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Extreme Magnetic Separation of Geminal Protons in Protonated *N,N,N′*-Trimethyl-1,8-diaminonaphthalene. A Puzzle of the Fourth Methyl Group

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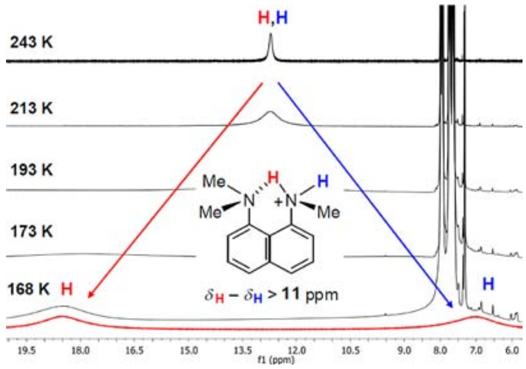
ABSTRACT



Monoprotonated *N,N,N′*-trimethyl-1,8-diaminonaphthalene demonstrates fast exchange of H_{in} and H_{out} protons, in which a counterion (BF_4^- and Br^- were tested) participates. The process can be frozen below 185 K revealing a tremendous magnetic separation (up to $\Delta\delta = 11.6$ ppm) of these otherwise equal NH protons with the enzyme-like proton transfer and a ~7 kcal mol^{-1} energetic barrier.

It is known that the amine basicity on going from 1,8-diaminonaphthalene (pK_a 10.99, MeCN) to its *N,N,N′*-trimethyl derivative (pK_a 12.91) slightly increases due to the +*I*-effect of the growing number of *N*-methyl groups.[1] However, after the introduction of the fourth methyl group, the basicity of 1,8-bis(dimethylamino)naphthalene (**1**, proton sponge) jumps up by almost million times reaching pK_a 18.62 in MeCN[1,2] or 12.1 in H_2O.[3] A traditional explanation of this phenomenon is that in **1** a strong repulsion between *peri*-NMe_2 groups exists and, therefore, an enormous free energy gain takes place on protonation owing to a strain relief and the formation of a short and strong intramolecular hydrogen bridge (IHB) in cation **1H**$^+$.[3,4] Surprisingly, that until now only a few

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(1) Pozharskii, A. F.; Suslov, A. N.; Starshikov, N. M.; Popova, L. L.; Klyuev, N. A.; Adanin, V. A. *Zh. Org. Khim.* **1980**, *16*, 2216–2228. *Chem. Abstr.* **1981**, *94*, 120385s.

(2) Kaljurand, I.; Kütt, A.; Soovali, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019–1028.

(3) (a) Hibbert, F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1862–1866. (b) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *J. Chem. Soc., Chem. Commun.* **1968**, 723–724.

(4) (a) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215–1223. (b) Perrin, C. L.; Ohta, B. K. *J. Mol. Struct.* **2003**, *644*, 1–12. (c) Howard, S. T. *J. Am. Chem. Soc.* **2000**, *122*, 8238–8244. (d) Pozharskii, A. F.; Ozeryanskii, V. A. *Mendeleev Commun.* **2012**, *22*, 117–124.

(5) Lloyd-Jones, G. C.; Harvey, J. N.; Hodgson, P.; Murray, M.; Woodward, R. L. *Chem.–Eur. J.* **2003**, *9*, 4523–4535.

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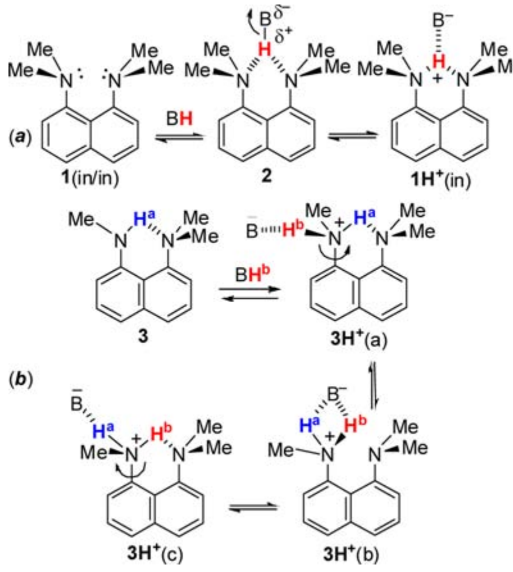
investigations[1,5] have been done for the lesser methylated analogs of **1**, e.g. **3** (Scheme 1). Meanwhile, understanding the proton transfer in protonated **3** might help to solve a puzzle of the fourth CH_3 group in this series. Here we report for the first time on hydrogen transfer in cation $\mathbf{3H}^+$ at different temperatures and anions, including hydrogen bonding characteristics: geometry, unusual stereodynamics and energy.

