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Proton Sponges

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1,8-Bis(dimethylamino)naphthalene-2,7-diolate: A Simple Arylamine Nitrogen Base with Hydride-Ion-Comparable Proton Affinity**

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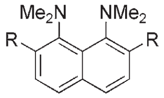
Since the discovery by Alder et al.[1] of the anomalously high basicity (pK_a = 12.1, H_2O, 25 °C) of 1,8-bis(dimethylamino)naphthalene (**1**), widely known as a "proton sponge", much effort has been made to design even stronger bases of similar type.[2] The synthesis of 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene (**2**) with pK_a = 16.1 has become the currently unsurpassed success in this direction.[3] The high basicity of **2**[4] was attributed to the +M effect of the two MeO groups, which in conjunction with their "buttressing effect" destabilizes the base and leads to a large gain in free energy on protonation. This explanation allows one to expect that further increases in pK_a may be achieved by substitution of methoxy groups in **2** by more strongly electron-donating dimethylamino groups in **3**. However, due to steric hindrance, the electron-donating ability of the NMe_2 groups at C-2 and C-7 is diminished, and the basicity of **3** (pK_a = 15.8)[5] does not exceed that of **2**. We therefore assumed that more promising and more basic candidates are **4** and **5** with less sterically demanding OH and O^- substituents in the *ortho* positions.



1 R = H; **2** R = OMe; **3** R = NMe_2; **4** R = OH; **5** R = O^-

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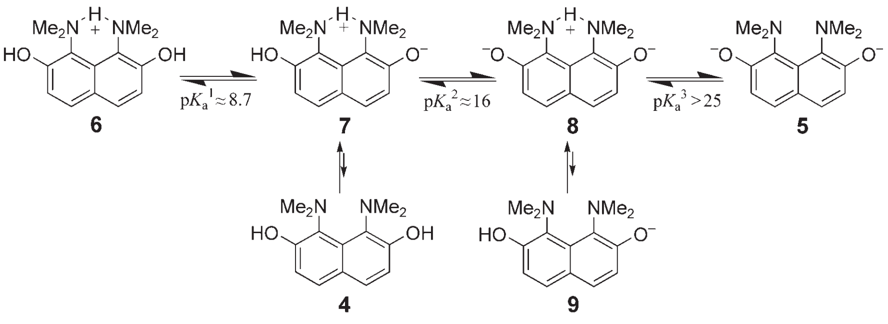
This assumption has been fully confirmed, and herein we report a novel 1,8-bis(dimethylamino)naphthalene derivative with the highest basicity among all currently studied aminoarene systems.



Scheme 1. Protonation equilibria and possible tautomeric forms between **6** and diolate **5**.

Table 1: Selected ^{1}H NMR spectroscopic data for **2** and the bromide of **6** and deprotonation of hydrobromide **6**.

Entry	Starting material	Solvents and conditions	Species in solution	NMe$_2$	δ_H [ppm] H-3, H-6	N–H···N[a]
1	**2**	[D$_6$]DMSO	**2**	2.82 (s)	7.16	–
2	**2**·HBr	[D$_6$]DMSO	**2**+H$^+$	3.18 (d)	7.53	19.38
3	**6**	[D$_6$]DMSO	**6**	3.19 (d)	7.14	19.30
4	**6**	D$_2$O/[D$_6$]DMSO (1:3)	**6**	3.12 (d)	7.07	19.33
5	**6**	CD$_3$OD	**6**	3.31 (d)	7.11	19.65
6	**6**	CD$_3$OD + KOH (1 equiv)	**7**	3.27 (br s)	6.78	18.70
7	**6**	CD$_3$OD + KOH (3 equiv)	**8**	3.26 (s)	6.58	19.66
8	**6**	D$_2$O/[D$_6$]DMSO (1:3) + KOH (6 equiv)	**8**	3.03 (s)	6.23	19.26
9	**6**	D$_2$O/[D$_6$]DMSO (1:3) + KOH (18 equiv)	**8**	3.04 (s)	6.22	19.25
10	**6**	D$_2$O/[D$_6$]DMSO (1:3) + KOH (18 equiv), 100 °C	**8**	3.08 (s)	6.21	–[b]
11	**6**	[D$_6$]DMSO + LiH (10 equiv)[c]	**8**	3.12	6.17	19.12

[a] Chemical shift of the chelated proton. [b] Complete H/D exchange. [c] See also text.

