

# Engineering exceptionally strong oxygen superbases with 1,8-diazanaphthalene di-*N*-oxides†

Ines Despotović and Robert Vianello\*

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DFT calculations revealed that 1,8-diazanaphthalene di-*N*-oxides provide extraordinary oxygen superbases, whose gas-phase and acetonitrile basicities surpass those of classical naphthalene-based nitrogen proton sponges. Such high basicity is almost entirely a consequence of a large strain-induced destabilization in neutral forms, while only a small contribution is offered by the intramolecular [O–H···O]<sup>−</sup> hydrogen bonding upon protonation.

For more than four decades, the design and synthesis of neutral organic superbases have attracted much attention<sup>1–3</sup> because their unique characteristics allow deprotonation of a wide range of weak acids resulting in weakly coordinated and highly reactive anionic species. Although usually weaker than their inorganic counterparts, uncharged organobases have become broadly used standard reagents in organic synthesis. Their practical usefulness involving mild reaction conditions, very good stability at low temperatures, efficient solubility in most organic solvents, and excellent recycling possibilities makes them superior to their ionic alternatives,<sup>2,4</sup> having an expansive range of applications in base-mediated transformations,<sup>2</sup> carbon dioxide storage,<sup>5,6</sup> and polymerization.<sup>7</sup>

In 1968, Alder's discovery of the exceedingly high basicity of 1,8-bis(dimethylamino)naphthalene<sup>8</sup> (DMAN **1**, Fig. 1) spurred interest in the area of neutral organic superbases, in particular, promoting a quest to create compounds with the highest basicity.<sup>1–3</sup> Since then, numerous diverse new superbases containing amines, imines, guanidines, phosphazenes, quinoimines, or cyclopropenimines have been synthesized, mostly by Staab,<sup>9</sup> Alder,<sup>10</sup> Schwesinger,<sup>11</sup> Verkade,<sup>12</sup> and other groups,<sup>13</sup> and their properties broadly characterized by means of experimental and computational methods. The extensive investigations by Koppel, Leito and their co-workers<sup>14</sup> should be highlighted, since they include both experimental and theoretical results in designing,

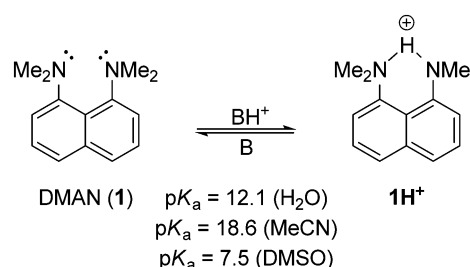


Fig. 1 Basicity of 1,8-bis(dimethylamino)naphthalene.

preparing and measuring basicities of a huge variety of organic bases and superbases.

A general feature of a large number of organic superbases is the presence of two (or more) basic centers that are placed close to each other and oriented in such a way that the incoming proton forms a strong stabilizing intramolecular hydrogen bond (Fig. 1). The favorable influence of multiple hydrogen bonds on enhancing the basicity (and acidity) of simple organic amines and alcohols has recently been particularly emphasized by Bachrach<sup>15</sup> and Kass.<sup>16</sup> Basic centers are usually nitrogen moieties due to their strongly attractive interactions with protons, since nitrogen lone pair orbitals are energetically higher-lying compared to, for example, those of oxygen in ethers and ketones,<sup>17</sup> in line with reports that ketones<sup>18</sup> and aldehydes<sup>19</sup> are less basic than the corresponding imines.<sup>20</sup> Yet, herein we wish to demonstrate that the oxygen basicity of *N*-oxides surpasses that of the related nitrogen compounds and that molecules containing two neighboring *N*-oxide moieties are several orders of magnitude stronger bases than the analogous nitrogen proton sponges, approaching a gas-phase proton affinity of 300 kcal mol<sup>−1</sup>, proposed as a borderline between superbases and hyperbases.<sup>21</sup> The series of selected organic bases involving pyridine and naphthalene scaffolds is shown in Fig. 2.

