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Proton sponges and hydrogen transfer phenomena

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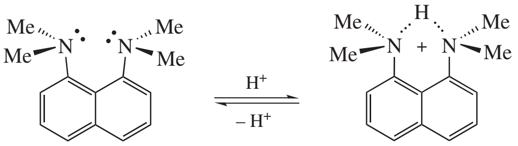
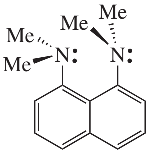
Recent advances in the studies of hydrogen transfer (protonation, hydrogen bonding, hydride transfer and CH acidity) in proton sponges, its influence on the structure, stereodynamics and reactivity of these superbasic compounds and the use of the above phenomena for modelling enzyme catalysis have been discussed.

Hydrogen and proton transfer (acid catalysis and acid–base equilibrium, hydrogen bonding, prototropism, crystal packing, supramolecular interactions *etc*.) is undoubtedly the most abundant phenomenon in chemistry, equally important in nature and human activity.[1] This is caused by both the absolute predominance of hydrogen in the Universe and the unique properties of a proton: its exceedingly tiny size, enormous affinity to electrons and high polarizing ability. Protons exist in a free state only in a deep vacuum. Under ordinary conditions, as a rule, they are bound to other species, which compete for protons and distribute protons *via* proton transfer. Naturally, the study of such species, called bases, is of great importance from both fundamental and applied points of view. In 1968, the discovery of the abnormally high basicity (pK_a 12.1, H_2O)[2] of 1,8-bis(dimethylamino)naphthalene (DMAN, **1**) had opened a new chapter in this field. This compound had got the name 'proton sponge'[3] for its ability to hold a proton tightly. For organic chemistry, the appearance of a proton sponge conception had led to a number of substantial consequences. Some of them seem rather curious. Thus, along with DMANs, different sponges for binding other types of species (hydride,[4] chloride and fluorine ions,[5] acetylene[6] *etc*.) have also been announced.

To this time, the conception of proton sponges has been developed in three main directions. The first one has considerably influenced the acid-base theory. Its practical outcome was the synthesis of neutral organic bases (superbases) with the basicity close to that of hydride and amide ions and even alkyl carbanions.[7,8] Remarkably, the design of such compounds is usually based on the same structural principles, which are responsible for the high basicity of DMAN. The second direction was connected with the study of short, strong and low-barrier hydrogen bonds. The matter is that cation **2**, forming on the protonation of DMAN, represents a stable chelate with a short intramolecular hydrogen bond (IHB). Such IHB is of great interest, which is connected with modelling enzyme catalysis and deeper insight into its mechanism.[9–11] The third direction, started somewhat later, dealt with the reactivity of proton sponges. This article is focused on the second topic. It summarizes the latest achievements in the study of hydrogen bonding in proton sponges and its influence on different facets of their behaviour, first of all, structure, stereodynamics and reactivity. Moreover, the broader aspects of hydrogen transfer in proton sponges are also discussed since it has been recently demonstrated that DMANs can serve as not only strong bases but also hydride donors and even CH acids. Comprehensive surveys on proton sponge properties can be found elsewhere.[12,13]



1 **2**



3

Inside hydrogen bonding

Under ambient conditions, DMAN and its derivatives exist in conformation **1** with the nitrogen lone electron pairs pointing to each other.[12–14] This results in the strong destabilization of a free base leading, in particular, to a distortion of the ring planarity. The formation of cation **2** cancels such a repulsion that restores the planarity of the aromatic system and gives a substantial free energy input. Many data testify that the protonation–deprotonation of DMAN occurs through the internitrogen space (see below). It is generally believed that IHB forming at inside protonation also contributes to a free energy gain thus providing an additional

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increase in pK_a. Another principal point is that, because of shielding the internitrogen space by four methyl groups, the protonation–deprotonation rate for diamine **1** is by 4–6 powers of ten lower than the rate of diffusion (~10^{10} dm^3 mol^{-1} s^{-1}), which limits the formation–decomposition of ordinary ammonium salts.[15] Thus, the high thermodynamic basicity of DMAN is coupled with its low kinetic basicity. The appearance of the term 'proton sponge' coins namely this circumstance. The narrow cleft between the nitrogen atoms in DMAN also hinders their coordination with electrophiles other than a proton. This substantially lowers the N-nucleophilicity of DMAN that in conjunction with the high basicity has led to its wide application in organic synthesis.[13]

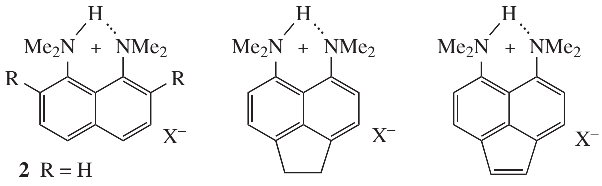
Previously, based on the data of time-resolved fluorescent spectroscopy and quantum-chemical calculations, it was proposed that the DMAN molecule could also exist as *in*,*out* conformer **3**, whose energy is 4.7 kcal mol^{-1} higher than that of form **1**.[16] Indeed, stable compounds with such a structure were disclosed in a solid state and solutions; in particular, it was shown that *in*,*out*-configuration can be fixed *via* outside hydrogen bonding.[17] In connection with this finding, the outside hydrogen bonding is also discussed in this article.

a. Geometry and energy of IHB

The studies of the DMAN cation with its two tertiary amino groups placed in a spatial proximity have led to a conclusion that the IHB in **2** has a two-well low-barrier potential for proton motion [Figure 1(*b*)].[10,18,19] As it follows from quantum-chemical estimations, the barrier height for this process does not exceed 4.5 kcal mol^{-1}.[14] Accordingly, the current point of view is that the bridging proton in **2** rapidly equilibrates between isoenergetic forms **2a** and **2b** with a postulated rate of about 10^{10} s^{-1} (tunnelling mechanism).[18,19]

