36*, 301.
- (263) Marino, T.; Russo, N.; Silicia, E.; Toscano, M.; Mineva, T. *Adv. Quantum Chem.* **2000**, *36*, 93.
- (264) Russo, N.; Toscano, M.; Grand, A.; Jolibois, F. *J. Comput. Chem.* **1998**, *19*, 989.
- (265) Topol, I. A.; Burt, S. K.; Russo, N.; Toscano, M. *J. Mol. Struct. (THEOCHEM)* **1998**, *430*, 41; *J. Am. Soc. Mass Spectrom.* **1999**, *10*, 318.
- (266) Roy, R. K.; De Proft, F.; Geerlings, P. *J. Phys. Chem. A* **1998**, *102*, 7035.
- (267) Koopmans, T. *Physica* **1933**, *1*, 104.
- (268) Sharpe, P.; Richardson, D. E. *Thermochim. Acta* **1992**, *202*, 173.
- (269) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247.
- (270) Chamorro, E.; Duque-Noreña, M.; Pérez, P. *J. Mol. Struct. (THEOCHEM)* **2009**, *901*, 145.
- (271) Pérez, P.; Domingo, L. R.; Aizman, A.; Contreras, R. *Theor. Comput. Chem.* **2007**, *19*, 139.
- (272) Jaramillo, P.; Pérez, P.; Fuentealba, P. *J. Phys. Org. Chem.* **2007**, *20*, 1050.
- (273) Jaramillo, P.; Pérez, P.; Contreras, R.; Tiznado, W.; Fuentealba, P. *J. Phys. Chem. A* **2006**, *110*, 8181.
- (274) Chamorro, E.; Escobar, C. A.; Sienra, R.; Pérez, P. *J. Phys. Chem. A* **2005**, *109*, 10068.
- (275) Pérez, P.; Aizman, A.; Contreras, R. *J. Phys. Chem. A* **2002**, *106*, 3964.
- (276) Pérez, P.; Simón-Manso, Y.; Aizman, A.; Fuentealba, P.; Contreras, R. *J. Am. Chem. Soc.* **2000**, *122*, 4756.
- (277) Deakyne, C. A. *Int. J. Mass Spectrom.* **2003**, *227*, 601.
- (278) Vianello, R.; Kovačević, B.; Maksić, Z. B. *New J. Chem.* **2002**, *26*, 1324.
- (279) (a) McMombie, J. F. W. *Protective Groups in Organic Chemistry*; Plenum Press: London, NY, 1973. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.
- (280) Vianello, R.; Maskill, H.; Maksić, Z. B. *Eur. J. Org. Chem.* **2006**, *2581*.
- (281) Yoshikawa, K.; Hashimoto, M.; Morishima, I. *J. Am. Chem. Soc.* **1974**, *96*, 288.
- (282) Aue, D. H. *Gas-Phase Ion Chemistry*; Academic Press: New York, 1979; Vol. 2, Chapter 9.
- (283) Ohwada, T.; Hirao, H.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 7486.
- (284) Tang, J.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.
- (285) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, *591*.
- (286) Hibbert, F.; Hunte, K. P. P. *J. Chem. Soc., Perkin Trans. 2* **1983**, *1895*.
- (287) Schuchardt, U.; Vargas, R. M.; Gelbard, G. *J. Mol. Catal. A* **1996**, *109*, 37.
- (288) Gelbard, G. J.; Vilefaure-Joly, F. *React. Funct. Polym.* **2001**, *48*, 65.
- (289) Ishikawa, T.; Isober, T. *Chem.-Eur. J.* **2002**, *8*, 553.
- (290) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Wiley: New York, 2009.
- (291) Pozharskii, A. F.; Ozeryanskii, V. A.; Filatova, E. A. *Chem. Heterocycl. Compd.* **2012**, *48*, 200.
- (292) Kovačević, B.; Maksić, Z. B. *John von Neumann Inst. Comput. Ser.* **2004**, *20*, 71.
- (293) Seminario, J. M., Ed. *Recent Developments and Applications of Modern Density Functional Theory, Theoretical and Computational Chemistry Series*; Politzer, P., Maksić, Z. B., Series Eds.; Elsevier: Amsterdam, 1996; Vol. 4.
- (294) Koch, W.; Holthausen, M. A. *Chemist's Guide to Density Functional Theory*; Wiley-VCH: New York-Weinheim, 2000.
- (295) Maksić, Z. B.; Kovačević, B. *J. Org. Chem.* **2000**, *65*, 3303.
- (296) Raczyńska, E. D.; Cyranski, M. K.; Gutowski, M.; Rak, J.; Gal, J.-F.; Maria, P.-C.; Darowska, M.; Duczmal, K. *J. Phys. Org. Chem.* **2003**, *16*, 91.
- (297) Amekraz, B.; Tortajada, J.; Morizur, J.-P.; González, A. I.; Mó, O.; Yáñez, M.; Leito, I.; Maria, P.-C.; Gal, J.-F. *New J. Chem.* **1996**, *20*, 1011.