Gas-phase proton affinities (PAs) and basicities (GBs) were calculated as protonation enthalpies and free-energies, respectively, employing the M06-2X/6-311++G(2df,2pd)//M06-2X/6-31+G(d,p) level of theory.<sup>1</sup> Atomic charges were obtained through the Natural Bond Orbital<sup>22</sup> (NBO) analysis at the M06-2X/6-31+G(d,p) level. Absolute

Quantum Organic Chemistry Group, Ruđer Bošković Institute, Bijenička cesta 54, HR-10000 Zagreb, Croatia. E-mail: robert.vianello@irb.hr

† Electronic supplementary information (ESI) available: Cartesian coordinates of all investigated systems and NBO charge analysis of molecules **1a–1d** and **2a–2d** and their protonated forms. See DOI: 10.1039/c4cc05125d

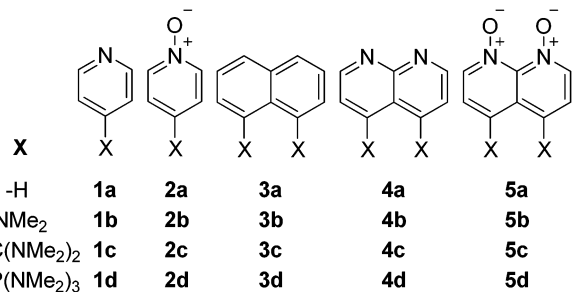


Fig. 2 Schematic representation of investigated bases.

solution phase  $pK_a$  values in acetonitrile were calculated from the gas-phase basicities corrected for the solvation free-energies attained through the (SMD)/M06-2X/6-31+G(d,p)/M06-2X/6-31+G(d,p) model and utilizing the experimental value of  $\Delta G_{\text{SOL}}(\text{H}^+)_{\text{MeCN}} = -254.3$  kcal mol<sup>-1</sup>.<sup>23</sup> All calculations were performed using the Gaussian 09<sup>24</sup> software.

Calculated basicity constants are given in Table 1. It is a well established fact that simple pyridines are stronger solution-phase bases than their *N*-oxides. This has been experimentally demonstrated for various solvents, as, for example,  $pK_a$  values of **1a** and **2a** assume 5.21 and 0.79 (in water),<sup>25</sup> 11.64 and 9.03 (in acetonitrile),<sup>26,27</sup> 5.35 and 2.69 (in methanol),<sup>27</sup> 3.57 and 1.68 (in DMF),<sup>28</sup> and 11.54 and 8.55 (in propylene carbonate),<sup>29</sup> respectively. However, the pyridine *N*-oxide **2a** is intrinsically a slightly stronger base than pyridine **1a**, with differences of 0.1 and 0.6 kcal mol<sup>-1</sup> in the respective PA and GB values. The same holds for all *para*-substituted derivatives **1b–1d** and **2b–2d** investigated here, culminating with  $\Delta\text{PA}(\mathbf{2d-1d}) = 1.2$  kcal mol<sup>-1</sup>. Our calculated values for **2a** are in excellent agreement with experimental values,  $\text{PA}(\mathbf{2a})_{\text{EXP}}$  being 220.7 and  $\text{GB}(\mathbf{2a})_{\text{EXP}}$  being 213.4 kcal mol<sup>-1</sup>,<sup>30</sup> lending credence to

Table 1 Calculated gas phase proton affinities PAs and basicities GBs (in kcal mol<sup>-1</sup>), together with  $pK_a$  values in acetonitrile solution (in  $pK_a$  units). The site of the protonation is indicated in the column preceding values<sup>a</sup>

