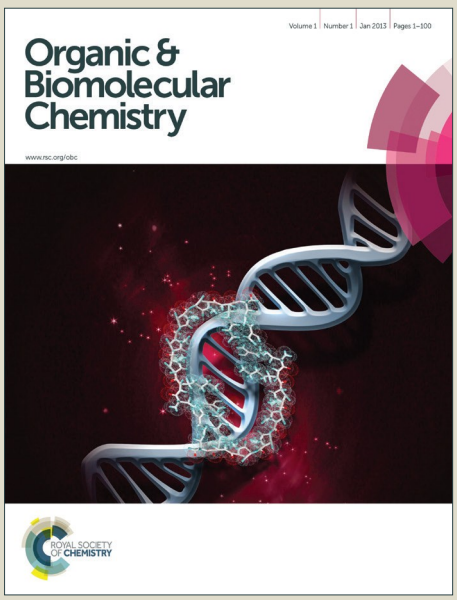
Organic & Biomolecular Chemistry

Accepted Manuscript



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The first proton sponge-based amino acids: synthesis, acid-base properties and some reactivity

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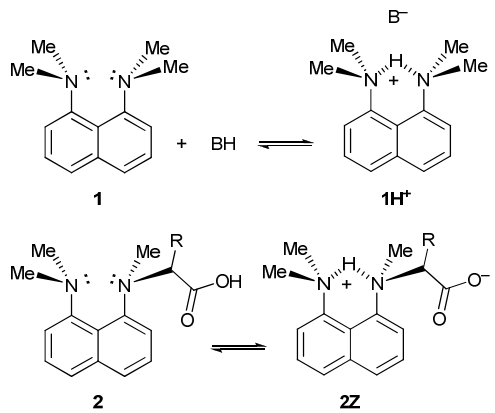
Abstract: The first hybrid base constructed of 1,8-bis(dimethylamino)naphthalene (proton sponge or DMAN) and glycine, *N*-methyl-*N*-(8-dimethylamino-1-naphthyl)aminoacetic acid, was synthesised in high yield and its hydrobromide was structurally characterised and used to determine the acid-base properties via potentiometric titration. It was found that the basic strength of the DMAN-glycine base (pK_a = 11.57, H_2O) is on the level of amidine amino acids like arginine and creatine and its structure, zwitterionic vs neutral, based on the spectroscopic (IR, NMR, mass) and theoretical (DFT) approaches, have strong preference to the zwitterionic form. Unlike glycine, the DMAN-glycine zwitterion is *N*-chiral and is hydrolytically cleaved with the loss of glycolic acid on heating in DMSO. This reaction together with the mild decarboxylative conversion of proton sponge-based amino acids into 2,3-dihydroperimidinium salts under air-oxygen was monitored with the help of the DMAN-alanine amino acid. The newly devised amino acids are unique as they combine fluorescent, strongly basic and redox-active properties.

Introduction

Amino acids in the form of proteins are Nature's main chemical constituents that perform crucial role in biosynthesis and function of biological systems, including humans. Outside proteins, individual amino acids are easily involved in proton transfer processes to give molecules with charge separated states providing acid-base control in tissues and bloodstream and even acting as neurotransmitters.[1,2] Apart from 23 proteinogenic amino acids, unnatural amino acids (non-standard amino acids used in synthetic biology) are presently added to the genetic codes to deeply

understand structure and function of proteins,[3] to introduce labels and fluorescent tags,[4] while redox active amino acids are used to probe and modulate electron transfer.[5] New applications as well as new amino acid compounds with unusual physicochemical and biological properties are continuously sought.[6]

From the other side, 1,8-bis(dimethylamino)naphthalene (proton sponge or DMAN, **1**), known for its remarkable proton accepting (pK_a = 12.10 in H_2O)[7] and high electron donating properties (IP_1 = 7.05 eV),[8] was successfully chosen as a key fragment to construct new hybrid structures with unique physicochemical behaviour. Over the past decade, by our group and others, this molecule was linked, mainly via its 4-carbon atom, to fullerene C_{60} (redox active compounds),[9] 4-aminonaphthalimide and other electron-accepting groups (pH-sensitive fluorescent switches and colorimetric indicators),[10,11] phosphane ligands[12] and magnetic cobalt nanoparticles (homogeneous catalysis and heterogeneous catalysts).[13] At the same time, nitrogen derivatization was rarely explored in DMAN chemistry with the exception of expanding the *N*-alkyl groups[14,15] including chiral alkyls[16] and a few *N*-acyl derivatives.[17] In this context, the main idea of the present work was to synthesize and investigate reactivity and acid-base properties of proton sponge-based amino acids **2**, bearing in mind easiness of formation $\mathbf{1H^+}$, which may lead to **2Z** (zwitterionic) as a result of inter- or intramolecular prototropy (Scheme 1). A question of *N*-chirality of α-amino acids is also discussed.