This motion is displayed differently depending on the aggregate state of a sample, the nature of counter-ion and solvent, temperature and other factors. Even for the same cation, the crystallographic data can give perfectly symmetric IHB in one case or asymmetric in another one (Table 1). Thus, solid **2** as a bromide at room temperature (RT) exhibits symmetric IHB with the N···N distance of 2.55 Å but, in the salt with the tetrachlorocuprate dianion, IHB becomes asymmetric and the internitrogen distance increases to 2.58 Å. The average N···N distance for several tens of DMAN salts is ~2.59 Å, which is much shorter than that in parent base **1** (2.80 Å). An intriguing question to answer is whether the barrier-free hydrogen bond with a single minimum potential [Figure 1(*a*)] could be possible for protonated DMANs and related systems. To clarify this point, proton sponge cations with bulky functionalities in the 2- and 7-positions, *e.g.*, **4**–**9**, were prepared and studied. It was thought that, due to the buttressing effect, such *ortho* substituents will bring the nitrogen atoms closer thus strengthening IHB. To a large extent these expectations were proven for 2,7-bis(trimethylsilyl) derivative **8**, in which the IHB remains symmetric with the shortest N–H bonds even at a low temperature. Undoubtedly, the most remarkable in **8** is shortening the N···N distance to 2.52 Å that is very close to a theoretical limit (2.48–2.50 Å) for a barrier-free hydrogen bond of the NHN type.[14] The advanced quantum-chemical calculations have confirmed the practically barrier-free character of IHB in cation **8**.[19,26]

Table 1 X-ray parameters of IHB in proton sponge cations.



2 R = H
4 R = C≡C-Tol-*p*
5 R = OMe
6 R = Cl
7 R = Br
8 R = SiMe$_3$
9 R = CH$_2$OH

10

11

Compound	Anion	*T*/K	N···N/ Å	N–H/ Å	N···H–N/ Å	∠NHN/°	Ref.
2	Br$^-$	RT	2.55	1.31	1.31	153	20
	$^1/_2$CuCl$_4^{2-}$	RT	2.58	1.21	1.43	158	21
4	ClO$_4^-$	100	2.57	1.19	1.42	161	22
5	Br$^-$	100	2.57	1.30	1.30	160	23
6	Br$^-$	RT	2.56	1.29	1.29	165	24
7	Br$^-$	100	2.55	0.85 (1.73)[a]	1.73 (0.85)[a]	162	25
8	ClO$_4^-$	163	2.52	1.28	1.28	163	26
9	Cl$^-$	120	2.56	1.16	1.50	149	26
	Cl$^-$	RT	2.57	1.30	1.34	154	26
	$^1/_2$SiF$_6^{2-}$	100	2.56	0.87 (1.68)[a]	1.71 (0.89)[a]	165	26
10	Br$^-$	200	2.67	0.99	1.72	159	27
11	Br$^-$	200	2.67	0.98	1.75	156	27

[a] The NH proton is situated in two equivalent positions with the same probability.

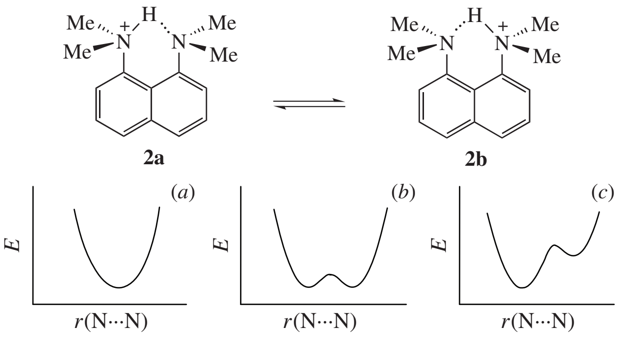


Figure 1 Possible types of IHB potential energy profiles in proton sponge cations.

On average, the NHN angle in salts **2** is about 155°. However, in 2,7-disubstituted DMANs, a 'pressure' of the *ortho* substituents onto the NMe$_2$ groups leads to their noticeable flattening (the sum of the CNC angles in compounds **4**–**9** exceeds 340°) and 'pushing-in' of the NH proton deeper into the internitrogen space exerted by the rising N–Me groups. As a result, the average NHN angle increases up to 162°.

Some more tendencies in variation of the NHN angle are followed from the structural analysis of salts **9** with *ortho*-hydroxymethyl groups.[26] In a salt with the Cl$^-$ anion, the IHB is practically symmetrical with the N···N distance of 2.57 Å at RT. However, in another sample measured at 120 K, the symmetry of IHB is lost. Obviously, it is caused by the electric field of the chloride ion in a somewhat rearranged crystal lattice. In Figure 2(*a*), one can see that the NH proton and the Cl$^-$ anion lie approximately in the ring plane and both in-line with the naphthalene C(9)–C(10) bond indicating their electrostatic interaction.[†] The situation looks as if the Cl$^-$ anion is already pre-organized for the extraction of the NH proton from its cavity. Indeed, if the NH···Cl$^-$ distance for the room temperature structure is 3.85 Å, it decreases to 3.33 Å for the structure measured at 120 K. A noticeable decrease in the NHN angle in chloride **9** (154° and 149° at 293 and 120 K, respectively) can be considered as another indirect confirmation

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[†] Actually, the positive charge in the hydrogen bridge is distributed between the NH proton (~40%), both nitrogen atoms (~30%) and the aliphatic carbons (40%). This is why a counter-ion interacts electrostatically with all these centers at the same time.[28]

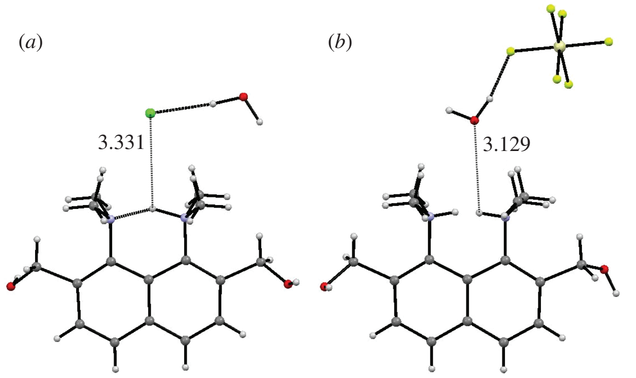


Figure 2 Fragments of crystal structures showing electrostatic interaction of the NH proton and the counter-ion in proton sponge cations as revealed by X-ray analysis: (*a*) **9**$\cdot$2H$_2$O$\cdot$Cl$^-$ at 120 K, (*b*) **9**$\cdot$2H$_2$O$\cdot{}^1\!/_2$SiF$_6^{2-}$ at 100 K.