	Most favorable protonation				Alternative protonation			
	Site	PA	GB	$pK_a$	Site	PA	GB	$pK_a$
<b>1a</b>	N <sub>pyr</sub>	220.8	213.1	11.3				
<b>1b</b>	N <sub>pyr</sub>	238.9	230.6	16.7	N <sub>am</sub>	212.0	203.9	6.0
<b>1c</b>	N <sub>pyr</sub>	245.6	237.7	17.6	N <sub>gv</sub>	240.2	231.8	18.0
<b>1d</b>	N <sub>pyr</sub>	252.4	245.6	20.5	N <sub>ph</sub>	246.4	239.1	20.3
<b>2a</b>	O	220.9	213.7	7.6				
<b>2b</b>	O	240.5	232.9	14.6	N <sub>am</sub>	210.7	202.9	6.1
<b>2c</b>	O	245.8	238.5	14.9	N <sub>gv</sub>	237.5	229.7	17.3
<b>2d</b>	O	253.6	246.0	16.4	N <sub>ph</sub>	243.7	234.6	17.4
<b>3b</b>	N <sub>am</sub>	241.4	234.2	18.3				
<b>3c</b>	N <sub>gv</sub>	260.3	251.4	24.7				
<b>3d</b>	N <sub>ph</sub>	272.6	265.1	32.7				
<b>4a</b>	N <sub>pyr</sub>	228.0	220.4	9.8				
<b>4b</b>	N <sub>pyr</sub>	250.1	242.6	19.2	N <sub>am</sub>	227.1	220.7	11.1
<b>4c</b>	N <sub>pyr</sub>	260.4	251.9	19.9	N <sub>gv</sub>	253.2	244.3	22.8
<b>4d</b>	N <sub>pyr</sub>	270.2	262.2	22.2	N <sub>ph</sub>	264.6	256.8	26.1
<b>5a</b>	O	243.3	235.1	18.3				
<b>5b</b>	O	267.9	259.6	31.7	N <sub>am</sub>	228.8	221.9	12.7
<b>5c</b>	O	279.0	269.4	31.1	N <sub>gv</sub>	249.6	239.3	19.8
<b>5d</b>	O	294.2	285.4	36.5	N <sub>ph</sub>	266.4	255.4	24.3

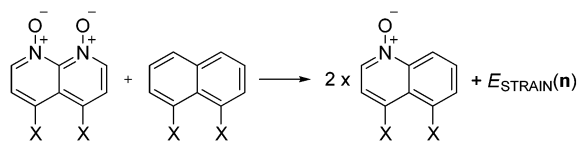
<sup>a</sup> N<sub>pyr</sub>, N<sub>am</sub>, N<sub>im</sub>, N<sub>ph</sub> and O stand for the pyridine nitrogen, amino nitrogen, imino nitrogen, phosphazeno nitrogen, and oxygen of an *N*-oxide group, respectively.

the computational methodology used here. Protonation of **2a** yields the O–H bond perpendicular to the aromatic ring, and it is a general feature of all investigated mono *N*-oxides **2a–2d**, in line with previous reports.<sup>31</sup> The planar **2aH**<sup>+</sup> conformation with the in-plane O–H bond is a transition state structure 1.9 kcal mol<sup>-1</sup> higher in energy. Interestingly, the N–O distance becomes elongated upon protonation, from 1.274 in **2a** to 1.371 Å in **2aH**<sup>+</sup>, which leaves more of the initial positive charge on nitrogen together with the excess positive charge after protonation for the resonance stabilization within the aromatic ring (Table S1, ESI<sup>†</sup>). The variation of the nitrogen charges in **1a–1d** is negative, implying that N gains 0.03, 0.05, 0.07 and 0.06 electrons when it binds to the proton, respectively, in full agreement with the results obtained by the QTAIM charge analysis.<sup>32</sup> This counterintuitive observation indicates that the formation of the N–H<sup>+</sup> bond induces a full rearrangement of the electron density within the aromatic ring, so that, following protonation, all five C-atoms donate their electrons to nitrogen (Table S1, ESI<sup>†</sup>). These variations are even larger in *N*-oxides **2a–2d**, where nitrogen gains 0.10, 0.12, 0.13 and 0.13 electrons upon protonation, respectively, which enhances cationic resonance stabilization, thus providing a principal reason for the higher intrinsic basicity of *N*-oxides compared to pyridines.