- (298) See also guanidine derivatives: Glasovac, Z.; Štrukil, V.; Eckert-Maksić, M.; Schröder, D.; Kaczarowska, M.; Schwartz, H. *Int. J. Mass Spectrom.* **2008**, *270*, 39.
- (299) Vianello, R.; Kovačević, B.; Maksić, Z. B. *New J. Chem.* **2002**, *26*, 1324.
- (300) Maksić, Z. B.; Kovačević, B. *J. Phys. Chem. A* **1999**, *103*, 6678.
- (301) Kovačević, B.; Maksić, Z. B.; Vianello, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, *886*.
- (302) Despotović, I.; Maksić, Z. B.; Vianello, R. *New J. Chem.* **2007**, *31*, 52.
- (303) Maksić, Z. B.; Glasovac, Z.; Despotović, I. *J. Phys. Org. Chem.* **2002**, *15*, 499.
- (304) Maksić, Z. B.; Kovačević, B. *J. Phys. Chem. A* **1998**, *102*, 7324.
- (305) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletchinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, H. G.; Walz, L. *Liebigs Ann. Chem.* **1996**, *1055*.
- (306) Schwesinger, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1164.
- (307) Kovačević, B.; Barić, D.; Maksić, Z. B. *New J. Chem.* **2004**, *28*, 284.
- (308) Kolomeitsev, A.; Koppel, I. A.; Rodima, T.; Barten, J.; Lark, E.; Röskenthaler, G.-V.; Kaljurand, I.; Kütt, A.; Koppel, I.; Mäemets, V.; Leito, I. *J. Am. Chem. Soc.* **2005**, *127*, 17658.
- (309) Kovačević, B.; Maksić, Z. B. *Tetrahedron Lett.* **2006**, *47*, 2553.
- (310) Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3.
- (311) Kisanga, P. B.; Verkade, J. G.; Schwesinger, P. *J. Org. Chem.* **2000**, *65*, 5431.
- (312) Kovačević, B.; Maksić, Z. B. *Chem. Commun.* **2006**, *1524*.
- (313) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483.
- (314) Raytchev, P. D.; Martinez, A.; Gornitzka, H.; Dutasta, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 2157.
- (315) Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1973**, *9504*.
- (316) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1973**, *95*, 2699.
- (317) Raczyńska, E. D.; Maria, P. C.; Gal, J. F.; Decouzon, M. *J. Org. Chem.* **1992**, *57*, 5730.
- (318) Kovačević, B.; Glasovac, Z.; Maksić, Z. B. *J. Phys. Org. Chem.* **2002**, *15*, 765.
- (319) Glasovac, Z.; Kovačević, B.; Meštrović, E.; Eckert-Maksić, M. *Tetrahedron Lett.* **2005**, *46*, 8733.
- (320) Eckert-Maksić, M.; Glasovac, Z.; Trošelj, P.; Kütt, A.; Rodima, T.; Koppel, I.; Koppel, I. A. *Eur. J. Org. Chem.* **2008**, *5176*.
- (321) Tian, Z. T.; Fattah, A.; Lis, L.; Kass, S. R. *Croat. Chem. Acta* **2009**, *82*, 41.
- (322) Bachrach, S. M.; Wilbanks, C. C. *J. Org. Chem.* **2010**, *75*, 2651.

- (323) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. *R. J. Chem. Soc., Chem. Commun.* **1968**, 723.
- (324) Alder, R. *Chem. Rev.* **1989**, 89, 1215.
- (325) Staab, H. A.; Saupe, T. *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 859.
- (326) Kovačević, B.; Maksić, Z. B. *Chem.-Eur. J.* **2002**, 8, 1694. Raab, V.; Kipke, J.; Gschwind, R. M.; Sundermeyer, J. *Chem.-Eur. J.* **2002**, 8, 1682.
- (327) Raab, V.; Gauchenova, E.; Merkulov, A.; Harms, K.; Sundermeyer, J.; Kovačević, B.; Maksić, Z. B. *J. Am. Chem. Soc.* **2005**, 127, 15738.
- (328) Raab, V.; Harms, K.; Sundermeyer, J.; Kovačević, B.; Maksić, Z. B. *J. Org. Chem.* **2003**, 68, 8790.
- (329) Coles, M. P.; Aragón-Sáez, P. J.; Oakley, S. H.; Hitchcock, P. B.; Davidson, M. G.; Maksić, Z. B.; Vianello, R.; Leito, I.; Kaljurand, I.; Apperley, D. C. *J. Am. Chem. Soc.* **2009**, 131, 16858.
- (330) Kovačević, B.; Maksić, Z. B.; Vianello, R.; Primorac, M. *New J. Chem.* **2002**, 26, 1329.
- (331) Singh, A.; Ganguly, B. *New J. Chem.* **2008**, 32, 210.
