ORGANIC LETTERS
2012
Vol. 14, No. 16
4134–4137

4,5-Bis(dimethylamino)quinolines: Proton Sponge versus Azine Behavior

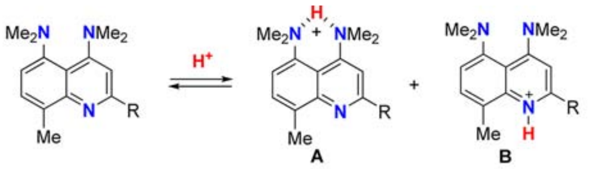
Olga V. Dyablo,[†] Elena A. Shmoilova,[†] Alexander F. Pozharskii,[*,†]
Valery A. Ozeryanskii,[†] Oleg N. Burov,[†] and Zoya A. Starikova[‡]

Department of Organic Chemistry, Southern Federal University, Zorge str. 7, Rostov-on-Don 344090, Russian Federation, and A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova str. 28, Moscow 119991, Russian Federation

apozharskii@sfedu.ru

Received June 28, 2012

ABSTRACT



R = NMe_2: only form **A** is observed in the solid, but **A** and **B** forms coexist in solution
R = Me: only form **B** is realized regardless of the aggregate state

Two first representatives, 5 and 6, of the still unknown 4,5-bis(dimethylamino)quinoline have been synthesized and studied. While the former, being protonated either at the peri-NMe_2 groups or at the ring nitrogen, has been shown to display properties of both a proton sponge and azine, its counterpart 6 behaves exclusively as azine giving only a quinolinium salt.

It is well-known that the abnormally high basicity (pK_a = 12.1, H_2O;[1] 7.5, DMSO[2]) of 1,8-bis(dimethylamino)naphthalene **1** ('proton sponge') is commonly attributed to (1) the steric and electrostatic repulsion of *peri*-NMe_2 groups and (2) the formation of rather strong intramolecular H-bonding in protonated form **2**.[3] Both of these structural principles are widely used for the design of many other superbases.[4] For example, quino-[7,8:7′,8′]quinoline **3** is somewhat more basic (pK_a = 12.8)[5] than **1** although, strictly speaking, it cannot be classified as a proton sponge because of its high kinetic activity and nucleophilicity.[4a] In view of this, still unknown 4,5-bis(dimethylamino)quinoline **4** appears to a much larger extent as a member of the proton sponge family. In the present letter we report the synthesis and some properties of the two first derivatives of **4**, namely quinolines **5** and **6** (Scheme 1). Our interest in the compounds of this group was initiated by not only their basic properties but also close structural proximity to 4-dimethylaminopyridine **7**, a popular catalyst (known as DMAP) for acylation and alkylation reactions.[6] Compound **7** with a rather high basicity (pK_a = 9.66, H_2O)[6c] is protonated exclusively at the ring N-atom producing cation **7H**$^+$ due to the strong +M-effect of the 4-NMe_2 group. Therefore, an intriguing question about the protonation site in molecules **4**–**6** arises: will they behave more as proton sponges or azines similar to **1** or **7**, respectively? Obviously, answering the question can be important for the catalytic activity of compounds **4**–**6**.

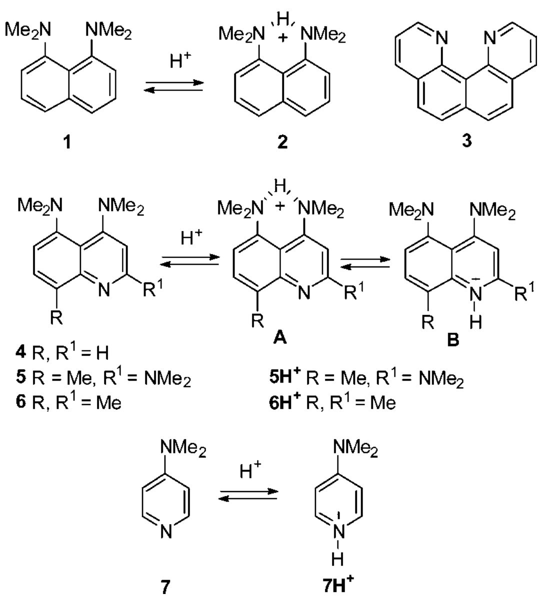
Quinolines **5** and **6** together with minor quantities of monomethylated products **10** and **11** were obtained by alkylation of **8** and **9** in accordance with the protocol previously suggested for such kinds of diamines (Scheme 2).[7,8] Amines **8** and **9**, in turn, were prepared via quite simple

