

## Acidifying Effect of an *N*-Oxide Group – A Useful Motif in Enhancing Acidity towards Superacidic Values\*

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**Abstract.** DFT calculations carried out on *trans*-decahydronaphthalene and 4b,8b-dihydronaphthalene, important structural features of many alkaloids, revealed that they are moderately acidic carbon acids in the gas-phase and in DMSO solution. Substitution with a nitrogen atom of a neighbouring C(sp<sup>3</sup>)–H fragment bonded to an acidic centre reduces the corresponding acidity in both phases. Following that, oxidation of the nitrogen atom to an *N*-oxide group enhances the acidity significantly. This acidifying effect of an *N*-oxide moiety in the vicinity of a deprotonation centre was estimated to be around 9–17 kcal mol<sup>-1</sup> in the gas-phase deprotonation enthalpy and about 5–11 p*K*<sub>a</sub> units in DMSO. Therefore, this electronic effect could be applied in the design of novel strong acids and superacids. Such acidity enhancement is identified through triadic analysis to be a consequence of the final state effect of anion, where compounds bearing an *N*-oxide group benefit from the favourable charge-dipole interaction between the negative charge and an N–O group. A dramatic increase in acidity is observed upon multiple cyanation. For example, octacyanoquinolizine *N*-oxide is an extremely strong superacid as seen by the gas-phase  $\Delta H_{\text{acid}} = 254.8$  kcal mol<sup>-1</sup> and p*K*<sub>a,DMSO</sub> = –20.2, and its synthesis is highly desirable and strongly recommended. Triadic analysis suggests that this huge acidifying effect takes place because of strong resonance in anions of polycyano compounds, efficiently assisted by multiple CN groups, which stabilizes the corresponding principal molecular orbitals.

**Keywords:** triadic analysis, deprotonation, isodensity polarized continuum model, p*K*<sub>a</sub> value, superacids

### INTRODUCTION

The amine-*N*-oxide moiety (R<sub>3</sub>N<sup>+</sup>–O<sup>–</sup>) is a very common and useful functional group in organic chemistry and biochemistry.<sup>1–3</sup> It is easily prepared by oxidation of tertiary amines or pyridines with hydrogen peroxide or peroxy acids and it serves as a convenient protective group for amino or imino nitrogen in synthetic work.<sup>4</sup> On the other hand, amine oxides are readily converted to the parent amine by common reduction reagents or by thermal treatment.<sup>5</sup> It is known that many heteroaromatic *N*-oxides exhibit a wide range of biological activity and are used as drugs<sup>1</sup> for the treatment of, for example, SARS (Severe Acute Respiratory Syndrome)<sup>6</sup> or HIV (Human Immunodeficiency Virus) infected individuals.<sup>7</sup> The former class of compounds also exhibits insecticide and herbicide activity,<sup>8</sup> antiviral, antifungal and antibacterial activity,<sup>9</sup> antitumoral and antimicrobial activity,<sup>10,11</sup> and anti-ulcerative, antihypertensive and antihistaminic activity.<sup>12</sup> Moreover, Zieba and coworkers<sup>13</sup>

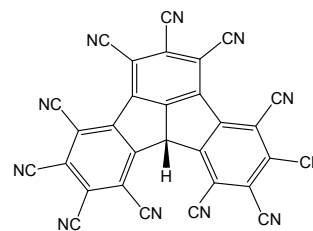
demonstrated that substituted pyridine *N*-oxides represent a novel generation of radio-sensitizers acting as drugs that make tumour cells more sensitive to radiation therapy. In addition, substituted *N*-oxides form an interesting group of compounds that find use as catalysts,<sup>14–16</sup> and as ligands in metal complexes,<sup>17</sup> and they have been implicated as potentially useful in nonlinear optical devices.<sup>18,19</sup>

As part of our continuing studies concerned with identification of electronic and geometric effects responsible for high acidity of organic compounds, we report here on the effect that an *N*-oxide group exhibits on the acidity of a neighbouring C(sp<sup>3</sup>)–H chemical bond. In our previous papers, we have convincingly demonstrated that substitution of selected hydrogen atoms by cyano groups (CN) enhances the acidity of a particular molecule to a great extent.<sup>20–22</sup> The cyano group was selected since it combines the optimal compromise between high electron-withdrawing strength and very modest steric requirements.<sup>20</sup> For example, the

\* Dedicated to Professor Zvonimir Maksić on the occasion of his 70<sup>th</sup> birthday.

gas-phase deprotonation enthalpy of methane, one of the least acidic organic compounds, is reduced by almost  $120 \text{ kcal mol}^{-1}$  upon substitution by 3 cyano groups.<sup>20</sup> Analogously, record values in acidity can be easily obtained if multiple CN groups are strategically positioned so that they participate in resonance stabilization of the conjugate bases. As a typical illustrative example, Richardson and Reed recently synthesized pentacyano-cyclopentadiene  $\text{HC}_5(\text{CN})_5$  by protonating  $\text{C}_5(\text{CN})_5^-$  anion using carborane superacids.<sup>23</sup> The above-mentioned strategy has led us to predict theoretically many different families of polycyano compounds exhibiting superacidity<sup>24</sup> and even hyperacidity.<sup>25</sup> The first theoretically predicted neutral organic hyperacid is the undecacyano derivative of fluoradene **I** (Scheme 1), with the gas-phase deprotonation enthalpy  $\Delta H_{\text{acid}}(\mathbf{I}) = 246.3 \text{ kcal mol}^{-1}$ .<sup>25</sup>

The term "hyperacid" has been defined for compounds possessing the gas-phase deprotonation enthalpies below  $245 \text{ kcal mol}^{-1}$ ,<sup>25</sup> a value that equals the gas-phase proton affinity of the paradigmatic first proton sponge 1,8-bis(dimethylamino)naphthalene, DMAN,<sup>26</sup> and is widely accepted as the superbasicity threshold. Our approach in tailoring new highly acidic molecules is closely related to that of Terrier and co-workers<sup>27</sup> who made use of the concept of the electronic super acidifier  $\text{SO}_2\text{CF}_3$ , proposed by Yagupolskii,<sup>28</sup> in carbanion stabilization. This idea was extended further by Koppel and co-workers who have recently demonstrated the acidifying influence of pentakis(trifluoromethyl)phenyl substituent<sup>29</sup> and have designed the new electron-superacceptor substituent based on modifying the  $\text{SO}_2\text{CF}_3$  group by replacing the oxygen atoms with intrinsically more electron-withdrawing groups, which proved very useful in enhancing acidity.<sup>30–33</sup> All of these efforts are valuable since strong acids are irreplaceable reagents in organic syntheses<sup>34,35</sup> and in industrial catalysis.<sup>36–38</sup> In particular, superacids are crucial in general acid catalysis, where the reaction rate is proportional to the concentration of the superacidic species.<sup>34</sup> Moreover, molecules that can very easily donate protons could play an important role in spontaneous proton transfer reactions in the gas-phase<sup>39–41</sup> and subsequent formation of novel ion-pairs and improved materials. Since anions of organic  $\pi$ -systems have a very effectively dispersed electron density of negative charge they have diminished nucleophilicity. This means that their reactivity in solution is reduced and anions produced upon deprotonation of strong organic superacids are promising candidates for two extremely useful classes of compounds – noncoordinating anions,<sup>42–44</sup> as nicely exemplified recently in the case of carborane anions,<sup>45</sup> and protic ionic liquids.<sup>46</sup> For all of the reasons stated, design of novel acids and superacids is vital from both scientific and practical points of view.