of this interaction.[‡] Presumably, the hydrogen bond between Cl$^-$ and a water molecule also contributes to the desymmetrisation of the IHB [Figure 2(*a*)]. Note that, in salt **9** with a low nucleophilic and bulky SiF$_6^{2-}$ dianion, there are no direct contacts between the cationic NHN$^+$ bridge and the anion that leads to a distinct linearization of the H bridge (165°). It is interesting that, in many proton sponge salts with bulky anions, the water molecule often penetrates into the space between the hydrogen bridge and the anion, interacting electrostatically or *via* hydrogen bonds with both ones [Figure 2(*b*)].

Among the cations of symmetrical proton sponge bases, the most asymmetrical IHBs were detected for acenaphthene **10** and acenaphthylene **11** sponges due to a tightening effect of the CH$_2$CH$_2$ and CH=CH bridges. They force the nitrogen atoms to move apart to weaken the IHB (Table 1). For asymmetrical DMANs, the asymmetry of IHB in their cations changes even in a wider range. The energy profile for such cases is shown in Figure 1(*c*).

A question of the ‘strength’ (energy) of IHB in proton sponge salts is ambiguous. Commonly, bond energy is defined as the enthalpy of a system without the bond in question minus the enthalpy with it. The problem is that, for polar bonds, the energy value in a solid or solution cannot be measured properly owing to a strong influence of the crystal lattice and solvation. Therefore, the IHB energies for DMAN cations have been largely obtained from gas phase quantum-chemical calculations. Usually, such estimates for **2** and its close analogues lie in the range of 17–20 kcal mol^{-1} (HF, B3LYP).[30,§] A key point here is that, for the same atoms, the shorter bonds are generally accepted as being the stronger due to the contribution of a covalent resonance structure. However, in a solution, this is not always true since the ease of IHB disruption is strongly dependent on the asymmetry of IHB and the basicity (proton affinity for gas phase) of both nitrogen atoms. For example, while in protonated DMAN **2**, as well as in its 4-nitro derivative **12**, the N$\cdots$N distance is about 2.57 Å, the hydrogen bridge in the former remains unchanged in DMSO in a wide range of temperatures, but in **12** the IHB is easily broken as followed from ^{1}H NMR data and impressive colour changes.[32] Anyway, in solutions, the energy of IHB in **2** and its derivatives is about 10 kcal mol^{-1}, as judged from experimental measurements[13,33] or chosen arbitrarily.[34]

b. NMR appearance of IHB

The simplest way to make sure of IHB formation in the proton sponge cations is the appearance of an extremely low-field signal of the NH proton at δ >16–17 ppm in their ^{1}H NMR spectra. Its exact position mainly depends on the geometry of IHB, the N$\cdots$N distance and the solvent and varies from 20.7 ppm for **8** (in CD$_3$CN) to 15.8 ppm for **11** (DMSO-d_6).[13] For the cations of symmetrical proton sponges, *e.g.*, **2**, the NH signal in a high-resolution spectrum splits into 13 lines due to a spin–spin interaction with the protons of the four methyl groups. Accordingly, the signal of the latter is split into a doublet with the twelve-proton intensity and $^3J_{\text{NMe,NH}}$ ~2.6 Hz.[35] Obviously, the symmetry of IHB for the symmetrical cations is illusive at RT, since it reflects a fast motion of the NH proton relative to the symmetry plane on the NMR time scale (**2a** $\leftrightarrows$ **2b**).

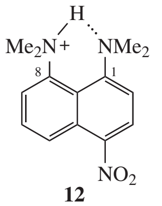
In asymmetrically substituted cations, the NMe$_2$ groups are no more equivalent, and they display two doublets with different $J_{\text{NMe,NH}}$ coupling constants (Table 2). The relationship between these constants expressed as simple equation

$$\text{PL} = [J_{1(8)\text{-NMe,NH}}/(J_{1\text{-NMe,NH}} + J_{8\text{-NMe,NH}})] \times 100\% \qquad (1)$$

was suggested for estimating the IHB asymmetry *via* the so-called ‘proton localization index’ (PL).[35] Thus, in cation **12** the NH proton localization on the N-8 atom is ~60%. The record IHB asymmetry was reported for the cation of acenaphthylene sponge derivative **13**, in which the PL-6 index reaches 92% (Table 2). Other types of coupling constants, first of all $^1J_{^{15}\text{N}-^1\text{H}}$, can also be used to estimate IHB asymmetry.[37,38] As a rule, a close agreement exists between these approaches.[39]

When the identification of IHB is ambiguous, a scalar coupling between the ^{15}N centres through the NHN hydrogen bond, $^{2\text{h}}J_{\text{NN}}$, may be helpful.[31,40] A series of N-methylated 1,8-diaminonaphthalenes and their cations can serve as a typical example (Table 3). Unfortunately, the $^{2\text{h}}J_{\text{NN}}$ values are very sensitive to the hydrogen bond geometry. This was a reason why primary expectations of a distinct correlation between this parameter and the N$\cdots$N distance failed. Nevertheless, at least a qualitative correlation of this kind seems reasonable. Thus, the general trend of increasing $^{2\text{h}}J_{\text{NN}}$ in cations **14**$\cdot$H$^+$–**18**$\cdot$H$^+$ and **2** as basicity of the corresponding *peri*-diamine grows is unquestionable. One can also see that rather weak IHBs do exist in 1,8-diaminonaphthalene **14** and all its partially N-methylated derivatives **15–18**, while for base **1** the constant $^{2\text{h}}J_{\text{NN}}$, as expected, is 0.

Table 2 Asymmetry of IHB in cations of two proton sponges expressed *via* proton localization index PL (%).