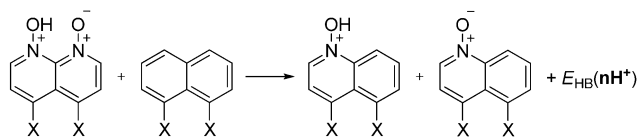
Although dimethylamino, guanidino and phosphazeno moieties are highly basic motifs on their own,<sup>1</sup> in systems **2b–2d** the most favorable protonation site is the *N*-oxide, yielding PA values of 240.5, 245.8 and 253.6 kcal mol<sup>-1</sup>, respectively, being 29.8, 8.3 and 9.9 kcal mol<sup>-1</sup> higher than those corresponding to the substituent nitrogen protonation. This suggests that, in **2b–2d**, the latter groups play a role in promoting the *N*-oxide basicity by participating in the resonance stabilization, rather than being the sites of the H<sup>+</sup> attack.

As mentioned, 1,8-bis(dimethylamino)naphthalene **3b** is widely accepted as the first superbase,<sup>8</sup> and its proton affinity is taken as a threshold of superbasicity. The calculated  $\text{PA}(\mathbf{3b})$  of 241.4 kcal mol<sup>-1</sup> is further increased by substituting  $-\text{NMe}_2$  groups with more basic moieties, as in **3c** and **3d**,<sup>13a</sup> whose proton affinities assume  $\text{PA}(\mathbf{3c}) = 260.3$  and  $\text{PA}(\mathbf{3d}) = 272.6$  kcal mol<sup>-1</sup>, being in a fair agreement with the earlier computed values of 257.7<sup>33</sup> and 274.0 kcal mol<sup>-1</sup>,<sup>13b</sup> respectively. Replacing the C–H groups at 4- and 5-positions on the naphthalene ring with the nitrogen atoms leads to **4b–4d**, which change their most favorable protonation site to the pyridine nitrogen. Interestingly enough, the first two cases, **4b** and **4c**, are even stronger bases than parent compounds **3b** and **3c**, exhibiting an increase in PA values of 8.3 and 0.1 kcal mol<sup>-1</sup>, respectively. This is surprising, since 1,8-diazanaphthalene **4a** is only a moderately strong base with  $\text{PA}(\mathbf{4a}) = 228.0$  kcal mol<sup>-1</sup>, particularly when compared with the basicities of **3b–3d**, which are much higher. Moreover, the PA of **4a** is comparable to that of *N,N*-dimethylaniline (PA = 224.9 kcal mol<sup>-1</sup>),<sup>30</sup> and considerably lower than for *N''*-phenyl-*N,N,N'*-tetramethylguanidine (PA = 248.2 kcal mol<sup>-1</sup>).<sup>30</sup> This suggests that in **4b** and **4c** the strong electron donating ability of  $-\text{NMe}_2$  and  $-\text{N}=\text{C}(\text{NMe}_2)_2$  substituents outperforms their high intrinsic basicity and the favorable  $[\text{N}-\text{H} \cdots \text{N}]^+$  hydrogen bond, and promotes the pyridine protonation. In **4d**, this is exhibited to a smaller degree making it 2.4 kcal mol<sup>-1</sup> less basic than **3d**.