**Scheme 1.** Undecacyanofluoradene (**I**), the first theoretically predicted neutral organic hyperacid.

The purpose of the present study is to reveal the acidifying effect that an *N*-oxide group exhibits in the vicinity of a deprotonation centre. This will be carried out in the gas-phase and in the moderately polar and aprotic solvent DMSO. To the best of our knowledge, no systematic study underlying the impact of an *N*-oxide group in the enhancement of the acidity of organic compounds is available in the literature although it has been demonstrated that *N*-oxidation of hydroxyquinolines leads to a dramatic increase in their excited-state acidity<sup>47</sup> making them candidates for superphotoacids. Through a combined experimental and computational study, Ren showed that the gas-phase deprotonation enthalpy of carboxylic protons in *N,N*-dimethylaminoacetic acid *N*-oxide [ $\text{Me}_2\text{N}(\text{O})\text{CH}_2\text{COOH}$ ] is lower by  $11.5 \text{ kcal mol}^{-1}$  compared to sarcosine [ $\text{MeNHCH}_2\text{COOH}$ ].<sup>48</sup> A lot of work in rationalizing basicity trends and hydrogen bonding ability of substituted pyridine *N*-oxides in the gas-phase and in various solvents was done by Chmurzynski and his co-workers.<sup>49–51</sup> In addition, Stare, Hadži and co-workers demonstrated computationally and experimentally the capacity of an *N*-oxide group in picolinic acid *N*-oxide to act as an intramolecular hydrogen bond acceptor.<sup>52</sup> Due to the high availability and enormous importance of compounds bearing an *N*-oxide group, we feel that the above-mentioned analysis is well justified.

## COMPUTATIONAL DETAILS

As a measure of acidity, we use the enthalpy change  $\Delta H_{\text{acid}}$  for the gas-phase reaction:



where  $\Delta H_{\text{acid}} = \Delta E_{\text{acid}} + \Delta(pV)$ . Here,  $\Delta E_{\text{acid}}$  is the change in the total energy of the acid AH, its conjugate base  $\text{A}^{-}$  and the proton  $\text{H}^{+}$ , including both the zero-point vibrational energy (ZPVE) and the finite temperature (298.15 K) correction. The term  $\Delta(pV)$  denotes the pressure-volume work contribution. It is useful to keep in mind that stronger acids have smaller numerical  $\Delta H_{\text{acid}}$  values, which implies that less energy is required for the release of the acidic proton. As a good compromise

between accuracy and practicality, our model of choice is B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) (abbreviated as B3LYP) implying that all nuclear geometries were optimized, and ZPVEs and thermal corrections were calculated at the efficient B3LYP/6-31G(d) level of theory. Thermochemical quantities were obtained from frequency calculations, where a scaling of the calculated harmonic vibrational frequencies was not applied. Also, based on the same vibrational analysis, it was verified that all of the calculated structures were true minima on the corresponding potential-energy surfaces by checking the absence of imaginary vibrational frequencies. The final single-point energy calculations were attained using the more flexible 6-311+G(2d,p) basis set, since the triple-zeta sets coupled with B3LYP DFT scheme give the total molecular energies close to their asymptotic values.<sup>53</sup> This selection of the method was additionally prompted by its success in reproducing molecular electron affinities<sup>54-56</sup> and gas-phase acidities.<sup>57-60</sup>

As to the computational rationalization of the gas-phase reactivity trends, we recently put forward a very useful tool for the quantitative interpretation of Lewis and Brønsted acidities and basicities in the gas-phase called the triadic formula.<sup>61,62</sup> Regarding Brønsted acidity which is considered here, the triadic analysis treats deprotonation of acid AH as its reversed process – protonation of its conjugate base A<sup>-</sup>.<sup>61</sup> The corresponding gas-phase deprotonation enthalpy  $\Delta H_{\text{acid}}(\text{AH})$  is given as the proton affinity of A<sup>-</sup>, denoted as PA(A<sup>-</sup>), and is dissected into three variable and one constant contribution according to the following formula:

$$\Delta H_{\text{acid}}(\text{AH}) = \text{PA}(A^-)_\alpha = -E_i(A^-)_n^{\text{Koop}} + E(\text{ei})_{\text{rex}} + (\text{BDE})_\alpha + 313.6 \text{ kcal mol}^{-1} \quad (2)$$

where the site of the protonation is indicated by  $\alpha$ . The starting point of the triadic analysis is the familiar and well-known thermodynamic cycle in which protonation of any neutral or charged base is separated into three steps: (a) removal of an electron from the base in question (here A<sup>-</sup>) to create radical A<sup>•</sup>, (b) capture of the ejected electron by the incoming proton H<sup>+</sup> to give the hydrogen atom H<sup>•</sup>, and (c) homolytic construction of the chemical bond between the two newly formed radicals, A<sup>•</sup> and H<sup>•</sup>. An important modification in the triadic approach to the mentioned thermodynamic cycle is the inclusion of the Koopmans' ionization energy  $E_i(A^-)_n^{\text{Koop}}$  of the conjugate base anion A<sup>-</sup> calculated in the frozen density and clamped nuclei approximation, assuming ejection of an electron to be a sudden process.<sup>63</sup> This is particularly important and beneficial since Koopmans' ionization energies depend exclusively on the electron density of A<sup>-</sup> and have no relation to the

neutral acid AH whatsoever. Therefore, in a series of acids investigated, changes in the corresponding Koopmans' ionization parameters of A<sup>-</sup> reflect only properties of the final states (conjugate bases A<sup>-</sup>) that contribute to their acidity differences. It should be mentioned that the index  $n$  in the  $E_i(A^-)_n^{\text{Koop}}$  term signifies  $n$ -th ionization energy within Koopmans' approximation counting HOMO as the first molecular orbital. Index  $n$  is related to a specific MO that is most affected by protonation, which is a distinct advantage of the triadic approach. The latter MO bears the particular lone pair localized (or partially localized) on the atom of A<sup>-</sup> under proton attack that leads to the formation of the neutral acid AH, and its identification in the molecular orbital picture of A<sup>-</sup> presents no problem. Such an appropriate molecular orbital is called the Principal Molecular Orbital (PRIMO). The reorganization of electron density and geometrical parameters upon electron loss from the anion is described by the relaxation energy  $E(\text{ei})_{\text{rex}}$ , which is defined as:

$$E(\text{ei})_{\text{rex}} = E_i(A^-)_n^{\text{Koop}} - E_i(A^-)_1^{\text{ad}} \quad (3)$$

This represents the difference between Koopmans' ionization energy and the "true" first adiabatic ionization energy of A<sup>-</sup>, denoted as  $E_i(A^-)_1^{\text{ad}}$ . Changes in relaxation energies are coupled with the properties of an intermediate stage in the protonation event. Finally, a gain in energy after the formation of the new A-H bond in the process of protonation of A<sup>-</sup> is denoted by a (BDE) term. The latter stands for the Bond Dissociation Energy, and will be used and interpreted in connection with the properties of the initial state, or in other words with the features of the neutral acid AH. A constant term of 313.6 kcal mol<sup>-1</sup> corresponds to experimentally determined electron affinity of the proton H<sup>+</sup>. The triadic analysis presented here is carried out at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level of theory, whereas Koopmans' ionization energies are computed by the restricted HF/6-311+G(2d,p)//B3LYP/6-31G(d) model. Bond dissociation energies are obtained by using the unrestricted UB3LYP/6-311+G(2d,p)//UB3LYP/6-31G(d) approach. This triadic approach proved useful in the interpretation of proton affinities<sup>62,64-67</sup> and deprotonation enthalpies<sup>20-22,24,25,68,69</sup> of organic and inorganic molecules, the Lewis acidity of inorganic boranes,<sup>70</sup> as well as substituent effects,<sup>21,22</sup> and has recently been reviewed.<sup>71</sup>

In order to obtain a useful insight into whether the properties of the initial, final or intermediate state effects are predominantly responsible for the change in acidity between two carefully selected acids, it is important to define a relative difference in their PA(A<sup>-</sup>) values given by the following triad:

**Table 1.** Total molecular energies of molecules studied in the gas-phase (GP) and in dimethyl sulfoxide (DMSO) obtained at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level of theory.  $H_{\text{corr}}$  denotes the gas-phase thermal correction to enthalpy obtained by the B3LYP/6-31G(d) model. Theoretical  $\text{p}K_{\text{a}}$  values are obtained by Eq. (10).