---

[†] Southern Federal University.
[‡] Institute of Organoelement Compounds.
(1) Hibbert, F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1862.
(2) Benoit, R. L.; Lefebvre, D.; Frechette, M. *Can. J. Chem.* **1987**, *65*, 996.
(3) (a) Pozharskii, A. F.; Ozeryanskii, V. A. In *The Chemistry of Anilines*; Rappoport, Z., Ed.; J.Wiley & Sons: Chichester, 2007; Part 2, Chapter 17, pp 931–1026. (b) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215. (c) Howard, S. T. *J. Am. Chem. Soc.* **2000**, *122*, 8238.
(4) (a) Pozharskii, A. F.; Ozeryanskii, V. A.; Filatova, E. A. *Chem. Heterocycl. Compd.* **2012**, *48*, 200. (b) Ishikawa, T., Ed. *Superbases for Organic Synthesis*; J. Wiley & Sons: 2009.
(5) (a) Zirnstein, M. A.; Staab, H. A. *Angew. Chem., Int. Ed.* **1987**, *26*, 460. (b) Wüstefeld, H.-U.; Kaska, W. C.; Schüth, F.; Stucky, G. D.; Bu, X.; Krebs, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3182.
(6) (a) Scriven, F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (b) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4826. (c) Soovali, L.; Rodima, T.; Kaljurand, I.; Kütt, A.; Koppel, I. A.; Leito, I. *Org. Biomol. Chem.* **2006**, *4*, 2100.

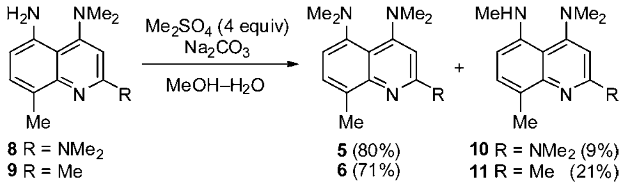
10.1021/ol301777s

Scheme 1. Naphthalene Proton Sponge **1**, 4-Dimethylaminopyridine **7**, and Their Quinoline Analogues **3**−**6**



multistep synthesis starting from *o*-toluidine (Schemes S1−S3, Supporting Information (SI)).

Scheme 2. Methylation of 5-Amino-4-dimethylaminoquinolines **8** and **9**



Heterocyclic diamines **5** and **6** are pale yellow oils with yellow-green fluorescence, whose structure was proven by ^{1}H, ^{13}C NMR and mass spectra. Both bases were also characterized as picrates and perchlorates. For the monopicrates, X-ray structural analysis has been performed (Figure 1), which revealed the completely different behaviors of bases **5** and **6** upon protonation.[9] The molecular structure of **5·PicOH** is formed by two independent proton-sponge-like cations **5H^{+}A** having an asymmetric hydrogen bridge between the *peri*-NMe$_2$ groups with the following parameters: N(1)−H, 0.88 Å; N(2)...H, 1.80−1.81 Å; N...N, 2.620−2.634 Å; ∠NHN, 155°. To our knowledge, this is the first example of protonation of a dimethylamino group conjugated with the aza-group in the azine series. Unlike **5**, base **6** is protonated exclusively at the ring nitrogen atom giving quinolinium cation **6H^{+}B**.