- (332) (a) Margetić, D.; Ishikawa, T.; Kumamoto, T. *Eur. J. Org. Chem.* **2010**, 6563. (b) Margetić, D.; Trošelj, P.; Ishikawa, T.; Kumamoto, T. *Bull. Chem. Soc. Jpn.* **2010**, 83, 1055.
- (333) Singh, A.; Ganguly, B. *Eur. J. Org. Chem.* **2007**, 420.
- (334) Singh, A.; Ganguly, B. *New J. Chem.* **2009**, 33, 583.
- (335) Ganguly, B.; Koley, D.; Thiel, W. *Tetrahedron* **2007**, 63, 7970.
- (336) Baldridge, K. K.; Cozzi, F.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2012**, 51, 2903.
- (337) Peran, N.; Maksić, Z. B. *Chem. Commun.* **2011**, 47, 1327.
- (338) Alder, R. W. *J. Am. Chem. Soc.* **2005**, 127, 7924.
- (339) Toom, L.; Kütt, A.; Kaljurand, I.; Leito, I.; Ottosson, H.; Grennberg, H.; Gogoll, A. *J. Org. Chem.* **2006**, 71, 7155.
- (340) Singh, A.; Chakraborty, S.; Ganguly, B. *Eur. J. Org. Chem.* **2006**, 4938.
- (341) Singh, A.; Ganguly, B. *J. Phys. Chem. A* **2007**, 111, 6468.
- (342) Galeta, J.; Potáček, M. *J. Org. Chem.* **2012**, 77, 1010.
- (343) Despotović, I.; Kovačević, B.; Maksić, Z. B. *New J. Chem.* **2007**, 31, 447.
- (344) Suzuki, Y.; Yanagi, T.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, 263.
- (345) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, 9, 1101.
- (346) Vianello, R.; Maksić, Z. B. *J. Phys. Chem. A* **2007**, 111, 11718.
- (347) Koppel, I. A.; Burk, P.; Koppel, I.; Leito, I.; Sonoda, T.; Mishima, M. *J. Am. Chem. Soc.* **2000**, 122, 5114.
- (348) Vianello, R.; Maksić, Z. B. *New J. Chem.* **2008**, 32, 413.
- (349) Meyer, M. M.; Kass, S. R. *J. Phys. Chem. A* **2010**, 114, 4086.
- (350) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, 9, 4709.
- (351) Decouzon, M.; Gal, J.-F.; Maria, P.-C.; Raczyńska, E. D. *Rapid Commun. Mass Spectrom.* **1993**, 7, 599.
- (352) Kaljurand, I.; Rodima, T.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. A.; Mishima, M. *J. Org. Chem.* **2003**, 68, 9988.
- (353) Leito, I.; Koppel, I. A.; Burk, P.; Tamp, S.; Kutsar, M.; Mishima, M.; Abboud, J.-L. M.; Davalos, J. Z.; Herrero, R.; Notario, R. *J. Phys. Chem. A* **2010**, 114, 10694.
- (354) de Petris, G.; Cartoni, A.; Rosi, M.; Barone, V.; Puzzarini, C.; Troiani, A. *ChemPhysChem* **2011**, 12, 112.
- (355) Maksić, Z. B.; Kovačević, B. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2623.
- (356) Legon, A. C.; Wallwork, A. L.; Rego, C. A. *J. Chem. Phys.* **1990**, 92, 6397.
- (357) Legon, C. A. *Chem. Soc. Rev.* **1993**, 22, 153.
- (358) Johnson, G. L.; Andrews, L. *J. Am. Chem. Soc.* **1982**, 104, 3043.
- (359) Schriver, L.; Schriver, A.; Perchard, J. P. *J. Am. Chem. Soc.* **1983**, 105, 3043.
- (360) Barnes, A. J. *J. Mol. Struct.* **2004**, 704, 3.
- (361) Andrews, L.; Wang, X. F.; Mielke, Z. *J. Phys. Chem. A* **2001**, 105, 6054.
- (362) Mó, O.; Yáñez, M.; González, L.; Elguero, J. *ChemPhysChem* **2001**, 465.
- (363) Alkorta, I.; Elguero, J. *J. Phys. Chem. A* **1999**, 103, 272.
- (364) Burk, P.; Tamp, S. *J. Mol. Struct. (THEOCHEM)* **2003**, 119.
- (365) Koppel, I. A.; Burk, P.; Koppel, I.; Leito, I. *J. Am. Chem. Soc.* **2002**, 124, 5594.
- (366) Reed, C. A. *Chem. Commun.* **2005**, 1669.
- (367) Lipping, L.; Leito, I.; Koppel, I.; Koppel, I. A. *J. Phys. Chem. A* **2009**, 113, 12972.
- (368) Burk, P.; Koppel, I.; Trummel, A.; Koppel, I. A. *J. Phys. Org. Chem.* **2008**, 21, 571.
- (369) Raczyńska, E. D.; Gal, J.-F.; Maria, P.-C.; Szelag, M. *Croat. Chem. Acta* **2009**, 82, 87.