| molecule                      | $\frac{E_{\text{GP}}}{\text{hartree}}$ | $\frac{E_{\text{DMSO}}}{\text{hartree}}$ | $\frac{H_{\text{corr}}}{\text{hartree}}$ | $\frac{\Delta H_{\text{acid}}}{\text{kcal mol}^{-1}}$ | $\frac{\Delta_{\text{r}} H_{\text{DMSO}}}{\text{kcal mol}^{-1}}$ | $\text{p}K_{\text{a}}(\text{theor})$ |
|-------------------------------|--|--|--|---|--|--------------------------------------|
| methane                       | -40.53486                              | -40.53493                                | 0.04901                                  | 417.7   | 92.6   | 53.5                                 |
| methane <sup>-</sup>          | -39.85416                              | -39.96183                                | 0.03168                                  |   |  |                                      |
| propane                       | -119.18371                             | -119.18384                               | 0.10959                                  | 416.4   | 107.6  | 63.4                                 |
| propane <sup>-</sup>          | -118.50372                             | -118.58531                               | 0.09081                                  |   |  |                                      |
| 1                             | -237.15609                             | -237.15633                               | 0.19869                                  | 406.1   | 104.4  | 61.3                                 |
| 1 <sup>-</sup>                | -236.49234                             | -236.56294                               | 0.17982                                  |   |  |                                      |
| 2                             | -253.18031                             | -253.18180                               | 0.18696                                  | 407.8   | 104.8  | 61.6                                 |
| 2 <sup>-</sup>                | -252.51350                             | -252.58718                               | 0.16761                                  |   |  |                                      |
| 3                             | -328.35748                             | -328.37027                               | 0.19261                                  | 397.1   | 95.9   | 55.7                                 |
| 3 <sup>-</sup>                | -327.70884                             | -327.79119                               | 0.17452                                  |   |  |                                      |
| 4                             | -392.04414                             | -392.04432                               | 0.27500                                  | 402.2   | 103.7  | 60.8                                 |
| 4 <sup>-</sup>                | -391.38670                             | -391.45207                               | 0.25622                                  |   |  |                                      |
| 5                             | -408.07537                             | -408.07657                               | 0.26316                                  | 403.8   | 104.6  | 61.4                                 |
| 5 <sup>-</sup>                | -407.41625                             | -407.48368                               | 0.24520                                  |   |  |                                      |
| 6                             | -483.25392                             | -483.26409                               | 0.26870                                  | 393.0   | 94.3   | 54.6                                 |
| 6 <sup>-</sup>                | -482.61309                             | -482.68865                               | 0.25180                                  |   |  |                                      |
| 7                             | -387.12040                             | -387.12315                               | 0.17759                                  | 345.1   | 44.1   | 21.5                                 |
| 7 <sup>-</sup>                | -386.55696                             | -386.62881                               | 0.16179                                  |   |  |                                      |
| 8                             | -403.17578                             | -403.17964                               | 0.16579                                  | 369.5   | 68.7   | 37.7                                 |
| 8 <sup>-</sup>                | -402.57225                             | -402.64486                               | 0.14876                                  |   |  |                                      |
| 9                             | -478.31273                             | -478.32683                               | 0.16995                                  | 328.5   | 27.2   | 10.3                                 |
| 9 <sup>-</sup>                | -477.77699                             | -477.86066                               | 0.15534                                  |   |  |                                      |
| 7 <sub>CN</sub>               | -1125.19493                            | -1125.22795                              | 0.17941                                  | 263.9   | -11.9  | -15.6                                |
| 7 <sub>CN</sub> <sup>-</sup>  | -1124.76390                            | -1124.82586                              | 0.16652                                  |   |  |                                      |
| 8 <sub>CN</sub>               | -1141.22990                            | -1141.26102                              | 0.16736                                  | 267.1   | -10.2  | -14.4                                |
| 8 <sub>CN</sub> <sup>-</sup>  | -1140.79315                            | -1140.85550                              | 0.15386                                  |   |  |                                      |
| 9 <sub>CN</sub>               | -1216.35165                            | -1216.38632                              | 0.17047                                  | 254.8   | -18.9  | -20.2                                |
| 9 <sub>CN</sub> <sup>-</sup>  | -1215.93554                            | -1215.99586                              | 0.15811                                  |   |  |                                      |
| 10 <sub>CN</sub>              | -1217.43147                            | -1217.46209                              | 0.17878                                  | 255.9   | -17.5  | -19.3                                |
| 10 <sub>CN</sub> <sup>-</sup> | -1217.01320                            | -1217.07342                              | 0.16594                                  |   |  |                                      |

$$\text{PA}(\text{A}_{\text{M}}^{-}) - \text{PA}(\text{A}_{\text{ref}}^{-}) = \Delta[\text{PA}(\text{A}_{\text{M}}^{-})] = \left[ -\Delta E_{\text{i}}(\text{A}_{\text{M}}^{-})_{\text{n}}^{\text{Koop}}; \Delta E(\text{ei})(\text{A}_{\text{M}}^{-})_{\text{rex}}^{(\text{n})}; \Delta \text{BDE}(\text{A}_{\text{M}}^{-}) \right] \quad (4)$$

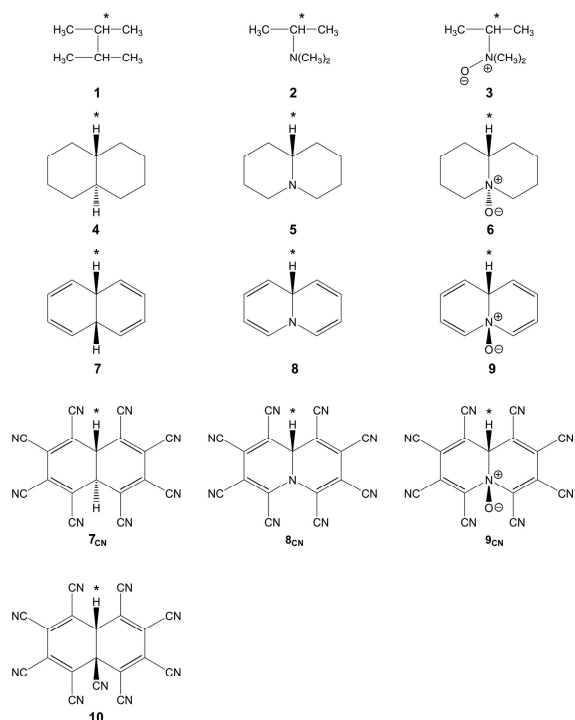
where subscripts M and ref denote the molecule under study and the reference molecule, respectively. The square parentheses in Eq. (4) imply summation of relative differences in the three triadic terms between the studied and reference molecule.

All calculations reported in this work were performed using the GAUSSIAN 03 suite of programs.<sup>72</sup>

## RESULTS AND DISCUSSION

### Gas Phase Acidity

The molecules studied in this work are depicted in Figure 1, and their B3LYP acidity parameters are presented in Table 1. Triadic resolution of the proton affinities of conjugate base anions is given in Table 2. It has to be said that deprotonation enthalpies calculated in a standard way using Eq. (1) and by the triadic analysis using Eq. (2) in principle give the same values. However, due to a rounding of numbers, these two sets of data could



**Figure 1.** Schematic representation of acids studied in this work. The proton of the acidic C–H bond is marked with an asterisk.

occasionally differ by a maximum of  $0.2 \text{ kcal mol}^{-1}$  in absolute terms, which is negligible for the present purpose.