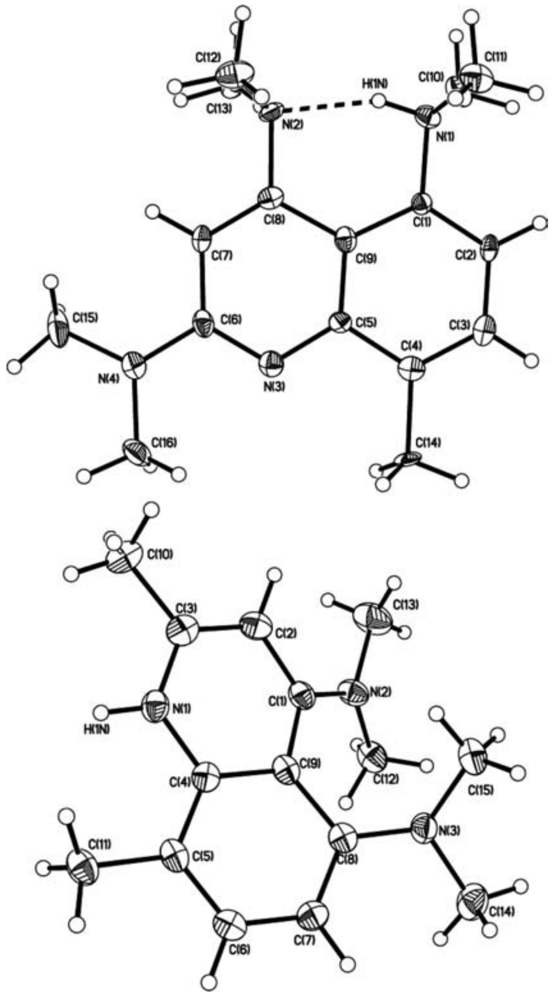


Figure 1. Molecular structures of ammonium-type **5H^{+}A** (above) and quinolinium-type cations **6H^{+}B** (below) (picrate anions are omitted for clarity; thermal ellipsoids drawn at the 50% probability level).

A more complicated picture is observed for the protonation of compounds **5** and **6** in solution. According to the ^{1}H NMR spectra, the equilibrium of two protonated forms (**5H^{+}A** and **5H^{+}B**) is established for hydrogen picrate or hydrogen perchlorate of quinoline **5**. Indeed, proton NMR spectroscopy demonstrates two clear sets of hydrogen signals, of which NH-peaks are especially indicative (Figure 2). Thus, the proton bound to the pyridine nitrogen (**5H^{+}B** form) resonates at δ 7.4−9.1 ppm, while the

---

(7) Sorokin, V. I.; Ozeryanskii, V. A.; Pozharskii, A. F. *Eur. J. Org. Chem.* **2003**, 496.

(8) The high total yields of **5**,**6** and **10**,**11** testify that no alkylation at the ring heteroatom seems to occur under these conditions. Obviously, such low nucleophilicity of the quinoline nitrogen atom in these compounds results from its strong shielding by 2- and 8-substituents (see, for example, Pozharskii, A. F. *Theoretical bases of heterocyclic chemistry*; Khimia: Moscow, 1985; p 135).

(9) Selected data for **5H·PicO**: $C_{22}H_{27}N_{7}O_{7}$, M = 501.51, orthorhombic, $Pca2_1$, a = 20.6019(14) Å, b = 7.0886(5) Å, c = 32.075(3) Å, V = 4684.2(6) Å^{3}, Z = 8, D_{calcd} = 1.422 g/cm^{3}, μ = 0.108 mm^{-1}, T = 100 K, independent reflections 9151, variables 663, R_1 = 0.0535 ($I > 2\sigma(I)$), wR_2 (all data) = 0.1015, CCDC Ref. No. 888288. Selected data for **6H·PicO·H$_2$O**: $C_{21}H_{26}N_{6}O_{8}$, M = 490.48, monoclinic, $P2_1/n$, a = 17.4712(13) Å, b = 6.9550(5) Å, c = 19.6475(14) Å, β = 108.812(2)°, V = 2259.9(3) Å^{3}, Z = 4, D_{calcd} = 1.442 g/cm^{3}, μ = 0.112 mm^{-1}, T = 100 K, independent reflections 5948, variables 317, R_1 = 0.0562 ($I > 2\sigma(I)$), wR_2 (all data) = 0.1045, CCDC Ref. No. 888289.