Heating a solution of **2** in 46 % aqueous HBr gave the protonated form **6** of naphthalenediol **4** as hydrobromide monohydrate in nearly quantitative yield. In the ^{1}H NMR spectrum (Table 1, entries 3–5), the N-H-N chelated proton resonates at very low field ($\delta = 19.30$ and 19.65 ppm in [D$_6$]DMSO and CD$_3$OD, respectively), as is typical for conjugate acids of 2,7-disubstituted proton sponges (e.g., entry 2 in Table 1).[2a,4] In contrast to the hydroxy protons ($\delta \approx 11.0$ ppm), which readily undergo rapid H/D exchange in CD$_3$OD- or D$_2$O-containing solutions, H/D exchange of the NH proton is complete only after several weeks at room temperature. Gradual addition of solid KOH to a solution of **6** in CD$_3$OD or D$_2$O/DMSO leads to consecutive formation of ions **7** (Table 1, entry 6) and **8** (Table 1, entries 7–10) in which the NH proton remains intact (Scheme 1). This process is accompanied by strong shielding of H-3 and H-6, the signals of which are shifted upfield to $\delta \approx 6.2$ ppm (cf. Table 1, entry 2). At the same time, the downfield shift (by more than 3 ppm) observed for the NMe$_2$ groups leaves no doubt to their involvement in N-H(D)-N bonding (Table 1, entries 9 and 10; cf. entry 1). Surprisingly, all attempts to deprotonate the diolate anion **8** further were unsuccessful. Thus, even after prolonged heating of **6** in KOH/D$_2$O/[D$_6$]DMSO (Table 1, entry 10) or with a large excess of LiH in [D$_6$]DMSO (Table 1, entry 11), the ^{1}H NMR spectra contained the well-defined low-field signal of the chelated proton.

Estimation of pK_a values for **6**–**8** seemed especially intriguing. We could measure directly only the first ionization constant for the phenolic hydroxy group in **6**. The pK_a^1 value determined potentiometrically in H$_2$O/EtOH (1:1) at 20 °C was 8.93 ± 0.04, which corresponds to approximately 8.6–8.7 for aqueous solution (cf. pK_a for β-naphthol: 9.63 in H$_2$O;[6] 9.94 ± 0.04 in H$_2$O/EtOH 1:1 (this work)). To estimate pK_a^2, the transprotonation NMR procedure was employed.[7] For example, the room-temperature ^{1}H NMR spectrum of a 3:1 mixture of **2** and **6** in [D$_6$]DMSO showed that only one equivalent of **2** was protonated to give a 2/1/1 mixture of **2**, **2**+H$^+$, and **7**. Hence, pK_a^2 definitely exceeds 11 (on the DMSO scale) or approaches 16 (in H$_2$O). The pK_a^3 value was evaluated by correlating known pK_a values for proton sponge **1** and some of its 2,7-disubstituted derivatives in DMSO with the sum of Hammett constants σ_p^{+}[8,9] of the *ortho* susbstituents (see Ref. [4]). The resulting linear relationship ($r^2 = 0.9970$) is shown in Figure 1. Extrapolation to (O$^-$)$_2$ gives a pK_a^3 value for dianion **5** of 21.0 in DMSO or about 25.5 on the water scale. It can be