Let us start our inspection of the data with the gas-phase results and the parent molecule 2,3-dimethylbutane (**1**), which has the gas-phase deprotonation enthalpy of  $406.1 \text{ kcal mol}^{-1}$ . It is somewhat more acidic than methane and propane, whose  $\Delta H_{\text{acid}}$  values are  $417.7$  and  $416.4 \text{ kcal mol}^{-1}$ , respectively, obtained at the same level of theory (Table 1). The available experimental results for these two molecules,  $418.0$  and  $415.6 \text{ kcal mol}^{-1}$ ,<sup>73</sup> illustrate excellent agreement and lend confidence to the theoretical method applied. It turns out that alkylation in the vicinity of the deprotonation centre enhances the acidity of the molecule. Selecting propane, deprotonated at the middle C-atom, as a reference molecule, triadic analysis yields  $\text{PA}(\mathbf{1}^-) - \text{PA}(\text{propane}^-) = [-5.8; -2.4; -2.0] \text{ kcal mol}^{-1} = -10.2 \text{ kcal mol}^{-1}$  (Table 2). It turns out that 2,3-dimethylbutane (**1**) is  $10.2 \text{ kcal mol}^{-1}$  more acidic than propane, predominantly because of the properties of its conjugate base mirrored through the Koopmans' term. In other words, it becomes harder to eject an electron within Koopmans' picture from  $\mathbf{1}^-$  anion upon alkyl substitution at the carbanionic centre, since the anion becomes more stable, which leads to an increase in acidity. Although all three terms within the triadic picture act in synergy, meaning that each of them individually leads to an increase in acidity of molecule **1** com-

**Table 2.** Proton affinities (PAs) of conjugate base anions  $\mathbf{A}^-$  studied here and their dissection into components according to the triadic formula (2) obtained by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) method. Orbital energies and the corresponding Koopmans' ionization energies were obtained by the HF/6-311+G(2d,p)//B3LYP/6-31G(d) scheme.

| acid                    | $E_i(\mathbf{A}^-)_{\text{Koop}}$ | $E_i(\mathbf{A}^-)_{\text{rel}}$ | $E(\text{e}i)_{\text{rel}}$ | BDE                    | $\text{PA}(\mathbf{A}^-)$ |
|-------------------------|-----------------------------------|----------------------------------|-----------------------------|------------------------|---------------------------|
| AH                      | $\text{kcal mol}^{-1}$            | $\text{kcal mol}^{-1}$           | $\text{kcal mol}^{-1}$      | $\text{kcal mol}^{-1}$ | $\text{kcal mol}^{-1}$    |
| methane                 | (27.9) <sub>1</sub>               | 0.2                              | 27.7                        | 104.2                  | 417.6                     |
| propane                 | (16.2) <sub>1</sub>               | -6.5                             | 22.7                        | 96.1                   | 416.2                     |
| <b>1</b>                | (22.0) <sub>1</sub>               | 1.7                              | 20.3                        | 94.1                   | 406.0                     |
| <b>2</b>                | (24.1) <sub>1</sub>               | -4.1                             | 28.2                        | 89.9                   | 407.6                     |
| <b>3</b>                | (42.8) <sub>1</sub>               | 13.1                             | 29.7                        | 96.5                   | 397.0                     |
| <b>4</b>                | (24.8) <sub>1</sub>               | 5.6                              | 19.2                        | 94.1                   | 402.1                     |
| <b>5</b>                | (25.1) <sub>1</sub>               | -2.1                             | 27.2                        | 87.9                   | 403.6                     |
| <b>6</b>                | (51.9) <sub>1</sub>               | 16.3                             | 35.6                        | 95.5                   | 392.8                     |
| <b>7</b>                | (23.3) <sub>1</sub>               | 25.7                             | -2.4                        | 57.0                   | 344.9                     |
| <b>8</b>                | (9.8) <sub>1</sub>                | -3.0                             | 12.8                        | 52.8                   | 369.4                     |
| <b>9</b>                | (44.1) <sub>1</sub>               | 46.8                             | -2.7                        | 61.5                   | 328.3                     |
| <b>7</b> <sub>CN</sub>  | (129.4) <sub>1</sub>              | 118.1                            | 11.3                        | 68.2                   | 263.7                     |
| <b>8</b> <sub>CN</sub>  | (116.0) <sub>1</sub>              | 105.0                            | 11.0                        | 58.3                   | 266.9                     |
| <b>9</b> <sub>CN</sub>  | (142.1) <sub>1</sub>              | 130.9                            | 11.2                        | 72.0                   | 254.7                     |
| <b>10</b> <sub>CN</sub> | (140.9) <sub>1</sub>              | 128.1                            | 12.8                        | 70.3                   | 255.8                     |

pared to propane, the Koopmans' contribution quantitatively prevails over the remaining two terms. Therefore, the properties of the final state are decisive for such trend in acidity of these two simple hydrocarbons. Thus, substitution of one hydrogen atom of the  $\text{CH}_2$  group in propane with an isopropyl fragment lowers the deprotonation enthalpy of the other by  $10.2 \text{ kcal mol}^{-1}$ .

If a propane molecule is substituted with a dimethylamino group at the central C-atom, as in 2-dimethylaminopropane (**2**), the resulting acidifying effect is much smaller (deprotonation enthalpy is higher) by almost  $2 \text{ kcal mol}^{-1}$ . Triadic analysis  $\text{PA}(\mathbf{2}^-) - \text{PA}(\mathbf{1}^-) = [-2.1; 7.9; -4.2] \text{ kcal mol}^{-1} = 1.6 \text{ kcal mol}^{-1}$  suggests that this is a consequence of the intermediate state effect, since the higher relaxation energy (by  $7.9 \text{ kcal mol}^{-1}$ ) following electron loss from the conjugate base of molecule **2** diminishes its acidity. This contribution is largely counterbalanced by the Koopmans' term and the homolytic bond dissociation energy. Still, the resulting acidity of **2** is lower by  $1.6 \text{ kcal mol}^{-1}$ . This result provides evidence for the unfavourable influence that dimethylamino group exhibits in the stabilization of the neighbouring carbanionic centre. This, however, is not surprising, because it is well-known that the dimethylamino group represents one of the strongest electron donating substituent, as confirmed, for example, by its  $\sigma_{\text{m}}$  ( $-0.16$ ) and  $\sigma_{\text{p}}$  ( $-0.83$ ) Hammett substituent con-

stands.<sup>74</sup> Interestingly, oxidation of the amino group in **2** to an *N*-oxide group, which leads to system **3**, has as a consequence an acidity enhancement of the latter by 10.6 kcal mol<sup>-1</sup> to a value of 397.1 kcal mol<sup>-1</sup>. Comparing these two molecules, one obtains PA(**3**<sup>-</sup>) - PA(**2**<sup>-</sup>) = [-18.7; 1.5; 6.6] kcal mol<sup>-1</sup> = -10.6 kcal mol<sup>-1</sup> implying that this difference in acidity is exclusively due to the properties of the final state. In addition, it becomes almost 20 kcal mol<sup>-1</sup> easier to strip off the proton from molecule **3** than it is from propane. This is a consequence of the interaction between the lone pair of an *N*-oxide group and the carbanionic centre, the latter having depleted electron density due to the strongly electronegative N-O group. In other words, the deprotonation energy of molecule **3** is reduced and the acidity is increased, compared to propane, since the negative charge developed at the deprotonated centre of **3**<sup>-</sup> is stabilized by the charge-dipole interaction. In quantitative terms, this favourable interaction in the final state of compound **3**, namely its conjugate base **3**<sup>-</sup>, is shown to be due to the Koopmans' term as PA(**3**<sup>-</sup>) - PA(propane) = [-26.6; 7.0; 0.4] kcal mol<sup>-1</sup> = -19.2 kcal mol<sup>-1</sup>.

It is of interest to examine cyclic analogues of molecules **1-3**, because molecular fragments forming systems **4** and **5** are very common features in a large variety of natural products including terpenes and alkaloids.<sup>75,76</sup> Cyclic *trans*-decahydronaphthalene (**4**) is a stronger acid than its non-cyclic counterpart **1** by a small but significant amount (4 kcal mol<sup>-1</sup>). The same trend holds here for the amino derivative quinolizidine **5** and its *N*-oxide offspring **6**. The former is again less acidic, while the latter is more acidic than the hydrocarbon **4**, essentially by the same amounts already found for molecules **1-3**. These acidity trends can be rationalized using the following set of relationships:

$$\text{PA}(\mathbf{4}^-) - \text{PA}(\mathbf{1}^-) = [-2.8; -1.1; 0.0] \text{ kcal mol}^{-1} = -3.9 \text{ kcal mol}^{-1} \quad (5a)$$

$$\text{PA}(\mathbf{5}^-) - \text{PA}(\mathbf{2}^-) = [-1.0; -1.0; -2.0] \text{ kcal mol}^{-1} = -4.0 \text{ kcal mol}^{-1} \quad (5b)$$