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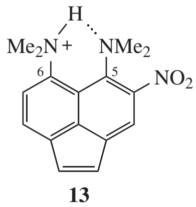

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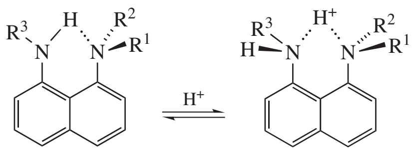
Compound	Solvent	δ_{NH}/ ppm	$^3J_{\text{NMe,NH}}$/ Hz	PL-1(5)	PL-8(6)	Ref.
12	CD$_3$CN	18.72	3.08, 3.19	39	61	35
	DMSO-d_6	18.50	3.17, 3.28	35	65	35
13	CDCl$_3$	15.67	0.4, 4.6	8	92	36

[‡] Apparently, the greatest closeness (2.76 Å) of the anion to the chelated proton and the sharpest (142°) NHN angle have been observed for the proton sponge hydrofluoride complex at 293 K.[29]

[§] For the gas phase, a hydrogen bond strength is commonly[31] broken down into three categories: (i) ‘strong’ with a large contribution of covalent interactions and a bond energy of 10–40 kcal mol^{-1}, (ii) ‘moderate’ (4–10 kcal mol^{-1}) and (iii) ‘weak’ (< 4 kcal mol^{-1}), for which electrostatic interactions strongly dominate. Largely, IHBs in proton sponges fall into the first category. Perhaps, a record belongs to naphthalene-2,7-diolate **27** (see below), where IHB is resistant even to such a potent base as LiH in DMSO.

Table 3 Scalar coupling between ^{15}N centres through the NHN hydrogen bond, $^{2h}J_{NN}$, in methylated 1,8-diaminonaphthalenes.[31]



14 $R^1 = R^2 = R^3 = H$ **14**·H$^+$
15 $R^1 = Me, R^2 = R^3 = H$ **15**·H$^+$
16 $R^1 = R^3 = Me, R^2 = H$ **16**·H$^+$
17 $R^1 = R^2 = Me, R^3 = H$ **17**·H$^+$
18 $R^1 = R^2 = R^3 = Me$ **18**·H$^+$

Base	pK_a (MeCN, 25 °C)	$^{2h}J_{NN}$/Hz	Cation^a	$^{2h}J_{NN}$/Hz
14	10.99	2.9	**14**·H$^+$	1.5
15	11.64	3.2	**15**·H$^+$	2.6
16	11.95	3.2	**16**·H$^+$	Not determined
17	12.87	3.3	**17**·H$^+$	4.5
18	12.91	3.7	**18**·H$^+$	6.7
1	18.18	0.0	**2**	8.5

^{a}Counter-ion is iodide.

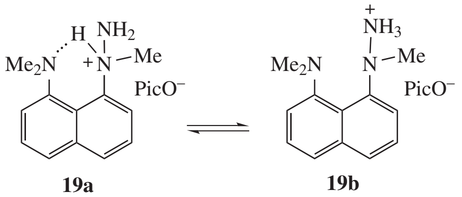
c. IR appearance of IHB

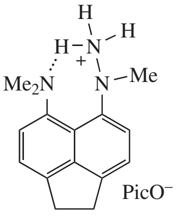
The appearance of stretching vibration bands of the hydrogen bridge, ν_{NHN} in the IR spectra of DMAN salts is very characteristic and informative. In solution, the band looks as a very broad ‘continuum’ at the background level extending from 3000 to about 300 cm^{-1}. In the solid, the band shifts towards 800–250 cm^{-1}, displaying a fine structure. This phenomenon is typical of strong, short hydrogen bridges with the N···N distance of 2.55–2.65 Å.[41] The dependence of the position of the ν_{NHN} band on the counter-ion structure[42] and deuteration[43] was repeatedly used for more deeply understanding the geometry and strength of IHB in DMAN salts. Thus, a tendency to the broadening and shifting of this band towards higher frequencies with increasing the proton-acceptor ability of the anion had been disclosed.[42] This was explained by the bifurcation of the NH proton, which should be stronger for more basic anions. However, the ability of DMAN cations to form strong intermolecular hydrogen bonds with counter-anions was questioned.[20] In the case of deuteration, an isotopic ratio, ISR = ν_{NHN}/ν_{NDN}, which for weak IHBs is usually less than 1.45, may reach 1.80–2.05. For the pair of salts **5**·HBr/**5**·DBr, this ratio reaches 2.08, the largest published value.[23] On the basis of the IR spectral data of proton sponge salts, it was concluded that the potential energy curve for the hydrogen bridge corresponds to a potential either with two minima and a very low barrier or one minimum with a flat bottom. This is the case even for the cation of 2,7-bis(trimethylsilyl) derivative **8**, whose abnormally compressed NHN bridge vibrates at 610 cm^{-1} with ISR = 1.60.[26]

d. Unconventional protonation

In some proton sponges additional basic centres, apart from the *peri*-amino functions, are present. In these cases, the external proton may prefer other modes of IHB formation or may not give any chelate at all. Thus, while monohydrazine proton sponge **19**, isolated as a picrate, in a crystalline state at 110 K exists as a ~3 : 1 mixture of tautomers **19a** and **19b**, in solution (DMSO, MeCN) a complete shift towards unchelated form **19b** occurs. The acenaphthene counterpart **20**, due to the elongated distance between the 5- and 6-positions, gives the seven-membered H-bonded pattern as the only existing form both in the solid and solution.[44] Another similar example is salt **21**.[45]

The protonation of phenalenone sponge **22** occurs at the carbonyl oxygen rather than at the NMe$_2$ groups, producing resonance stabilized hydroxyphenalenium ion **23**.[46] In a similar way, diazafluoranthene sponge **24** is protonated in DMSO at the pyridazine ring giving deeply coloured (λ_{max} = 560 nm) cation **24**·H$^+$-b, whereas in CD$_3$CN the proton is transferred to the NMe$_2$ groups producing chelate **24**·H$^+$-a (λ_{max} = 397 nm).[46]