Table 1. Chemical Shifts of NH Protons in the ^{1}H NMR Spectra of Quinolinium Picrates Containing Cations **5H$^+$** and **6H$^+$**, Polarity of the Protonated Forms, and Their Ratio

			δ_{NH} (ppm)		content (%)		calculated gas-phase dipole moment for forms **A** and **B** (D)	
cation	solvent	dipole moment of the solvent (D)[14]	**A**	**B**	**A**	**B**	**A**[a]	**B**
5H$^+$	$CDCl_3$	1.15	17.07	9.12	15	85	7.14	2.82
	ClD_2CCD_2Cl	1.85	17.45	7.36	5	95		
	CD_3CN	3.38	17.37	8.17	50	50		
	DMSO-d_6	4.26	17.07	9.12	55	45		
	DMSO-d_6[b]	"	17.07	9.12	55	45		
	acetone-d_6	2.70	17.78	8.85	58	42		
6H$^+$	$CDCl_3$	1.15	12.97		0	100	7.02	4.04
	ClD_2CCD_2Cl	1.85	11.92		0	100		
	CD_3CN	3.38	10.07		0	100		
	DMSO-d_6	4.26	11.58		0	100		
	DMSO-d_6[b]	"	11.57		0	100		
	acetone-d_6	2.70	11.42		0	100		

[a] Average value for two forms **A′** and **A″** with protons localized on the 4- or 5-NMe_2 groups, respectively. The difference in calculated dipole moments for both of these forms does not exceed 3%. [b] Data for perchlorates.

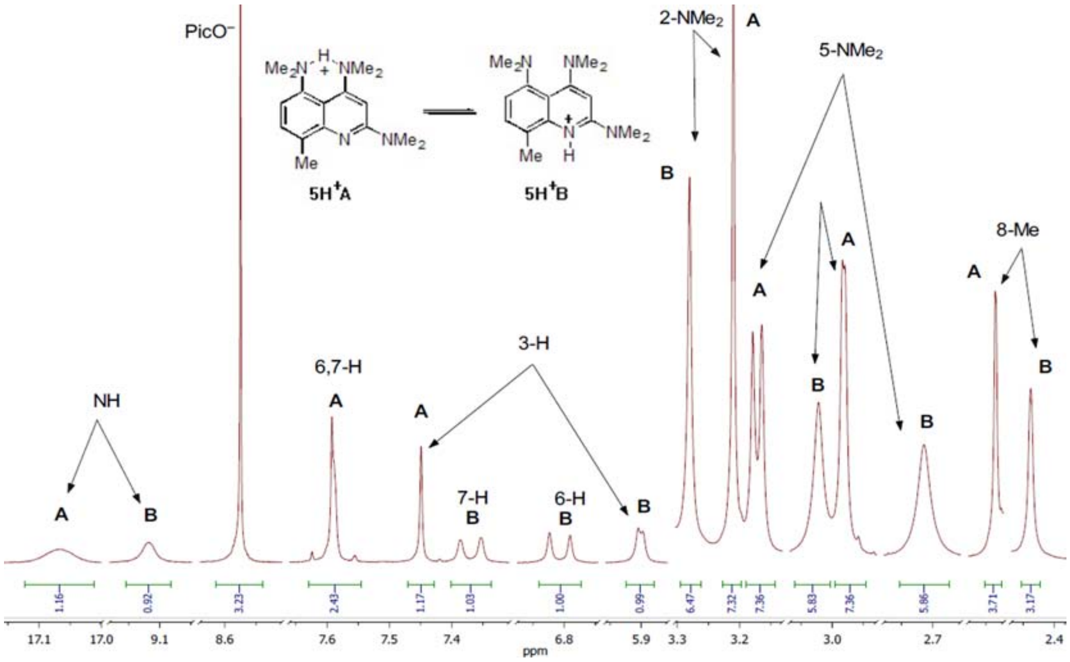


Figure 2. Equilibrium mixture of protonated forms **5H$^+$A** and **5H$^+$B** of compound **5** (as **5·PicOH**) as evidenced by ^{1}H NMR in DMSO-d_6 solution (only selected regions are presented).

proton captured by the amine nitrogens (**5H$^+$A** tautomer) gives a signal at a much lower field (17.1−17.8 ppm) typical for the cations of all proton sponges.[3a] The ratio of both forms is highly sensitive to the solvent used (Table 1). While form B strongly predominates in media of low polarity ($CDCl_3$, ClD_2CCD_2Cl), a percentage of two forms becomes commensurable in more polar solvents such as CD_3CN, DMSO-d_6, or CD_3COCD_3. This is in accord with the theoretical estimations (Table S1, SI), which show a much higher polarity of form **5H$^+$A** that enables its more effective solvation in polar media.