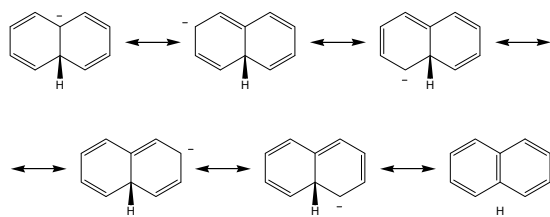
$$\text{PA}(\mathbf{6}^-) - \text{PA}(\mathbf{3}^-) = [-9.1; 5.9; -1.0] \text{ kcal mol}^{-1} = -4.2 \text{ kcal mol}^{-1} \quad (5c)$$

$$\text{PA}(\mathbf{5}^-) - \text{PA}(\mathbf{4}^-) = [-0.3; 8.0; -6.2] \text{ kcal mol}^{-1} = 1.5 \text{ kcal mol}^{-1} \quad (5d)$$

$$\text{PA}(\mathbf{6}^-) - \text{PA}(\mathbf{5}^-) = [-26.8; 8.4; 7.6] \text{ kcal mol}^{-1} = -10.8 \text{ kcal mol}^{-1} \quad (5e)$$

Interestingly, it turns out that cyclisation of molecules **1-3** into compounds **4-6**, having two saturated 6-membered rings, results in practically identical influences on the corresponding gas-phase acidity, being around 4 kcal mol<sup>-1</sup> to the benefit of the latter set of molecules. Although the relative contributions in triadic components are highest for *N*-oxide derivatives **3** and **6**, their acidity difference (Eq. (5c)) still matches the other two acidity variations (Eqs. (5a) and (5b)). We note in passing that only in the former pair of compounds does one observe a more pronounced contribution from the Koopmans' term and a relatively large unfavourable contribution from the relaxation energy. The triadic description given in Eqs. (5d) and (5e) is both quantitatively and qualitatively analogous to that already observed and expounded for the non-cyclic compounds **1-3** and needs no further explanation.

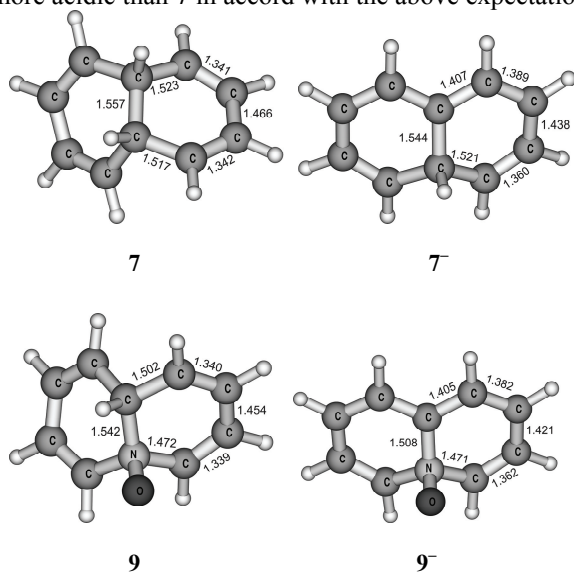
Let us now switch our attention to compounds **7-9**. It seems reasonable to assume that desaturation of single carbon-carbon chemical bonds around the perimeters of both six-membered rings in systems **4-6** will undoubtedly increase their acidity. This is indeed the case as we shall see in the following. 4b,8b-dihydronaphthalene (**7**) is already appreciably acidic. Its deprotonation enthalpy is 345.1 kcal mol<sup>-1</sup>. It is of interest to put this result into perspective by comparison with some known Brønsted mineral acids. For instance, molecule **7** is close in its acid strength to HNO<sub>2</sub> and H<sub>2</sub>S, whose experimentally determined gas-phase deprotonation enthalpies<sup>77</sup> are 340.2 ± 0.2 and 350.8 ± 2.9 kcal mol<sup>-1</sup>, respectively. It turns out that, by introducing four double bonds into system **4**, one gains as much as 57 kcal mol<sup>-1</sup> in acidity. This is not unexpected because deprotonation of compound **7** triggers anionic resonance, a stabilizing effect in the deprotonated form, which enhances the acidity. The latter can be visualized by Pauling's resonance structures depicted in Scheme 2, which include one aromatic naphthalene-like structure formed by anionic hyperconjugation with the neighbouring C(sp<sup>3</sup>)-H chemical bond.<sup>78</sup> More specifically, electron density is shifted away from the non-bonding p-orbital of the lone pair at the anionic centre and directed into a neighbouring C(sp<sup>3</sup>)-H antibonding orbital. As a result the latter C(sp<sup>3</sup>)-H bond should be weakened. This interaction is additionally prompted by the formation of the aromatic naphthalene 10 π-electrons pattern. The significant contribution of the latter resonance structure becomes evident by inspection of the appropriate geometrical and electronic parameters. Namely, in the neutral form of compound **7**, the lengths of the two equivalent C(sp<sup>3</sup>)-H bonds is 1.103 Å, while following deprotonation the remaining one is elongated to 1.126 Å (B3LYP/6-31G(d) results). In line with this, Mulliken's electron density partition analysis, performed at the same level of theory, reveals that the



**Scheme 2.** The resonance structures of anion  $7^-$ .

hydrogen atom attached to the  $C(sp^3)$  carbon atom bears a positive charge of 0.15 |e| in  $7$ , which is reduced to only 0.05 |e| in  $7^-$  upon deprotonation.

An amino nitrogen in the vicinity of the deprotonation centre prevents formation of such a structure, which is, to a great extent, evident in the corresponding higher deprotonation enthalpy. Namely, the quinolizine  $8$  is less acidic than molecule  $7$  by as much as 24.4 kcal mol<sup>-1</sup>. This is not surprising since deprotonated system  $8^-$  has antiaromatic number of 12  $\pi$ -electrons. It is worth saying that the quinolizine fragment is also a constituent fragment of many alkaloids present in nature.<sup>75,76</sup> Such large difference in acidity between molecules  $7$  and  $8$  is also evident between  $8$  and  $9$ , but in the opposite direction towards higher acidity. Interestingly, presence of the  $N^+-O^-$  dipole in  $9$  ensures the aromatic 10  $\pi$ -electron network over the molecular rim in  $9^-$ . The corresponding PRIMO orbital is stabilized contributing towards lower deprotonation enthalpy, which is a decisive effect. It is, therefore, expected that molecule  $9$ , carrying an  $N$ -oxide group will, by analogy with the results presented so far, exhibit the highest acidity of all compounds examined until now. Its deprotonation enthalpy is 328.5 kcal mol<sup>-1</sup>, making it 16.6 kcal mol<sup>-1</sup> more acidic than  $7$  in accord with the above expectation.



**Figure 2.** B3LYP/6-31G(d) optimized geometries of systems  $7$  and  $9$  together with their deprotonated forms. Relevant bond distances are given in Å.

A detailed insight into these pronounced acidity differences is offered by the following triadic descriptions:

$$PA(8^-) - PA(7^-) = [13.5; 15.2; -4.2] \text{ kcal mol}^{-1} = 24.5 \text{ kcal mol}^{-1} \quad (6a)$$

$$PA(9^-) - PA(8^-) = [-34.3; -15.5; 8.7] \text{ kcal mol}^{-1} = -41.1 \text{ kcal mol}^{-1} \quad (6b)$$

It is beneficial to compare these triads (6a) and (6b) with the corresponding differences presented in Eqs. (5d) and (5e). It turns out that, in conjugated compounds, introduction of an amino nitrogen next to the acidic C–H bond, as in  $8$ , results in lowering the acidity by 24.5 kcal mol<sup>-1</sup>, unlike in  $5$ , where the same electronic effect caused a change of only 1.5 kcal mol<sup>-1</sup>. Eq. (6a) suggests that this is a consequence not only of the higher relaxation energy in  $8$ , as was the case with molecule  $5$ . It is rather a combined effect of both the relaxation energy and the Koopmans' term. In other words, on top of their relaxation energy differences, the HOMO orbital in system  $7^-$ , which corresponds to the lone pair on the carbon atom to be protonated, is 13.5 kcal mol<sup>-1</sup> more stable than the HOMO of  $8^-$  because the anion of the former is more stable, which yields higher acidity of  $7$ . The conjugate base anion  $8^-$  suffers from an unfavourable repulsive interaction between negative charge at the deprotonated centre and the non-bonding lone pair of the neighbouring nitrogen atom. The fact that molecule  $9$  is by as much as 41.1 kcal mol<sup>-1</sup> more acidic than compound  $8$  is also striking and surprising. This electronic effect could be used in designing new very strong organic acids. As revealed, a simple oxidation of the nitrogen atom in the vicinity of the deprotonation centre to an  $N$ -oxide motif enhances acidity by more than 40 kcal mol<sup>-1</sup>. The lion's share of this enhancement in acidity can be traced to the final state effect as it becomes much harder to eject an electron from the HOMO of  $9^-$  than it is from the corresponding HOMO of  $8^-$ , supplemented additionally by a smaller relaxation energy in the neutral radical  $9^\bullet$ . On the other hand, in an analogous pair of compounds, molecule  $6$  is only 10.8 kcal mol<sup>-1</sup> more acidic than  $5$ . This is because the relaxation energy acts in the opposite direction (Eq. (5e)), meaning that if only this contribution was considered it would predict molecule  $5$  to be stronger an acid than compound  $6$ .