19a **19b**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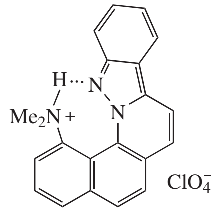
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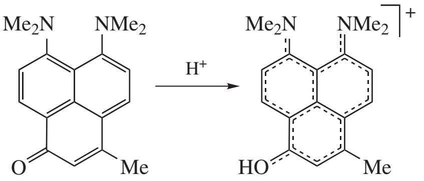
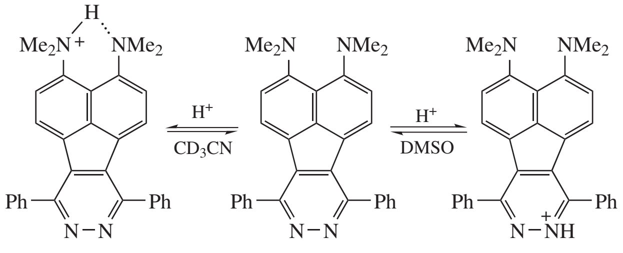
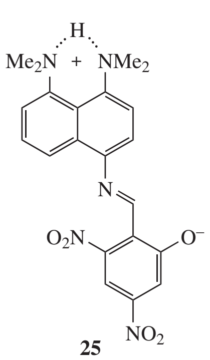

22 **23**


24·H$^+$-a **24** **24**·H$^+$-b

e. Zwitterionic structures

Proton sponge derivatives containing phenolic hydroxyls often occur as zwitterions, *e.g.*, **25**–**27**.[47–49] The intramolecular proton transfer is mainly determined by a difference between the basicity of the proton sponge fragment and the acidity of the hydroxy group and is only possible when ΔpK_a > 3.5.[50] If the OH proton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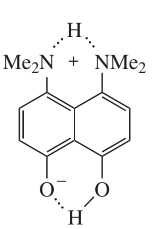
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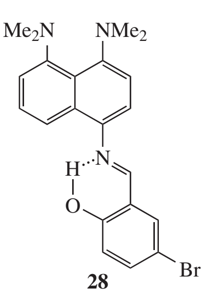
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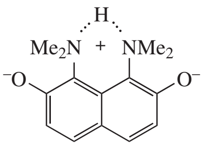
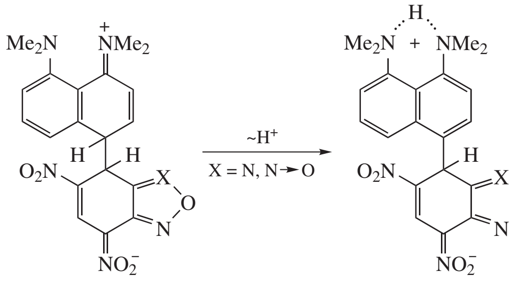

27

possesses a reduced acidity, as in the case of azomethine **28**, no proton transfer to the *peri*-NMe_2 groups takes place.[47]

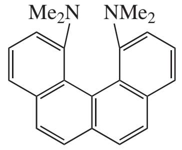
The reaction of the DMAN with 4,6-dinitro derivatives of benzofuroxan and benzofurazan results in the formation of zwitterionic σ-adducts **29**, which rapidly undergo intramolecular proton transfer to give more stable ions **30** with the aromatic naphthalene core and IHB.[51] A similar case was observed on attempt to employ DMAN for the deprotonation of the carborane $[\{Co(C_2B_9H_{10}S)_2\}CH]$.[52]



29 **30**

f. IHB and basicity

No strict connection seems to exist between the DMAN basicity and the strength, shortness or symmetry of IHB in their cations. Perhaps, one of the most instructive evidence of it is a pair of compounds **8**/**10** (Table 1). Although the IHB in the former is the shortest among all known DMAN cations and is perfectly symmetric, the 2,7-bis(trimethylsilyl) derivative of DMAN is by nearly half power of ten less basic ($pK_a = 7.0$, DMSO) than acenaphthene proton sponge ($pK_a = 7.4$), whose cation differs by strongly asymmetric and elongated IHB. An important role of IHB mostly consists in relief of the electrostatic repulsion and steric strain in the free base.[9,10] Best of all it can be seen in benzo[*c*]phenanthrene proton sponge **31**.[53] Its strongly helical structure **32** remains almost untouched in protonated chelate **33**, which explains why the basicity of this diamine ($pK_a = 5.8$, H_2O) is of the same order as that of ordinary arylamines. Factors influencing proton sponge basicity have been discussed elsewhere.[13,54]



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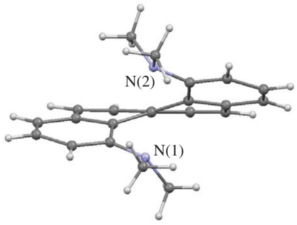

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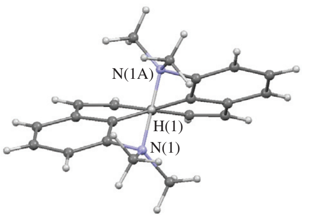
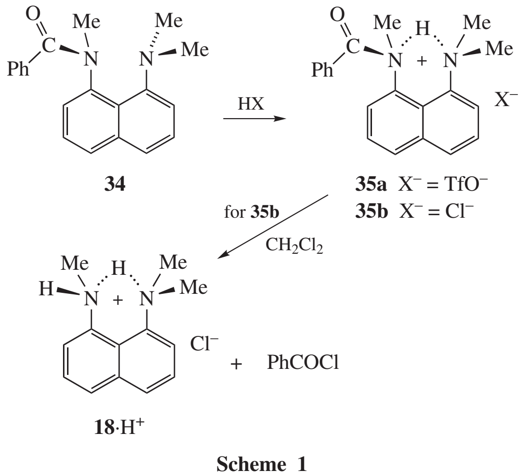