Scheme 1. Inside (a) and Outside (b) Modes for the Protonation−Deprotonation of Compounds **1** and **3**; Rotational Exchange of H^a (*in*) and H^b (*out*) Protons in **3** Is Also Shown



Normally, for compound **1** and a vast majority of its derivatives the conformation **1**(*in*,*in*) is typical, in which the methyl groups are turned outside and the axes of the nitrogen free electron pairs point inside of the internitrogen space.[6] Hence, the only mode of protonation−deprotonation is through the cleft between the amino groups (Scheme 1a, structure **2**). The X-ray studies of $\mathbf{1}\cdot HBF_4$ and $\mathbf{1}\cdot HF$, chosen as examples, clearly exhibit that this is indeed the case (Supporting Information (SI), Figure S1). From this one can conclude, that the pK_a values of **1** and its derivatives with the *in*,*in*-conformation are actually attributed to the inside protonation.

The starting amine **3** and its derivatives have a weak intramolecular N−H...N hydrogen bonding.[1,5,7] In the present work we have managed to grow single crystals of salts $\mathbf{3}\cdot HBF_4$ and $\mathbf{3}\cdot HBr$ and for the first time performed X-ray measurements on protonated diamine **3** (Figure 1). It was disclosed that similar to cation $\mathbf{1H}^+$,[7,8] the IHB is also realized in $\mathbf{3H}^+$ and, moreover, the both demonstrate a surprising geometrical similarity (Table 1). At the same time, remarkable differences arise when a counterion is brought into consideration. The most important is the location of a counterion relative to the bridge NH proton. While in $\mathbf{1H}^+$ the BF_4^- anion 'overhangs' the internal NH proton (SI, Figure S1a), in $\mathbf{3H}^+$ it is located outside from the lateral NH hydrogen at 1.92 Å (Figure 1a). The same is true for bromide $\mathbf{3}\cdot HBr$ except the larger distance (2.42 Å) between Br^- and the *out*-NH proton. Apparently, this is caused by the simultaneous long-range interaction (3.53 Å) of the bromide ion with the *in*-NH proton of the nearby cation (see Figure 1b) diffusing the electrostatic potential of Br^-.

Table 1. Selected Structural Characteristics of Monoprotonated *peri*-Diamines **1** and **3**

	bond lengths and distances (Å)				
salt	N...N	$N-H_{in}$	H_{in}...N	F(Br)...H^a	∠NHN (deg)
$\mathbf{1}\cdot HBF_4$[b]	2.564	1.31	1.30	2.91	159
$\mathbf{1}\cdot HBr$[c]	2.554	1.31	1.31	3.69	153
$\mathbf{1}\cdot HF$[d]	2.578	1.25	1.47	2.76	142
$\mathbf{3}\cdot HBF_4$[e]	2.546	1.31[f]	1.33	1.92	150
$\mathbf{3}\cdot HBr$[e]	2.582	0.88[f]	1.76	2.42	154

[a] Distance between the NH proton (H_{in} for **1**, H_{out} for **3**) and the nearest atom of the counteranion. [b] Reference 9a. [c] Dihydrate, ref 9b. [d] ref 9c. [e] This work. [f] 0.88 Å for the $N-H_{out}$ bond.