To strengthen further our conclusions regarding the acidity of molecules  $7$  and  $9$ , we now take a look at some relevant geometric parameters of these compounds and their conjugate bases  $7^-$  and  $9^-$ , respectively, in order to make these trends in acidity more obvious. It is evident from data presented in Figure 2

that deprotonation from  $sp^3$  carbon triggers anionic resonance in both conjugate bases. In these two compounds, practically all single chemical bonds examined are shortened, while all double bonds are elongated on going from neutral to deprotonated species. However, this effect is much more pronounced in the more acidic compound **9**. For example, consider the central chemical bond that is shared by both six-membered rings. In system **7**, its length is reduced from 1.557 to 1.544 Å after proton detachment, while in system **9**, the analogous chemical bond undergoes a much larger change (from 1.542 to 1.508 Å). It is also worth noting that in **9<sup>-</sup>** all six chemical bonds within the ring are closer to each other in length than they are in **7<sup>-</sup>**, providing further qualitative evidence of a stronger anionic resonance effect in the former anion. To give a more obvious idea of the high acidity of molecule **9** ( $\Delta H_{\text{acid}}(\mathbf{9}) = 328.5 \text{ kcal mol}^{-1}$ ), it is interesting to make again the comparison of its deprotonation enthalpy with those of some known Brønsted mineral acids. For instance, the acidity of compound **9** is between that of molecules  $\text{H}_3\text{PO}_4$  and  $\text{HNO}_3$ , which have gas-phase  $\Delta H_{\text{acid}}$  values of 330.5 and 324.5  $\text{kcal mol}^{-1}$ , respectively.<sup>77</sup> However, molecule **9** still does not qualify as a superacid since it is lower in acidity than sulphuric acid, which, according to a definition put forward by Gillespie and Peel,<sup>79</sup> is taken as a reference for solution-phase superacidity and whose deprotonation enthalpy is experimentally determined to be 306.3  $\text{kcal mol}^{-1}$ .<sup>77</sup> A more convenient and more practical definition of the superacidity threshold in the gas-phase was proposed by us,<sup>69</sup> taking perchloric acid  $\text{HClO}_4$  as a reference acid [ $\Delta H_{\text{acid}}(\text{HClO}_4) = 300 \text{ kcal mol}^{-1}$ ], calculated by a very accurate composite G3 methodology. The fact that molecule **9** is not a superacid employing either criterion can be easily overcome if we consider polycyano derivatives of molecules **7–9**, where dramatic increases in acidity occur (Table 1). Our earlier study of substituted methanes and cyclopentadienes showed that, for example,  $\text{NO}_2$  is a stronger acidifier than CN group for a singly substituted  $\text{C}(sp^3)$  carbon atom.<sup>20</sup> However, the three and five-fold cyanation and nitration of methane and cyclopentadiene, respectively, provide convincing evidence that the CN group is the most suitable substituent in polysubstituted systems, if high acidity is desired. Eight-fold cyanation of systems **7** and **8** lowers the corresponding  $\Delta H_{\text{acid}}$  values to around 265  $\text{kcal mol}^{-1}$ , being already very well below the superacidity threshold, the former compound (**7<sub>CN</sub>**) once more possessing the slightly lower deprotonation enthalpy. The highest place on the gas-phase acidity ladder is, nevertheless, occupied by compound **9<sub>CN</sub>**, whose deprotonation enthalpy, calculated by the B3LYP method, is the lowest yielding 254.8  $\text{kcal mol}^{-1}$ . To put this result into perspective, it is worth pointing out that compound **9<sub>CN</sub>** is 51.5  $\text{kcal mol}^{-1}$  stronger as an acid

than sulphuric acid in the gas-phase. Employing the thermodynamic equation  $\Delta G_{\text{acid}} = -R \cdot T \cdot \ln(K_{\text{acid}})$ , relating Gibbs free-energy with the equilibrium constant  $K_{\text{acid}}$  for the deprotonation reaction, one can estimate a difference in acidity between molecule **9<sub>CN</sub>** and  $\text{H}_2\text{SO}_4$ . Following that, it is straightforward that  $\Delta \log(K_{\text{acid}}) \approx \Delta \Delta H_{\text{acid}}/1.36$ , if the contribution arising from the  $\Delta(T\Delta S)$  entropy term can be neglected. Tacitly assuming that the latter is justified, it follows that, compared to  $\text{H}_2\text{SO}_4$ , compound **9<sub>CN</sub>** is around 38 orders of magnitude stronger as an acid in the gas-phase, which is a remarkable finding indeed. As already mentioned, another operational definition of the gas-phase superacidity threshold<sup>69</sup> should be the deprotonation enthalpy of perchloric acid  $\text{HClO}_4$ , which is 300  $\text{kcal mol}^{-1}$ . If this criterion is accepted and adopted, then molecule **9<sub>CN</sub>** is 33 orders of magnitude more acidic than the threshold of superacidity. It is an even stronger acid than the nonacyano derivative of molecule **7** (molecule **10** in Figure 1), whose acidity is calculated to be 255.9  $\text{kcal mol}^{-1}$ , despite the fact that the latter molecule possesses one more cyano group on its perimeter. Such a strong acidifying effect of cyano groups will be further illustrated by triadic analysis of compounds **7<sub>CN</sub>**, **8<sub>CN</sub>** and **9<sub>CN</sub>**. The data given in Table 2 yield:

$$\text{PA}(\mathbf{7}_{\text{CN}}^-) - \text{PA}(\mathbf{7}^-) = [-106.1; 13.7; 11.2] \text{ kcal mol}^{-1} = -81.2 \text{ kcal mol}^{-1} \quad (7a)$$

$$\text{PA}(\mathbf{8}_{\text{CN}}^-) - \text{PA}(\mathbf{8}^-) = [-106.2; -1.8; 5.5] \text{ kcal mol}^{-1} = -102.5 \text{ kcal mol}^{-1} \quad (7b)$$

$$\text{PA}(\mathbf{9}_{\text{CN}}^-) - \text{PA}(\mathbf{9}^-) = [-98.0; 13.9; 10.5] \text{ kcal mol}^{-1} = -73.6 \text{ kcal mol}^{-1} \quad (7c)$$

It appears that several observations are quite interesting and worth being pointed out. First of all, it is evident that the cyano groups exhibit the largest acidifying effect in **8<sub>CN</sub>**, where it equals 102.5  $\text{kcal mol}^{-1}$ . However, despite that, the molecule **8<sub>CN</sub>** is the least acidic system of all three octacyano derivatives. Secondly, it is quite obvious that such an enormous substituent effect is predominantly due to the final state effect and the higher Koopmans' ionization energy of anions in all three cases. This means that the HOMO orbital is much lower in energy and that the negative charge is better dispersed in polycyano derivatives, resulting in anions that are more stable. This is a consequence of the anionic resonance in deprotonated forms, which is efficiently assisted and considerably enhanced by a concerted resonance effect of numerous CN groups.