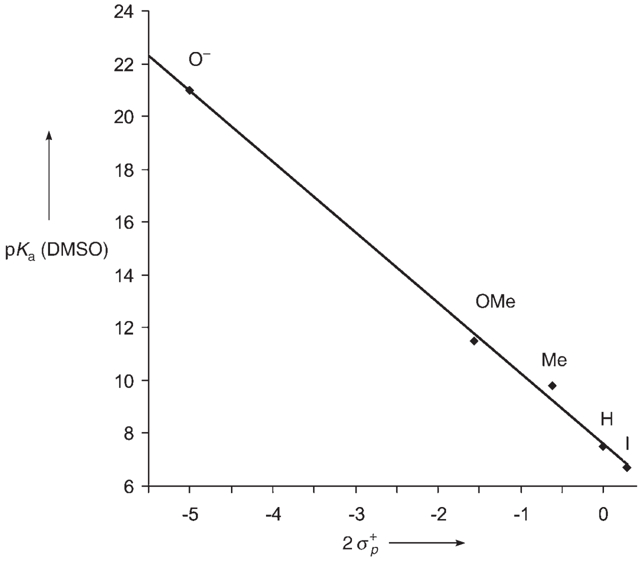
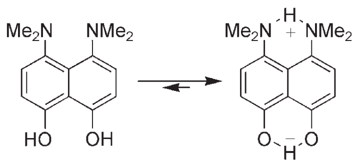


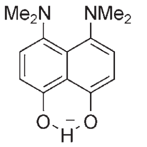
Figure 1. Correlation of basicities of 2,7-disubstituted proton sponges with the sum of the σ_p^+ constants of *ortho*-substituents.

assumed that the true basicity of **5** is even higher, since abstraction of the NH proton occurs neither on heating **5** with LiH/DMSO at 130–140°C for 1–2 h nor under ultrasonic irradiation of the mixture (140 W) for 20–25 min.

The existence of naphthols **4** and **9** exclusively in tautomeric forms **7** and **8** is similar to the behavior of 4,5-dihydroxy-1,8-bis(dimethylamino)naphthalene (**10**), for which the zwitterionic structure **11** was found to be the only molecular form existing in solution and in the solid state.[10] No estimation of pK_a for **11** was reported.



10 **11**



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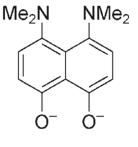

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To provide a theoretical basis for the above observations and to check whether dianion **5** is the most basic and simple system in which neutral amino groups are protonated, quantum-chemical calculations on molecules and ions **1**, **2**, **4**–**9**, and related compounds **10**–**13** were carried out. Selected results of the calculations are listed in Table 2 and shown in Figure 2. Further details are collected in the Experimental Section and in the Supporting Information.

Calculations with various basis sets yielded essentially identical results; hence, we concluded that the 6-31G** basis is quite sufficient for evaluating proton affinities (PA values) of such systems. Moreover, the results of single-point calculations are sufficient for correctly accounting for the influence of a solvent on PA values. The difference between

Table 2: B3LYP/6-31G** and B3LYP/6-311++G** gas-phase [PA(Gas)] and solution [PA(DMSO)[a]] proton affinities [kcal mol^{-1}] for structures **1**, **2**, **4**, **5**, **9**, **10**, **12**, and **13** and simple anions H$^-$, OH$^-$, and NH$_2^-$.

	R	B3LYP/6-31G**		B3LYP/6-311++G**	
		PA(Gas)	PA(DMSO)	PA(Gas)	PA(DMSO)
1	H	259.6[b]	293.5 (293.3)	253.4	287.3
2	2,7-(OMe)$_2$	274.7	303.9	268.2	298.2
4	2,7-(OH)$_2$	272.6	304.4 (304.2)	265.3	297.5
5	2,7-(O$^-$)$_2$	440.4	334.6 (334.8)	424.8	321.4
9	2-OH, 7-O$^-$	359.8	322.0 (322.7)	349.0	312.0
10	4,5-(OH)$_2$	263.5	296.8 (297.0)	256.6	290.5
12	4-OH, 5-O$^-$	340.5	310.1 (311.0)	331.5	301.5
13	4,5-(O$^-$)$_2$	419.8	312.7	406.1	301.7
OH$^-$	–	435.1	348.5 (348.4)	396.0	313.3 (313.3)
NH$_2^-$	–	445.2	369.9 (369.7)	412.5	340.0 (339.9)
H$^-$	–	449.7	–	405.0	–

[a] Single-point IEFPCM calculations; results of calculations with full geometry optimization in the presence of solvent in parentheses. [b] 245.9 (experimentally), see ref. [11].