*N*-Oxidation of **4a–4d** leads to **5a–5d**. System **5a** is appreciably basic,  $PA(5a) = 243.3 \text{ kcal mol}^{-1}$ , being  $22.4 \text{ kcal mol}^{-1}$  more basic than monomeric pyridine *N*-oxide **2a**, and  $15.3 \text{ kcal mol}^{-1}$  stronger base than 1,8-diazanaphthalene **4a**. Basicity of **5a** is dramatically enhanced by attaching substituents to 4- and 5-positions as the calculated PAs of **5b–5d** assume 267.9, 279.0 and  $294.2 \text{ kcal mol}^{-1}$ , respectively, spanning an increase of  $50.9 \text{ kcal mol}^{-1}$  and 18.2  $pK_a$  units. To put these numbers into perspective, let us mention that by making 4,5-bis(*N,N*-dimethylamino) substitution on **3b**, yielding 1,4,5,8-tetrakis(dimethylamino)naphthalene, one increases the  $pK_a$  value in DMSO only by 2.3 units,<sup>34</sup> whereas Himmel and co-workers reported that the  $pK_a$  of 1,4,5,8-tetrakis(tetramethylguanidino)naphthalene should be “in the same region as that of **3c**”.<sup>35</sup> In contrast, moving from **3b** to **5b**, one amplifies the basicity by 13.4  $pK_a$  units in MeCN. In analogy with classical proton sponges, the pronounced basicity of **5a–5d** should be a consequence of an interplay of two contributions: (a) strong electron repulsions between two neighboring negatively charged oxygen atoms, which destabilize the initial base, and (b) the formation of a favorable  $[O-H \cdots O]^-$  hydrogen bonding, which relieves steric strain and stabilizes conjugate acid. Both contributions could be quantitatively estimated by the following two homodesmotic reactions:<sup>36</sup>



and



Here,  $E_{\text{STRAIN}}(n)$  gives the steric interference of two basic N=O groups in **5a–5d**, whereas  $E_{\text{HB}}(nH^+)$  denotes the energy of the intramolecular hydrogen bond in protonated forms, and are both calculated as reaction enthalpies. We obtained  $E_{\text{STRAIN}}$  values of 20.8, 23.7, 22.2 and  $18.2 \text{ kcal mol}^{-1}$  for **5a–5d**, respectively, implying that the steric strain in **5b** is by far the largest. Interestingly, these values are much higher than those for **3b–3d**, which assume 6.1, 5.6 and  $14.1 \text{ kcal mol}^{-1}$ ,<sup>13b</sup> respectively, and some are even above  $21.1 \text{ kcal mol}^{-1}$  reported for the 1,8-bis(bis(diisopropylamino)cyclopropeniminyl) naphthalene,<sup>13g</sup> suggesting that steric strain might be the predominant factor leading to high basicity of **5a–5d**. Indeed, the hydrogen bond stabilization,  $E_{\text{HB}}$ , in  $5aH^+–5dH^+$  assumes 3.5, 2.0,  $-1.1$  and  $-5.4 \text{ kcal mol}^{-1}$ , respectively, meaning that this contribution is small, even disfavoring protonation in  $5aH^+$  and  $5bH^+$ . This is because, in order to form the HB interaction, the formed O–H<sup>+</sup> bond must move from its preferred out-of-plane position, as in **2a–2d**, to coplanar orientation,<sup>31b</sup> which turns out not to be so favorable. Such diminished influence of the hydrogen bonding is completely opposite to what was found for classical proton sponges, in which this effect is dominant. For

Table 2 Comparison of calculated and experimental  $pK_a$  values

System		$pK_a$ (calc.)	$pK_a$ (exp)	$\Delta_{\text{ABS}}$
	X = -H ( <b>1a</b> )	11.3	12.53 <sup>14d</sup>	1.2
	X = -NH <sub>2</sub>	16.3	17.62 <sup>14d</sup>	1.3
		24.4	24.34 <sup>14d</sup>	0.1
	X = -H ( <b>2a</b> )	7.6	9.03 <sup>28</sup>	1.4
	X = -NMe <sub>2</sub> ( <b>2b</b> )	14.6	14.18 <sup>27</sup>	0.4
	X = -Me	9.2	11.00 <sup>28</sup>	1.8
	X = -OMe	10.9	12.21 <sup>27</sup>	1.3
		20.3	20.84 <sup>14d</sup>	0.5
	X = -H	24.4	24.46 <sup>14a</sup>	0.1
	X = -Me	27.2	27.2 <sup>14a</sup>	0.0
	X = - <i>t</i> Bu	31.1	30.21 <sup>14a</sup>	0.9