Finally, let us use the data presented in Tables 1 and 2 to estimate the acidifying effect of an *N*-oxide group in the gas-phase upon substitution of the C(sp<sup>3</sup>)-H fragment in the vicinity of the deprotonation centre with an N-O motif. For that purpose we shall consider the following relationships:

$$\text{PA}(\mathbf{3}^-) - \text{PA}(\mathbf{1}^-) = [-20.8; 9.4; 2.4] \text{ kcal mol}^{-1} = -9.0 \text{ kcal mol}^{-1} \quad (8a)$$

$$\text{PA}(\mathbf{6}^-) - \text{PA}(\mathbf{4}^-) = [-27.1; 16.4; 1.4] \text{ kcal mol}^{-1} = -9.3 \text{ kcal mol}^{-1} \quad (8b)$$

$$\text{PA}(\mathbf{9}^-) - \text{PA}(\mathbf{7}^-) = [-20.8; -0.3; 4.5] \text{ kcal mol}^{-1} = -16.6 \text{ kcal mol}^{-1} \quad (8c)$$

$$\text{PA}(\mathbf{9}_{\text{CN}}^-) - \text{PA}(\mathbf{7}_{\text{CN}}^-) = [-12.7; -0.1; 3.8] \text{ kcal mol}^{-1} = -9.0 \text{ kcal mol}^{-1} \quad (8d)$$

It appears that a simple transformation of a C(sp<sup>3</sup>)-H group directly attached to the deprotonation site into an *N*-oxide group always results in an increase in acidity. This acidity enhancement is in all four cases predominantly caused by the features of deprotonated anion mirrored through Koopmans' ionization energies. In open and cyclic saturated compounds, this beneficial high contribution from Koopmans' term is diminished by the relaxation energy and very slightly by the bond dissociation energy to yield an acidity difference of around 9 kcal mol<sup>-1</sup> in both instances. On the other hand, a different situation occurs in unsaturated compound **7** and **9**. Here, the appropriate contribution from the final state effect is as large as in the previous two pairs of molecules. What is different is that the relaxation energies of both deprotonated acids are practically the same which, when combined, leads to an acidity difference of as much as 16.6 kcal mol<sup>-1</sup>. Polycyanated compounds **7**<sub>CN</sub> and **9**<sub>CN</sub> demonstrate the same pattern in the relaxation energies as their unsubstituted derivatives. Nevertheless, differences in their Koopmans' terms are much smaller, which is intuitively expected since steric crowding of eight cyano groups does not allow for a maximally efficient resonance stabilization of the negative charge. Taken all together, the acidity variation is reduced back to 9.0 kcal mol<sup>-1</sup> in favour of an N-O derivative. It can be safely concluded that the gas-phase acidifying effect of an *N*-oxide group in the vicinity of deprotonation centre is estimated to be in the range of 9–17 kcal mol<sup>-1</sup>. The magnitude of this effect is quite large and significant. To illustrate that, we could consider the effect that one cyano group exhibits on the gas-phase acidity of phenol and benzoic acid, which

were paradigmatic cases for the establishment of famous linear free-energy relationships and derivation of a useful sets of substituent constants.<sup>74</sup> Substitution of benzoic acid and phenol by a CN group in the *para*-position enhances their gas-phase deprotonation enthalpies by 9.9 (Ref. 22) and 16.6 (Ref. 21) kcal mol<sup>-1</sup>, respectively, as demonstrated earlier. Interestingly, the acidifying effect of an *N*-oxide group falls within the same range.

### Acidity in DMSO

To make these results closer and more familiar to experimental chemists, it is of great interest to estimate acidity constants of systems investigated in solution. One of the most suitable solvents is dimethyl sulfoxide (DMSO) which possesses many useful properties for acid-catalysed transformations due to being nonprotic, and of low polarity and large dielectric constant. This makes it a practical solvent in technological processes as pointed out in many papers published by Bordwell and his coworkers.<sup>80</sup> One of the approaches aiming at predicting p*K*<sub>a</sub> values is offered by the use of the quite accurate complete basis set CBS-QB3 method in conjunction with the polarizable continuum models, which gives good agreement with experiment as seen by root-mean-square errors of 0.4 p*K*<sub>a</sub> units.<sup>81,82</sup> Unfortunately, this approach is not applicable to the large polycyano systems studied here. Another less costly but successful method is provided by the hybrid cluster-continuum model, proposed by Pliego and Riveros, which proved useful in terms of predicting p*K*<sub>a</sub> values for a large variety of organic acids in different solvents, but yet again only for smaller systems.<sup>83,84</sup> Our approach is based on the proton transfer reaction (9) between an acid AH and solvent DMSO molecule, which takes place in solution:



and we employ the isodensity polarized continuum model (IPCM)<sup>85,86</sup> at the B3LYP level described earlier.<sup>87</sup> The enthalpies of proton transfer  $\Delta_r H_{\text{DMSO}}$  are very well correlated with the experimental p*K*<sub>a</sub> values for a wide variety of neutral organic C-H acids resulting in an empirical linear correlation:<sup>87</sup>

$$\text{p}K_a(\text{theor}) = 0.661 \cdot \Delta_r H_{\text{DMSO}} - 7.7 \quad (10)$$

with the average absolute error of 1.1 (in p*K*<sub>a</sub> units) and *R*<sup>2</sup> = 0.985. Hence, the predicted acidities in DMSO should be sufficiently reliable. It is worth keeping in mind that, as with gas-phase  $\Delta H_{\text{acid}}$  values, stronger acids have smaller numerical p*K*<sub>a</sub> values.

The  $\Delta_r H_{\text{DMSO}}$  values, together with the corresponding p*K*<sub>a</sub> data are also presented in Table 1. It is interest-

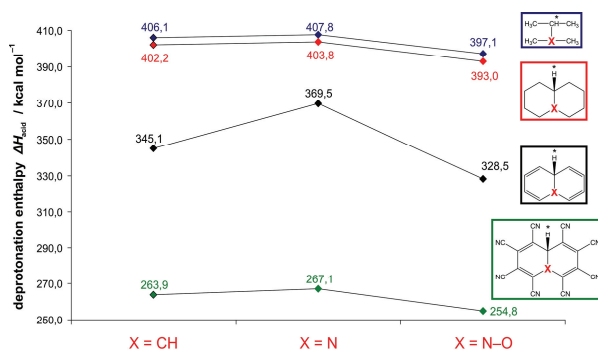
ing to observe that the trend in the gas-phase acidities is very well preserved in solution, meaning that the more acidic the molecule in the gas-phase is, at the same time, the more acidic it is in DMSO. The only exception is methane, which, among molecules studied, is the weakest acid in the gas-phase, while in DMSO solution there are seven molecules with larger  $pK_a$  values, all of them being saturated compounds **1–6**. This is a consequence of the profound solvation of  $\text{CH}_3^-$  anion that DMSO molecules exhibit, not hindered by the presence of any bulky substituents. This is in harmony with an early observation of Taft and Bordwell,<sup>88</sup> who concluded that the solvation effects stabilize the smaller anions of the CH acids in DMSO more than the larger ones. It should be mentioned that the estimated  $pK_a$  value for methane is in good agreement with the experimental result of Bordwell, who roughly estimated it to be around  $pK_a \sim 56$ .<sup>80</sup> It is also notable that  $\Delta_r H_{\text{DMSO}}$  enthalpies are negative for polycyano substituted molecules, which shows that proton transfer to solvent molecules is particularly favored for these molecules. Concomitantly, the matching  $pK_a$  values are well below zero. Unsaturated compounds **7–9** show the highest acidity in DMSO of all unsubstituted compounds. Like in the gas-phase, relative changes in the  $pK_a$  values on going from hydrocarbon to an amino derivative then to a compound containing an *N*-oxide group are the largest in this class of compounds. Insertion of amino nitrogen in the neighborhood of the deprotonation centre, as in **8**, lowers the acidity by 16  $pK_a$  units, while oxidation of the latter to an *N*-oxide enhances the  $pK_a$  value by as much as 27 units to a value of 10.3 for molecule **9**. Polycyano derivatives represent the most powerful acids studied here and are of the greatest interest. Making use of Eq. (10), one arrives at  $pK_a$  values of  $-15.6$ ,  $-14.4$  and  $-20.2$  for systems **7<sub>CN</sub>**, **8<sub>CN</sub>** and **9<sub>CN</sub>**, respectively (Table 1). Hence, it is fair to say that the multiply-substituted cyano hydrocarbons studied here represent superacids, both in the gas-phase and in dimethyl sulfoxide. We

note in passing that  $pK_a$  value for sulphuric acid in the same solvent is  $pK_a(\text{H}_2\text{SO}_4)_{\text{DMSO}} = 1.99$ , from which it follows that compound **9<sub>CN</sub>** is roughly 22 orders of magnitude ( $pK_a$  units) stronger as an acid in DMSO than this reference acid, which is remarkable indeed. The corresponding difference in the gas-phase was even larger (38 orders of magnitude) as discussed earlier. Finally, in order to assess acidifying effect of an *N*-O group in DMSO, it is worth pointing out the differences in  $pK_a$  values between molecules **3** and **1**, **6** and **4**, **9** and **7** as well as between **9<sub>CN</sub>** and **7<sub>CN</sub>**, which, in the same order, are  $-5.6$ ,  $-6.2$ ,  $-11.2$  and  $-4.6$ . Therefore, it can be safely concluded that the presence of an *N*-oxide group exerts acidifying effect of 5–11  $pK_a$  units in DMSO.