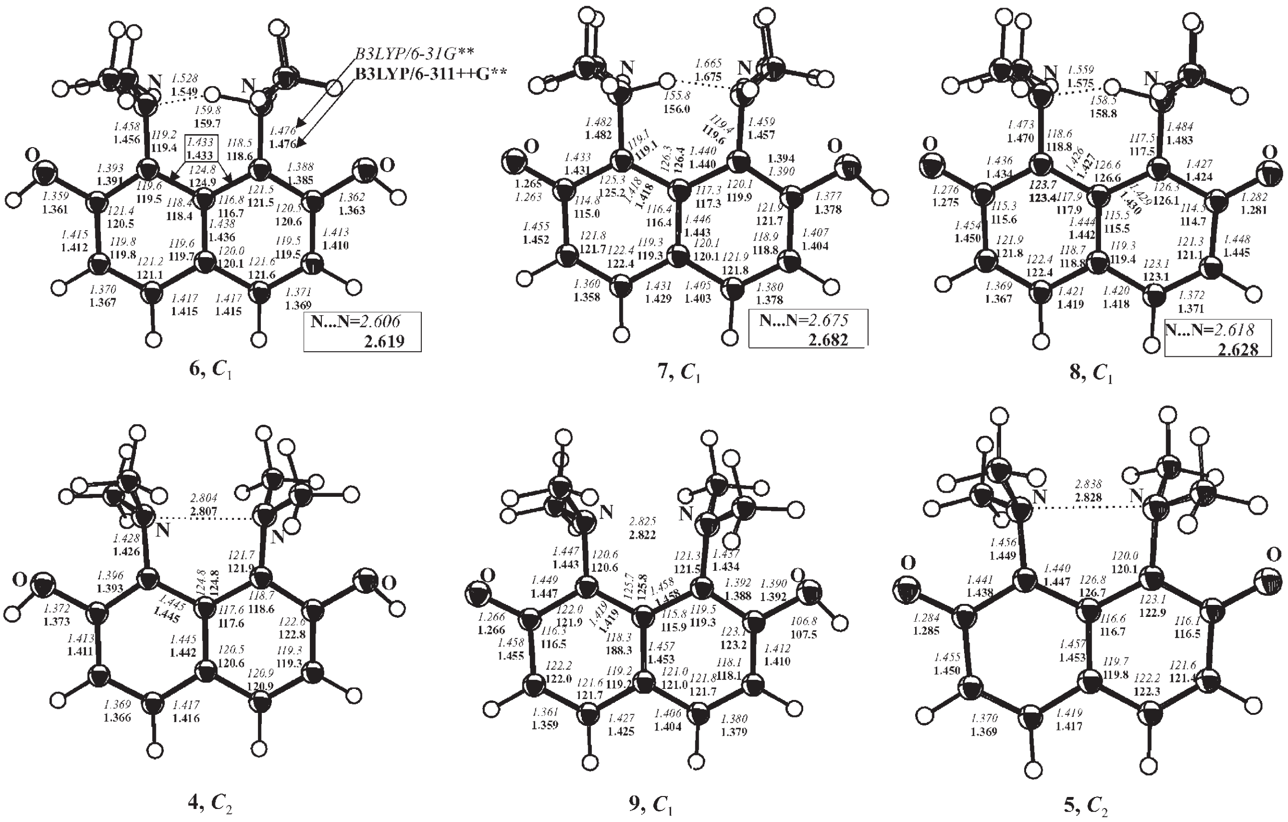
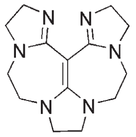


Figure 2. Optimized geometries of **4**–**9** calculated by B3LYP/6-311++G** and B3LYP/6-31G** methods. Bond lengths and angles are indicated in angstroms and degrees, respectively.

the results of the single-point and geometry-optimized calculations is less than 1 kcal mol^{-1}.