33

g. IHB and enzyme modelling

One of the cornerstones of living matter is the mechanism of enzymic catalysis providing an incredibly high rate of biochemical reactions, *e.g.*, protein synthesis, under mild physiological conditions.[11] This can be expressed somewhat differently: what factors promote the dramatic lowering of transition state energy for enzymic reaction? In general, the answer is quite obvious: enzymic catalysis results from the cumulative action of such phenomena as proximity effect, electrophilic, nucleophilic and acid-base catalysis, multiple electrostatic interactions, strain in the enzyme–substrate complex, which is sharply discharged in the transition state, *etc*. At last, the outstanding role of supramolecular interactions in the general organization of a process should be emphasised. A very sophisticated, multifunctional enzyme structure allows reactants to be effectively accommodated and oriented in specially tailored protein clefts, pockets and cavities. While scientists are still on the way to understanding the whole process in detail, the development of simple models for each catalytic step is of great importance. Since most of enzymic reactions, including protein synthesis on ribosome, occur with the participation of hydrogen transfer and, as a rule, in its cascade form, investigators have turned their attention to the proton sponge.[9,10,55] Its convenience as the proton transfer model is determined by the following reasons: high basicity, the existence of hydrophobic cleft between *peri*-NMe_2 groups and, especially, remarkable features of IHB in DMAN cation. The ideal enzymic reaction should proceed with a rate near to that of diffusion; thus, the activation barrier is almost zero. The wide range, in which the IHB length (N···N distance) is changed in DMAN cations, allows testing this point, at least its proximity effect constituent. Indeed, as it has been shown above for salt **8**, a compression of the N···N distance up to 2.52 Å makes the hydrogen transfer barrier negligibly small.

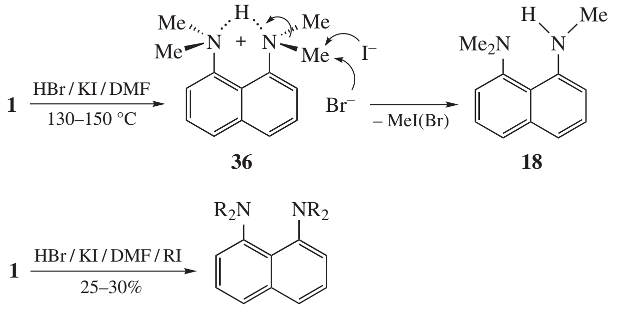
In addition, with the use of DMAN cations, biochemically important phenomena such as proton catalysis or cytochrome-like demethylation of NMe_2 group (see below) can be modelled. For example, the protonation of *N*-acyl-*N,N′,N′*-trimethyl-1,8-diaminonaphthalenes, *e.g.*, **34**, occurs not at carbonyl oxygen as in ordinary carboxamides but with the formation of NHN-chelate **35**.[56] This finding has supported a hypothesis that important protein reactions such as acid-catalyzed hydrolysis proceed *via* the preliminary protonation of the amide nitrogen atom. Interestingly, the above chelation allows unusual conversion of amide **34** into benzoyl chloride and hydrochloride of diamine **18** to occur (Scheme 1).[56]



Scheme 1

h. IHB and reactivity

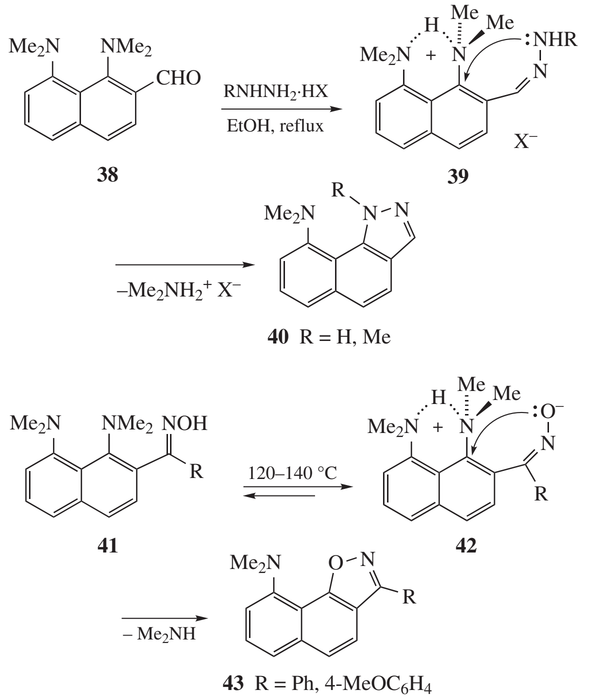
Perhaps, the IHB in DMAN cations most strongly influence the reactivity of *peri*-dialkylamino groups. In the simplest case, the NMe_2 group can be monodemethylated by heating a protonated substrate with soft nucleophiles such as thiocyanate, phenylthiolate, phenylselenolate or, that is better, iodide ions in the presence of hydrobromic acid.[57] The process is thought to proceed through the classical S_N2 mechanism when the IHB effectively stabilizes transition state **36** and *N*-trimethyl-1,8-diaminonaphthalene **18** plays the role of a good leaving group (Scheme 2). The reaction represents a convenient method for obtaining compound **18** from commercially available proton sponge **1**. Unlike methyl, the bulkier *N*-alkyl groups, even ethyl, are eliminated by this way much more difficult, if at all. This circumstance can be employed for exhaustive realkylation of the parent sponge. For example, heating **1** with a large excess of ethyl or propyl iodide in the presence of hydrobromic acid and KI in DMF results in the formation of tetraethyl or tetrapropyl proton sponges **37** in reasonable yields.[57] Note that this realkylation procedure has no analogy in the aniline series.