Under similar conditions protonated 4,5-bis(dimethylamino)-2,8-dimethylquinoline (**6H$^+$**) behaves differently. First, only one NH signal is observed in its ^{1}H NMR spectra with the δ_{NH} chemical shift varying, depending on the solvent, from 10.1 to 13.0 ppm; obviously, this corresponds to a protonation of the aza-group only. Second, a transition from nonpolar to polar solvents does not influence the picture though form $\mathbf{6H^+A}$ is again more polar than $\mathbf{6H^+B}$ (Table 1). Using a competitive method,[10] ^1H NMR spectra of equimolar mixtures of salts $\mathbf{5H^+ClO_4^-}$ or $\mathbf{6H^+ClO_4^-}$ and proton sponge **1** were measured in DMSO-d_6. From this, the pK_a value for protonation of **6** at the aza-group has been estimated as being 7.2 which is only slightly lower than that for the naphthalene sponge **1**. The pK_a values for protonation of **5** at the *peri*-NMe$_2$ groups and ring nitrogen atom are roughly equal to 6.5 and 6.3, respectively (Figures S3.21 and S3.22, SI). Thus, the proton sponge site in **5** is by one power of ten less basic than that in **1**. Evidently, such a difference reflects an interplay between the electron-acceptor action of the aza-group and the electron-donor ability of the 2-NMe$_2$ and 8-Me groups. Indeed, the basicity of structurally related 1,8-bis(dimethylamino)-4-nitronaphthalene is considerably lower (pK_a = 3.5, DMSO)[11] despite the fact that the electron-accepting strength of aza- and NO$_2$ groups is actually close.[12]

One of the most interesting phenomena observed in this work is an essentially higher basicity of **6** in comparison with **5**. This difference in basicity has been independently confirmed by the ^1H NMR competitive experiment between base **6** and perchlorate $\mathbf{5H^+ClO_4^-}$ (Figure S3.20, SI). We assume that using 2-Me instead of the much more electron-donating 2-NMe$_2$ group causes such dramatic consequences in protonation because of solvation factors. This assumption is in agreement with the DFT calculations of gas-phase proton affinities (PA) of both bases. Indeed, PA values of **5** and **6** are equal to 264.9 and 263.9 kcal mol^{-1}, respectively; that is, in the absence of solvation factors the former is more basic (Table S1, SI).[13]

Further studies on the synthesis of the parent proton sponge **4** as well as a more detailed exploration of the properties of compounds **4**–**6** are underway.

In summary, we have synthesized two first representatives of 4,5-bis(dimethylamino)quinoline and have found that they behave at protonation either as typical azines (2,8-dimethyl derivative) or as proton sponge and azine simultaneously (2-dimethylamino derivative). The proton sponge pattern is strongly dependent on the aggregate state, the solvent used and the nature of substituents. A possibility of protonation of the NMe$_2$ group in azine series conjugated with the ring heteroatom has been demonstrated for the first time.

Acknowledgment. This work was supported by the Russian Foundation for Basic Research (Project No. 11-03-00073).

Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(10) (a) Birchal, T.; Jolly, W. L. *J. Am. Chem. Soc.* **1966**, *88*, 5439. (b) Staab, H. A.; Kirsch, A.; Barth, T.; Krieger, C.; Neugebauer, F. A. *Eur. J. Org. Chem.* **2000**, 1617.

(11) Ozeryanskii, V. A.; Pozharskii, A. F.; Vistorobskii, N. V. *Russ. Chem. Bull.* **2000**, *49*, 1212.

(12) Deady, L. W.; Shanks, R. A. *Aust. J. Chem.* **1972**, *25*, 431.

(13) Geometrically, compound **5** is similar to 2,6-diisopropylpyridine (pK_a = 5.34, EtOH–H$_2$O, 1:1, v/v, 25 °C) which is less basic than 2,6-dimethylpyridine (pK_a = 5.77) despite the larger +I-effect of an *i*-Pr group in comparison with the methyl. It is generally accepted that this is caused by the lower solvation of the 2,6-diisopropylpyridinium cation because of steric hindrances. (a) Roithova, J.; Exner, O. *J. Phys. Org. Chem.* **2001**, *14*, 752. (b) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1966**, *88*, 986.

(14) Reichardt, Ch. *Solvents and Solvents Effects in Organic Chemistry*; VCH: Weinheim, 1988.

The authors declare no competing financial interest.