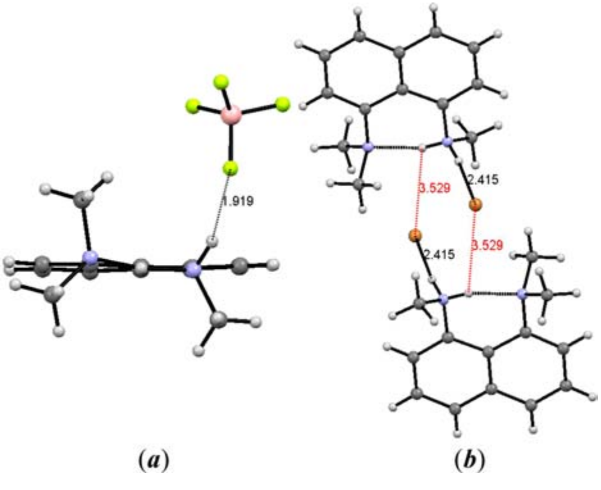


Figure 1. Incipient deprotonation and IHB motifs in protonated base **3** as realized by low temperature X-ray structures showing close interaction (Å) between (a) the *out*-NH proton and tetrafluoroborate and (b) both the *out*-NH and the *in*-NH protons and bromide counterions (see text and Table 1 for details).

Importantly, as it follows from the F...H(N) distance (1.92 Å in $\mathbf{3}\cdot HBF_4$ against 2.91 Å in $\mathbf{1}\cdot HBF_4$), the

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(6) (a) Pozharskii, A. F.; Ryabtsova, O. V.; Ozeryanskii, V. A.; Degtyarev, A. V.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. *J. Org. Chem.* **2003**, *68*, 10109–10122. (b) Pozharskii, A. F.; Degtyarev, A. V.; Ryabtsova, O. V.; Ozeryanskii, V. A.; Kletskii, M. E.; Starikova, Z. A.; Sobczyk, L.; Filarowski, A. *J. Org. Chem.* **2007**, *72*, 3006–3019.

(7) Ozeryanskii, V. A.; Pozharskii, A. F.; Koroleva, M. G.; Shevchuk, D. A.; Kazheva, O. N.; Chekhlov, A. N.; Shilov, G. V.; Dyachenko, O. A. *Tetrahedron* **2005**, *61*, 4221–4232.

(8) 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.

anion–NH interaction in **3**·HBF_4 is much stronger than that in **1**·HBF_4. Obviously, in solution this should cause an easier deprotonation of **3H**$^+$ and a rapid interchange of the inside (H^a) and outside (H^b) protons (Scheme 1). Indeed, both NH protons in the ^{1}H NMR spectra of **3H**$^+$ give a rather sharp two-proton singlet, which resonates in different solvents (CD_3CN, $CDCl_3$, CD_2Cl_2, DMSO-d_6) at δ ~12.5 ppm and is little sensitive to such low coordinating anions as BF_4^-, I^- or ClO_4^-. In contrast, more basic anions (e.g., Br^-) increase δ_{NH} up to 13.8 ppm.[10]

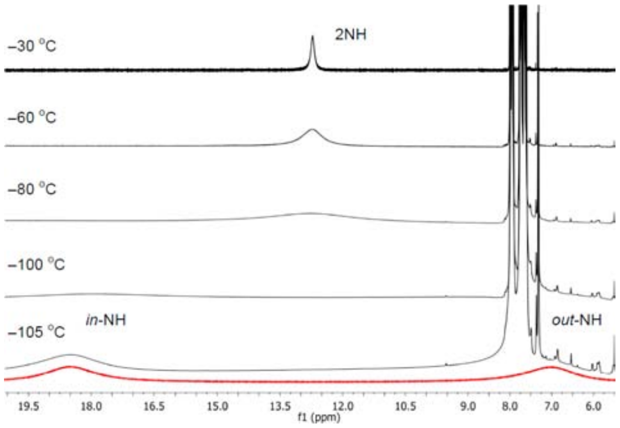
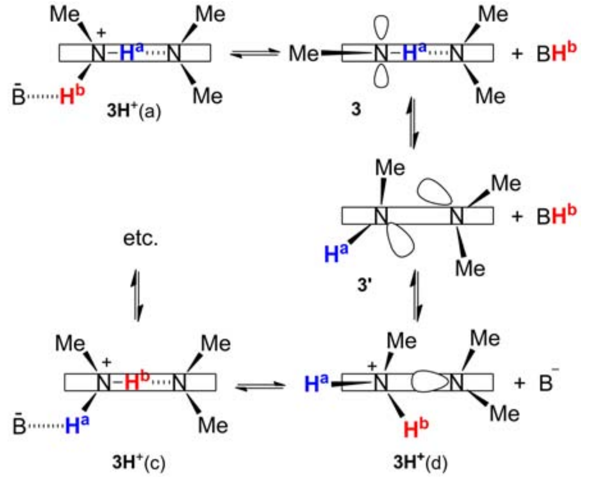