The calculations confirmed the observed experimental data and are in agreement with Scheme 1. For example, deprotonation of cation **6** results in zwitterion **7**, which, depending on the basis set used, is stabilized by 8.7–9.7 kcal mol^{-1} (in DMSO) relative to neutral structure **4**. Further deprotonation occurs with participation of the OH group to give anion **8**, which is 11.9–12.8 kcal mol^{-1} (in DMSO) more stable than its isomer **9**.

Structure **8** as the conjugate acid of dianion **5** is stabilized by an unsymmetrical, charge-assisted, intramolecular hydrogen bond (see Figure 2), and the gas-phase barrier to N–H···N proton transfer is calculated to be 0.91 kcal mol^{-1} (cf. 1.36 kcal mol^{-1} for the **2**+H$^+$ cation[12]). Compound **5** is indeed the most basic, both in solution and, predictably, in the gas phase. Remarkably, the PA value of **5** is as high as those of the simplest ions such as OH^-, NH_2^-, or even H^- (see Table 2). This value substantially exceeds the PAs calculated for amidines such as **14** (269.5), phosphazenes such as **15** (301.0 kcal mol^{-1}),[13] the phosphatranes of Verkade and coworkers, and 1,8-bis(tetramethylguanidino)naphthalene,[14] as well as other computationally designed nitrogen superbases.[15]



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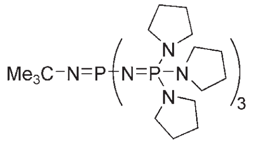

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Experimental Section

6: A solution of **2** (0.137 g, 0.5 mmol) in aqueous HBr (46 % 5 mL) was heated to reflux under a nitrogen atmosphere for 2 h. The reaction mixture was then evaporated to dryness to leave 0.16 g (100 %) of **6**-Br hydrate as gray lustrous needles (m.p. 285 °C, decomp., from MeCN/EtOH 3:1). Elemental analysis (%) calcd for $C_{14}H_{19}BrN_2O_2 \cdot H_2O$: C 48.74, H 6.14, Br 23.16; found: C 45.15, H 5.66, Br 22.33. IR (nujol): $\tilde{\nu} = 3370$, 3130, 2680 (OH); 1620, 1500 (ring); 460 cm^{-1} (br). ^{13}C NMR (75 MHz, [D$_6$]DMSO, TMS): $\delta = 42.1$ ($^2J_{C\text{–}N\cdots H} = 2.7$ Hz; NMe), 116.5 ($^1J = 163.1$ Hz; C-3, C-6), 122.9 (C-9), 123.1 (C-10), 123.7 (C-1, C-8), 130.1 ($^1J = 162.2$ Hz; C-4, C-5), 153.1 ppm ($^2J_{COH} = 9.9$ Hz; C-2, C-7).

DFT[16] calculations were carried out by the restricted Hartree–Fock method with the Gaussian 98 program suite[17] with the 6-31G** and 6-311++G** basis sets. Becke's three-parameter hybrid functional with the Lee–Yang–Parr correlation functional (B3LYP)[18] was used in the DFT calculations. All the structures corresponded to the stationary points on the respective potential energy surfaces (PES). Analytic harmonic frequencies at the same level of theory were used to characterize the nature of the stationary point corresponding to the gas-phase structure under study. The influence of solvent was taken into account by carrying out single-point and full-geometry optimization calculations with the PCM solvation method and the integral equation formalism model (IEFPCM).[19]

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Keywords: amines · basicity · density functional calculations · hydrogen bonds · organic bases

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