example, ( $E_{\text{STRAIN}}, E_{\text{HB}}$ ) contributions in **3b–3d** are (6.1,  $-12.8$ ), (5.6,  $-9.7$ ), and (14.1,  $-9.5$ )  $\text{kcal mol}^{-1}$ ,<sup>13b</sup> respectively. This analysis suggests that the very high PA of **5a–5d** is almost entirely a consequence of a strain-induced destabilization of neutral bases, while only a small contribution is offered by the hydrogen bonding, which is, anyway, not in optimal linear geometry as  $[O-H \cdots O]^-$  angles in  $5aH^+–5dH^+$  take values of 155.8, 156.6, 157.2 and  $157.3^\circ$ , respectively. We also mention that hydrogen bonds in  $5aH^+–5dH^+$  are all asymmetrical, meaning that the proton is directly attached to one functionality, where it causes a substantial cationic resonance effect. However, it is also partially bound to a neighboring moiety, inducing partial protonation and a less pronounced resonance.

It is of interest to estimate the  $pK_a$  values of superbases in acetonitrile solution (Table 1). Our model was first gauged against eleven molecules with known basicities (Table 2), selected to match the investigated class of compounds and to cover the  $pK_a$  ladder up to 30 units. The accuracy of the model is evidenced in the average absolute error of 0.8  $pK_a$  units, which is satisfactory for our purposes. It turns out that a trend in the gas-phase basicities is well preserved in acetonitrile, too. One notices that in **1c** and **1d** there is no obvious distinction among two protonation sites, while in **2c** and **2d**, as well as in 1,8-diazanaphthalenes **4c** and **4d**, the solution-phase protonation site is changed in favor of the substituent nitrogen atom. The calculated values for classical proton sponges **3b–3d** are 18.3, 24.7 and  $32.7 \text{ p}K_a$  units, respectively, being in very good agreement with experimental data of 18.6,<sup>8</sup> 25.1<sup>13a</sup> and  $29.9$ .<sup>13c</sup> The results in Table 1 also show that title systems **5b** and **5c** are very strong bases in acetonitrile, culminating with the exceptional basicity of  $pK_a(5d) = 36.5$ . Thus, the investigated molecules provide important rungs in the upper part of the superbasicity ladder in both phases, and their synthesis is highly recommended.

To summarize, DFT calculations demonstrate that 1,8-diazanaphthalene di-*N*-oxides provide very strong oxygen

1 superbases in both gas-phase and acetonitrile. Their basicity  
surpasses that of classical naphthalene-based 1,8-bis-substituted  
nitrogen proton sponges, particularly if the latter are further  
di-substituted at 4- and 5-positions with two *N*-oxide moieties,  
5 which become the preferred protonation site. Contrary to classical  
proton sponges, the high basicity of investigated *N*-oxides is  
almost entirely a consequence of destabilized neutral bases  
through the steric repulsions of the two negatively charged  
oxygen atoms, while only a small contribution is offered by the  
10 intramolecular [O-H...O]<sup>-</sup> hydrogen bonding in the conjugate  
acids. The most basic system is provided by the 4,5-diphos-  
phazeno substituted 1,8-diazanaphthalene di-*N*-oxide, **5d**, with  
PA = 294.2 kcal mol<sup>-1</sup> and pK<sub>a</sub> = 36.5. Given the growing interest  
in highly basic compounds together with related basic catalysts  
15 and metal complexing agents, we hope that the results presented  
here would open a new avenue of research in these fields and  
direct the attention towards utilizing *N*-oxides in designing  
improved organic materials.

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