## CONCLUSION

In conclusion, we would like to point out that the hydrocarbons *trans*-decahydronaphthalene (**4**) and 4b,8b-dihydronaphthalene (**7**) examined here were selected because they are important structural features of many alkaloids.<sup>75,76</sup> It was shown, using very efficient and quite reliable DFT B3LYP/6–311+G(2d,p)//B3LYP/6–31G(d) methods that these molecules are moderately acidic in the gas-phase and in DMSO solution. However, it has to be reiterated that **7** is more acidic in the gas-phase deprotonation enthalpy by 57 kcal mol<sup>-1</sup> and by 39 units on the  $pK_a$  ladder in DMSO. It was also demonstrated that substitution of a vicinal C(sp<sup>3</sup>)-H fragment with an amino nitrogen results in a reduction of acidity. Triadic analysis revealed that this is due to the intermediate state effect as the relaxation energy following electron departure from the conjugate base of the amino-derivative is larger, which makes it less acidic. Starting from that, succeeding oxidation of a nitrogen atom to an *N*-oxide moiety has the consequence of enhancing the acidity in both gas and condensed phases, even surpassing at the same time the acidity of the unsubstituted hydrocarbons. The reason for that is ascribed to the final state effects of the anions, which benefit from a favourable interaction between the negative charge and the neighbouring dipole of the *N*-O group. The latter interaction leads to increased Koopmans' ionization energies. These acidity trends are graphically presented in Figure 3.

Record values in acidity are obtained upon multiple substitution by CN groups yielding  $\Delta H_{\text{acid}}$  and  $pK_a$  values very well below the superacidity ceiling provided either by sulphuric acid or by perchloric acid. More precisely, the most potent superacids studied in this work are octacyano 4b,8b-dihydronaphthalene (**7<sub>CN</sub>**), octacyanoquinolizine (**8<sub>CN</sub>**), octacyanoquinolizine *N*-oxide (**9<sub>CN</sub>**) and nonacyanoquinolizine *N*-oxide (**10**)



**Figure 3.** Acidifying effect of the neighbouring group X (X = CH, N, N-O) on the acidity of the adjacent C-H chemical bond.

with  $\Delta H_{\text{acid}}$  values of 263.9, 267.1, 254.8 and 255.9 kcal mol<sup>-1</sup> and  $\text{p}K_{\text{a}}$  values of -15.6, -14.4, -20.2 and -19.3, in the same order. It follows that compounds **9**<sub>CN</sub> and **10** are around 38 orders of magnitude stronger as acids than H<sub>2</sub>SO<sub>4</sub> in the gas-phase. At the same time, they are by around 22 orders of magnitude more potent as acids than sulphuric acid in DMSO. If we accept another threshold of superacidity<sup>69</sup>  $\Delta H_{\text{acid}}(\text{HClO}_4) = 300.0$  kcal mol<sup>-1</sup>, it turns out that molecules **7**<sub>CN</sub>, **8**<sub>CN</sub>, **9**<sub>CN</sub> and **10** are by 26, 24, 33 and 33 orders of magnitude stronger gas-phase superacids than perchloric acid. The origin of such dramatic amplification of the acidity in multiply-cyanated derivatives is identified through triadic analysis as due to an increase in the anionic resonance of the resulting conjugate bases, which is further prompted by numerous CN groups. This interaction stabilizes the principal molecular orbital (HOMO in all cases here) making it less susceptible to electron ejection in our triadic picture, leading to enhanced acidities. Since these anions have a very effectively diffused electron density of the excess electron, they have low nucleophilicity. This means that their reactivity in solution should be diminished and that they might be useful as ligands of very low coordination power, which could be helpful in the design of new materials.

Finally, it is useful to stress that an *N*-oxide group in the vicinity of the deprotonation centre exerts an acidifying effect on the C-H acidity of around 9 kcal mol<sup>-1</sup> in the  $\Delta H_{\text{acid}}$  in the gas-phase and of around 5  $\text{p}K_{\text{a}}$  units in DMSO. The only exception is offered by cyclic unsaturated compounds **7** and **9** where this effect is quite large, being approximately 17 kcal mol<sup>-1</sup> and 11  $\text{p}K_{\text{a}}$  units, respectively. This structural effect could be successfully applied when designing new organic superacids. To the best of our knowledge, this is the first study relating electronic effects of *N*-oxide functionality on the acidity constants of structural features present in many biologically important compounds.

In the light of the high availability of such and similar unsubstituted compounds scrutinized here,<sup>1</sup> and well documented synthetic pathways of polycyanation of organic molecules,<sup>89-97</sup> we strongly recommend synthesis of polycyano derivatives **7**<sub>CN</sub>, **8**<sub>CN</sub>, **9**<sub>CN</sub> and **10**. This would provide novel and exceptionally acidic compounds which could improve many known synthetic protocols and make new chemical transformations possible. Also, such and similar compounds would contribute towards bridging the gap between the ladders of (super)acids and (super)bases into one continuous scale.

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## SAŽETAK

### Utjecaj N–O skupine na povećanje kiselosti – koristan strukturni motiv pri povećanju kiselosti prema superkiselim vrijednostima

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DFT računi provedeni na *trans*-dekahidronaftalenu i 4b,8b-dihidronaftalenu, važnim strukturnim podjedinicama mnogih alkaloida, pokazali su da se radi o blago kiselim ugljikovim kiselinama u plinskoj fazi i u DMSO otopini. Zamjena susjedne C(sp<sup>3</sup>)-H grupe direktno vezane na kiseli centar s dušikovim atomom smanjuje kiselost u obje faze. Oksidacija spomenutog dušikovog atoma do N-oksida znatno povećava kiselost. Ovakav utjecaj N–O grupe na kiselost susjedne C–H veze iznosi između 9–17 kcal mol<sup>-1</sup> u entalpiji deprotoniranja u plinskoj fazi, te između 5–11 pK<sub>a</sub> jedinica u DMSO-u. Stoga, ovakav elektronski efekt može se upotrijebiti pri dizajnu novih snažnih kiselina i superkiselina. Uzrok ovakvog povećanja kiselosti je, uz pomoć trihotomne formule, identificiran kao posljedica svojstava konačnog stanja konjugirane baze, pri čemu spojevi s N–O funkcionalnom skupinom pokazuju izraženu kiselost uslijed povoljne naboj-dipol interakcije između negativnog naboja i N–O grupe. Dramatično povećanje kiselosti primjećeno je uslijed policijiranja spomenutih spojeva. Na primjer, oktacijanokinolizin N-oksid je izuzetno jaka superkiselina s vrijednostima  $\Delta H_{\text{acid}} = 254.8 \text{ kcal mol}^{-1}$  i  $\text{p}K_{\text{a}} = -20.2$ , te je sinteza toga spoja potrebna i snažno ju preporučamo. Trihotomna analiza je pokazala da je ovako snažno povećanje kiselosti kod policijano-spojeva posljedica snažne anionske rezonancije u deprotoniranim formama dodatno potpomognute prisustvom brojnih CN skupina, koje stabiliziraju odgovarajuću principijelnu PRIMO molekulsku orbitalu.