37 R = Et, Pr

Scheme 2

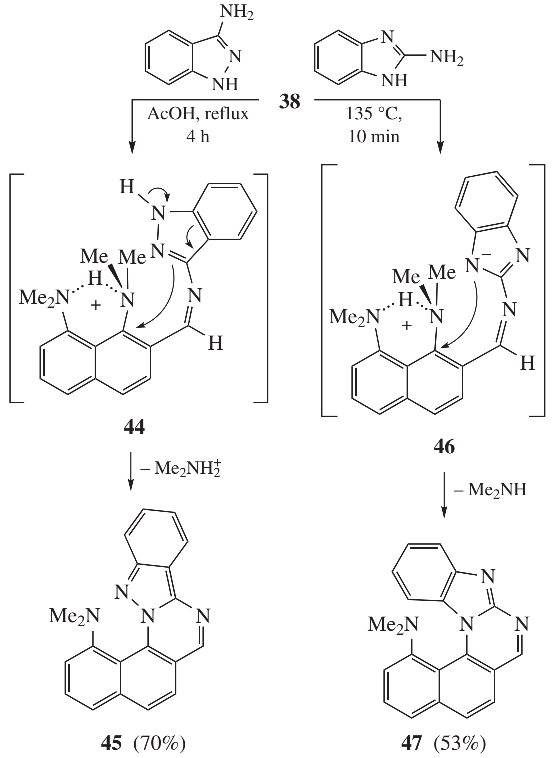
Although the NMe$_2$ groups in DMANs are not activated to a nucleophilic replacement, under conditions of acidic catalysis the intramolecular version of such reactions accompanying by a heterocyclization is possible. Thus, heating *ortho*-aldehyde **38** with a hydrazinium or *N*-methylhydrazinium salt produces benzo[*g*]-pyrazoles **40** in moderate to good yields (Scheme 3).[45] Evidently, hydrazones **39** participate here as intermediates and the dimethylammonium ion acts as a leaving group. Similarly, *ortho*-ketoximes **41** are converted into naphtho[2,1-*d*]isoxazole derivatives **43** upon melting. The conclusive evidences have been obtained that in the latter case the cyclization occurs with assistance of bifunctional catalysis when both the oxime moiety and the 1-NMe$_2$ group are activated as a result of intramolecular proton transfer with the formation of zwitterion **42**.[45]



43 R = Ph, 4-MeOC$_6$H$_4$

Scheme 3

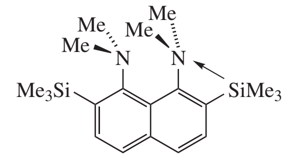
Another modification of such cyclizations was observed in the interaction of aldehyde **38** with 3-aminoindazole or 2-aminobenzimidazole (Scheme 4). Both transformations, producing polynuclear and strained naphthalene derivatives **45** and **47**, seem to proceed *via* azomethine intermediates **44** or **46**.[45] Many other examples of the influence of IHB on the reactivity of aromatic systems in proton sponges are cited in reviews.[12,13]



Scheme 4

Outside and switching hydrogen bonding

As mentioned above, for the proton sponge the *in*,*out* form **3** had been postulated in a gas phase as a minor admixture to energetically more favourable *in*,*in* form **1**. 1,8-Bis(dimethylamino)-2,7-bis(trimethylsilyl)naphthalene **48** was the first com-



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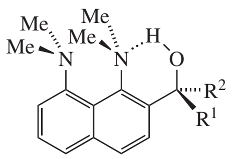
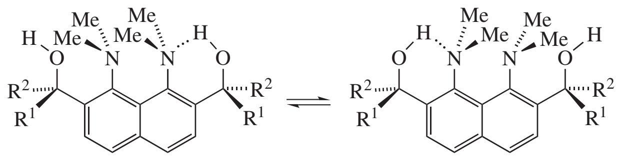
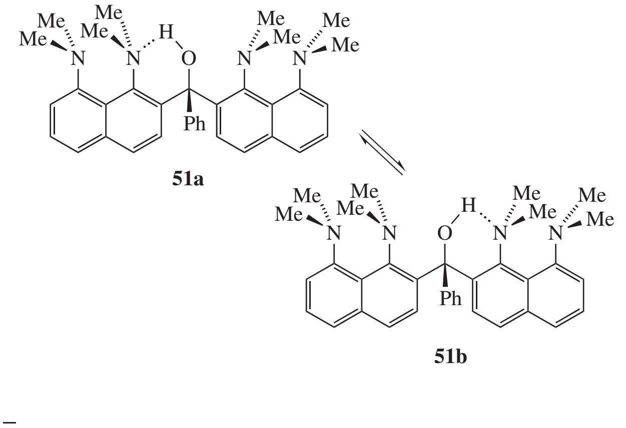


49 R^1, R^2 ≠ H



50a R^1, R^2 ≠ H

50b R^1, R^2 ≠ H



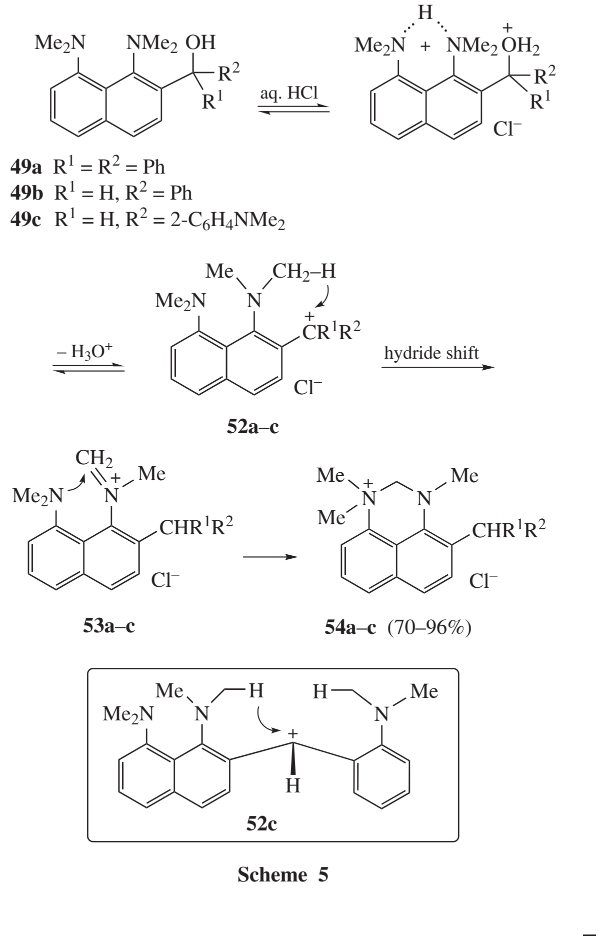
51b

pound for which such a conformation had been directly observed in the solid state.[54] Presumably, its stabilization is promoted by $n \rightarrow d$ interaction between the outside free nitrogen electron pair and vacant *d*-orbitals of a silicon atom. A much more effective way to fix the *in*,*out* form is the organization of intramolecular O–H···N hydrogen bonding between the NMe_2 group and a tertiary α-hydroxymethyl functionality in the *ortho*-position (**49**).[17,58] Unlike this, primary and secondary *o*-mono- and dialcohols prefer the *in*,*in* conformation, in which the OH groups participate in the formation of intermolecular ···OH···OH··· associates.[17,58]