Figure 2. Proton NMR evolution of the NH signals in **3**·HBF_4 (in CD_2Cl_2–$CDCl_3$–CCl_4). For convenience, the spectrum at −105 °C is fitted by a theoretical line (in red, with an offset in intensity) showing the positions of strongly separated NH_2 protons.

The low-temperature ^{1}H NMR behavior of **3H**$^+$ was intriguing. Down to −35 °C, the position and shape of the common NH signal of **3**·HBF_4 dissolved in CD_3CN undergo no change, while in CD_2Cl_2 its broadening occurs already at −30 °C reaching $\Delta\delta$ 6 ppm at −85 °C. To get lower temperatures, we used the CD_2Cl_2–$CDCl_3$–CCl_4 (v/v/v 60:27:13) system, in which a T_c −93 °C was registered with the hydrogen exchange barrier $\Delta G^{\#} = 6.9 \pm 0.2$ kcal mol^{-1}.[11] A clear separation of the H^a(*in*) and H^b(*out*) peaks (18.5 and 6.9 ppm)[12] was observed at −105 °C (Figure 2). The chemical shift difference for these protons attains $\Delta\delta = 11.6$ ppm! To our knowledge, this is a record value not only for an ammonium but also for any other geminal hydrogen atoms.[13]

Scheme 2. Alternative Deprotonation–Protonation Mechanism of Hydrogen Exchange in Cation **3H**$^+$



In principle, two mechanisms for the inside/outside exchange of hydrogens in **3**·HBF_4 and **3**·HBr seem possible: (1) libration of the $^+NH_2Me$ group within ~120° (rotational exchange, Scheme 1b) and (2) deprotonation–protonation (Scheme 2). The second mechanism includes abstraction by a base (counterion) of the *out*-proton with the following fission of IHB in the thus formed diamine **3**. Such disruption should result in the pyramidalization of the otherwise nearly planar[8] NHMe group and its restricted rotation.[14] During this rotation[15] the different conformations, e.g. **3′**, arise allowing their reprotonation with the hydrogen exchange: **3′** → **3H**$^+$(d) → **3H**$^+$(c). Remarkably, unlike **1H**$^+$ (Scheme 1a), the deprotonation of **3H**$^+$(a) or the protonation of **3** are not hindered by the fourth CH_3 group and, therefore, can proceed from the outside. Summing up all the 'pros and cons' we prefer the libration mechanism as extremely simple and requiring low energy consumption (~7 kcal mol^{-1} in solution).[16]

Another interesting point is that the both mechanisms should differently respond to the counterion nature. While the libration seemingly proceeds without assistance of an anion, participation of the latter is definitely necessary for the second mechanism. Therefore, we next studied the

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(9) (a) Wozniak, K.; Krygowski, T. M.; Kariuki, B.; Jones, W.; Grech, E. *J. Mol. Struct.* **1990**, *240*, 111–118. (b) Pyzalska, D.; Pyzalski, R.; Borowiak, T. *J. Crystallogr. Spectrosc. Res.* **1983**, *13*, 211–220. (c) Darabantu, M.; Lequeux, T.; Pommelet, J.-C.; Ple, N.; Turck, A.; Toupet, L. *Tetrahedron Lett.* **2000**, *41*, 6763–6767.

(10) Notably, that water does not participate in the rapid $H^a \rightleftarrows H^b$ proton exchange! This is confirmed by the fact that even in DMSO-d_6 traces of water give a separate signal at δ 3.9 ppm indicating the $H^a \rightleftarrows H^b$ exchange may, in principle, proceed without external species.

(11) One can assume that the energy of IHB in **3**·HBF_4 makes a certain contribution into this value. As to **1H**$^+$ salts, the question of IHB energy is ambiguous. Theoretically, it was estimated as lying near 17–20 kcal mol^{-1} (ref 4c). However, some authors challenge this value and consider it well below: Perrin, C. L.; Ohta, B. K. *J. Am. Chem. Soc.* **2001**, *123*, 6520–6526.

(12) This separation is likely close to a theoretical limit, which seems is restricted by the chemical shift of the NH proton in the absolute majority of protonated proton sponges (18–19 ppm, see ref 8).

(13) (a) Gulevskaya, A. V.; Besedin, D. V.; Pozharskii, A. F. *Russ. Chem. Bull.* **1999**, *48*, 1150–1153. (b) Wasylishen, R.; Schaefer, T. *Can. J. Chem.* **1971**, *49*, 3575–3576. (c) Gorobets, N. Yu.; Yermolaev, S. A.; Gurley, T.; Gurinov, A. A.; Tolstoy, P. M.; Shenderovich, I. G.; Leadbeater, N. E. *J. Phys. Org. Chem.* **2012**, *25*, 287–295.

(14) The limitation for a full turnover is caused by obvious impossibility for the *N*-methyl group to enter the internitrogen space.

(15) The rotational barrier in neutral **3** was estimated theoretically, see the Supporting Information for further details.

(16) See the Supporting Information for further details.

(17) Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. Y.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.* **2011**, *76*, 391–395.

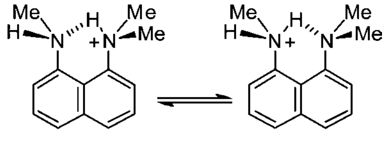
dynamic ^{1}H NMR spectra of **3**·HBr. We reasoned that since the basicity of Br$^-$ is much higher[17] if compared with that of BF_4^- one can expect minor spectral and thermodynamic differences between both salts if the libration mechanism prevails and vice versa.

In the ^{1}H NMR spectrum of **3**·HBr between −30° and 30 °C (SI, Figure S4), a two-proton singlet of the NH hydrogens is observed at δ 13.8 ppm evidencing their fast exchange as in the case for **3**·HBF_4. The exchange is slowed down below −30 °C (peak width $\Delta\delta = 3.5$ ppm at −60 °C) with the appearance of the two one-proton signals at −90 °C (Figure S4). The separation of the outside and inside protons in **3**·HBr ($\Delta\delta = 6.0$ ppm at −120 °C),[18] which is 2-fold less than that in **3**·HBF_4, gave the exchange barrier $\Delta G^{\#} = 7.5 \pm 0.2$ kcal mol^{-1} for T_c being near −87 °C.

Thus, the more basic bromide anion hampers hydrogen exchange in cation **3H**$^+$ increasing the energetic barrier by ~9%. A possible reason may be the above-mentioned (Figure 1b) bifurcation of Br$^-$ with both H_{in} and H_{out} protons in **3H**$^+$ (structure **3H**$^+$(b), Scheme 1b); clearly, the libration motion of the $-N(Me)H_2Br$ group should occur with more difficulty.[19] In solution, the bifurcation is seen via lesser chemical shifting of the NMe_2 group in **3**·HBr (2.98 vs 3.08 ppm for **3**·HBF_4) and larger deshielding of the H-7 proton (7.96 vs 7.80 ppm for **3**·HBF_4). All this indicates that the H_{in} in **3**·HBr is shifted more toward the NHMe rather than to the NMe_2 if compared with **3**·HBF_4 (*cf.* X-ray data, Figure 1 and Table 1).[20]

The chirality of cation **3H**$^+$ in the frozen state is also noteworthy. This follows from the solution ^{1}H NMR data of the NMe region (SI, Figure S5): below −100 °C all three methyls become nonequivalent. Moreover, at temperatures 0 to −30 °C the CH_3 signal of the $^+NH_2Me$ group at δ 3.18 ppm is split into a triplet ($^3J_{NH,NMe} = 5.3$ Hz) by scalar coupling[21] with dynamically and magnetically equivalent H_{in} and H_{out} protons. Hence, their exchange occurs along an intramolecular pathway *consistent with the libration mechanism.*