For tertiary 2,7-dialcohols, the situation is completely different. In crystals, they exist in the *in*,*out* form where one hydroxyl group is chelated while another is engaged in the intermolecular association. In solution, such diols equilibrate between two equivalent *in*,*out*-*out*,*in* forms **50a** and **50b**; this equilibrium is accompanied by a tandem nitrogen inversion of both NMe_2 groups.[59] The dynamic behaviour of bis[1,8-bis(dimethylamino)-naphth-2-yl]phenylmethanol **51** is even more impressive. It has been established that both proton sponge units in solid **51** exist in the nonconventional *in*,*out* form, one of which is fixed by intramolecular O–H···N hydrogen bonding. In solution, the fast interconversion of two isoenergetic hydrogen chelates **51a** ⇆ **51b** occurs, which can be frozen below 183 K.[59]

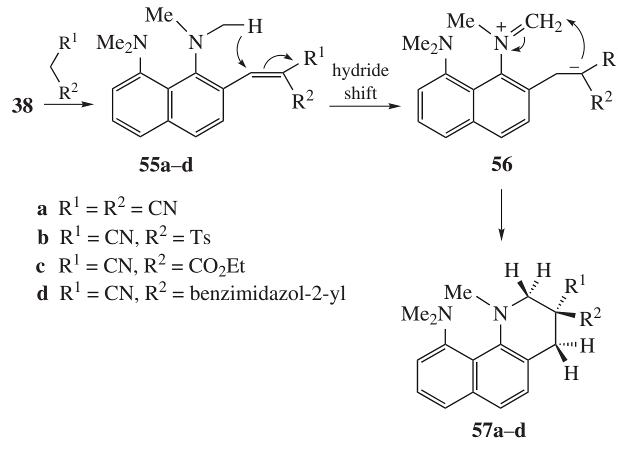
Proton sponges as hydride donors

The nearness of free nitrogen electron pairs in the molecule of **1** results in the splitting of their energetic levels that leads to a considerable lowering of the first ionization potential (IP_1 = 7.05 eV). Therefore, it is not surprising that the proton sponge is a strong electron donor, which easily generates a radical cation.[12,13] Another consequence of this phenomenon is the ability of NMe_2 groups in DMANs to donate a hydride ion to both external and internal hydride acceptors. This is manifested in multiple variations of the so-called '*tert*-amino effect', which is characteristic of such compounds.[60–62] Two typical examples are given below. In the first one, on the acidic treatment of secondary or tertiary *ortho*-alcohols **49a–c**, carbocations **52** are apparently generated, which isomerise by an internal hydride shift into methyleneiminium salt **53** with its subsequent cyclisation into 2,3-dihydroperimidinium salt **54** (Scheme 5). Note that in cation **52c** with two different hydride donor fragments, the proton sponge and the dimethylaniline residue, only the former works in this capacity.



Scheme 5

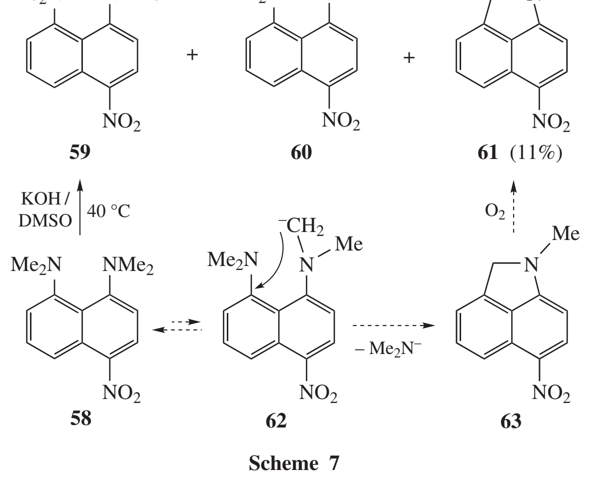
In the second example, the NMe_2 group donates a hydride ion onto the alkene C=C bond carrying cyano and other electron-accepting groups in the β-position (**55** → **56**, Scheme 6). In this case, intermediate methyleneiminium salt **56** cyclises on the carbanion centre arising in *ortho*-functionality that results in the formation of benzo[*h*]quinoline derivative **57**. Other modifications of these transformations have been recently disclosed, including tandem processes.[62]



Scheme 6

Proton sponges as CH acids

Paradoxically, under certain conditions, the proton sponge NMe_2 groups can display CH acidity. Thus, upon the treatment of DMAN 4-nitroderivative **58** with the superbasic KOH–DMSO system, compounds **59–61** were obtained in 40, 9 and 11% yields, respectively (Scheme 7).[63] While the first two are obviously the products of nucleophilic substitution at the aliphatic and aromatic carbon atoms, the formation of lactam **61** is thought to result from the acidic ionization of the NMe group and intramolecular substitution of the 8-NMe_2 group by carbanionic nucleophile **62** followed by the auto-oxidation of pyrroline intermediate **63**. Currently, we have disclosed several other reactions proceeding with the acidic ionization of NMe_2 groups in proton sponges, which will be reported elsewhere.



Scheme 7

In summary, due to a close proximity of *peri*-NMe_2 groups and their interaction with each other and with the ring π-system, proton sponge **1** manifests a unique set of acid-base properties. They include the exceedingly strong basicity, moderate hydride donacity and the weak CH acidity of NMe groups. Moreover, hydrogen bonding in DMANs is possible from both inside and outside, accompanied by interesting dynamic and hydrogen transfer phenomena. Many of them are useful for preparative chemistry, the design of various molecular devices, chemosensors and the modelling of enzymic catalysis.

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