The key dynamic processes were simulated theoretically by DFT calculations. First, we have found that the bridge proton in **3H**$^+$ in the gas phase is preferably located at the NMe_2 group [tautomer **3H**$^+$(A)] however the barrier of its transfer to the NHMe counterpart [structure **3H**$^+$(B)] is only 2.74 kcal/mol (Figure S6 in the SI). Such a small value should allow easy transfer of the NH proton to the NHMe function with its subsequent movement outside, resulting in the $^+NH_2Me$ group libration (two-mode proton motion). This view of the inside−outside proton exchange means that a limiting stage of the whole process should be the $[N-H...N]^+$ IHB fission.[22]



3H$^+$(A) **3H**$^+$(B)

The calculations of the rotational energy in tautomer **3H**$^+$(B) gave a gas phase barrier of 9.75 kcal/mol (Figure S7). A small difference (~2.5 kcal mol^{-1}) from the experimental data can be explained by solvation factors.

The data obtained are the most vivid illustration of the proton sponge phenomenon. The absence of at least one *N*-methyl group in **1** offers enough space for the bridge NH proton in cation **3H**$^+$ to escape outside, while in **1H**$^+$ the proton is hidden in a tight hydrophobic pocket. Although this idea is not considered as absolutely new,[23] in the present work it is shown for the first time *how effectively this pocket functions*. The situation is analogous to caged polyamines such as 1,6-diazabicyclo[4.4.4]-tetradecane,[24] in which the proton encapsulation is so strong that it cannot be extracted from the inside by ordinary means.

In summary, solution and solid state studies of protonated *N*,*N*,*N*′-trimethyl-1,8-diaminonaphthalene for the first time have very clearly explained the tremendous discrepancy in basicities of the proton sponge and its demethylated analogs via differences in their (de)protonation modes. Unlike **1**, the cations of lesser methylated diamines can undergo outside (de)protonation. The subsequent libration enables easy exchange of the inside and outside NH protons and requires only 7−8 kcal mol^{-1}. The exchange can be frozen leading to a discovery of the unprecedented separation (> 11 ppm) of geminal protons. We believe that salts **3H**$^+$**X**$^-$ can be considered as molecular devices for modeling the proton transfer enzymes, for example, such as serine proteases which act as a proton shuttle through "catalytic triads".[21,25] It is remarkable that, similar to natural enzymes, these can be regulated by external factors, particularly by temperature and counterion changes.[26]

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Supporting Information Available. Full experimental details, X-ray and additional dynamic NMR data, and DFT calculations on rotational barriers in neutral and protonated **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The $\Delta\delta$ parameter looks rather attractive for a quantitative description of basicities or even nucleophilicities of weakly coordinating anions but this demands a special study.

(19) For anion-dependent barriers to the $^+NH_3$ group rotation in phenylammonium salts, see: Ratcliffe, C. I.; Dunell, B. A. *Faraday Symp. Chem. Soc.* **1978**, *13*, 142–152. See also: Lesnichin, S. B.; Tolstoy, P. M.; Limbach, H.-H.; Shenderovich, I. G. *Phys. Chem. Chem. Phys.* **2010**, *12*, 10373–10379.

(20) Apparently, the bifurcation is a main factor that equalizes the shielding of the H_{in} and H_{out} protons.

(21) Limbach, H.-H.; Männle, F.; Detering, C.; Denisov, G. S. *Chem. Phys.* **2005**, *319*, 69–92.

(22) Notably, that both tautomers, **3H**$^+$(A) and **3H**$^+$(B), are realized in the solid state (Figure 1 and Table 1). Preference of **3H**$^+$(A) in the gas phase is due to a higher basicity of NMe_2 over NHMe group.

(23) Hibbert, F. *Acc. Chem. Res.* **1984**, *17*, 115–120.

(24) Alder, R. W.; Casson, A.; Sessions, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 3652–3653.

(25) Copeland, R. A. *Enzymes: A Practical Introduction to Structure, Mechanism, and Data Analysis*, Wiley-VCH, 2000, p 181.

(26) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines*; 2nd ed., Wiley−VCH, 2008, pp 343−346.

The authors declare no competing financial interest.