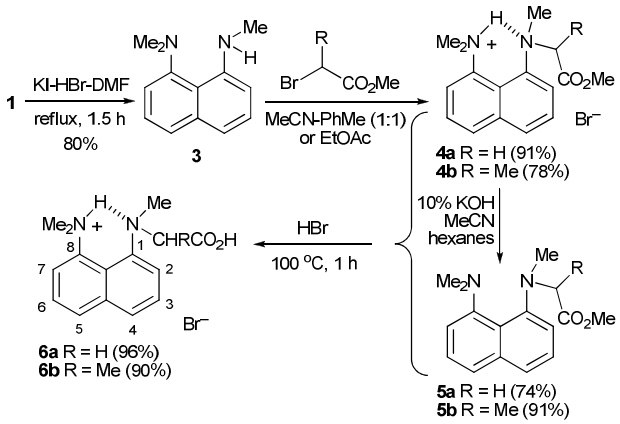


Scheme 1 Protolytic equilibria between DMAN (**1**) and its chelated monocation ($\mathbf{1H^+}$), and between neutral (**2**) and zwitterionic (**2Z**) DMAN-based amino acids.

Results and discussion

Synthesis, proton transfer reactions and acid-base properties

The protonated DMAN-based amino acids, **6a** and **6b**, were readily synthesized according to Scheme 2. We started with the proton sponge itself, which was successively mono-*N*-demethylated to give **3**[18] and then quaternized with methyl esters of α-bromoacetic or propionic acids to yield previously unknown glycine and alanine derivatives either in the form of hydrobromides (**4a**,**b**) or as free bases (**5a**,**b**). Both forms could be used to produce air-stable and non-hygroscopic salts **6a**,**b** on heating with aqueous HBr.



Scheme 2 Preparation of hydrobromides **6a** and **6b**.

Structures of compounds **4**–**6** were proven using a set of analytical methods. Thus, salts **4** and **6** possess intramolecular H-bonds, and the chelated NH proton resonates in their ^{1}H NMR spectra at δ = 16.2–17.8 ppm, depending on solvent and substituents. Relatively large ^3J(NH,8-NMe$_2$) constants (3.8–4.5 Hz) are evident for the NH proton is being markedly shifted more to the 8-NMe$_2$ group than to the other nitrogen, apparently due to electron-accepting nature of the carboxymethyl group, making the 8-NMe$_2$ fragment more basic.[19] The solid state structure of hydrobromide **6a** is in agreement with the solution measurements with the only exception is that the Br^- counterion is now involved in H-bonding with the OH hydrogen. Further details on both H-bonds, $[NHN]^+$ and $[OHBr]^-$, are given in Fig. 1.

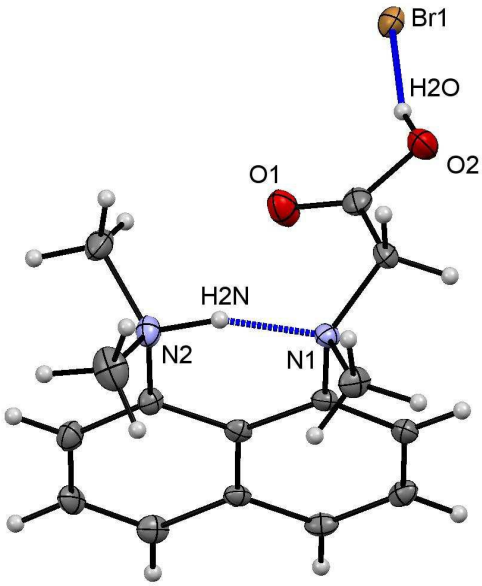
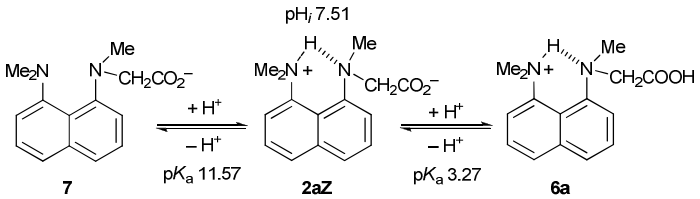


Fig. 1 ORTEP plot for X-ray structure of **6a** with two H-bonds marked in blue (P = 50%, 100 K). Key lengths (Å) and angles (°): N(2)–H(2N) 1.08(4), H(2N)...N(1) 1.59(4), N(2)...N(1) 2.610(4), N(2)–H(2N)...N(1) 156(2), O(2)–H(2O) 0.95(6), H(2O)...Br(1) 2.22(5), O(2)...Br(1) 3.154(4), O(2)–H(2O)...Br(1) 165(3).

All three N–Me groups in salts **4a** and **6a** are displayed in the ^{1}H and ^{13}C NMR spectra as separate peaks, which proved the [NHN]$^{+}$ bond in their molecules is a good lock for preventing stereoconversion, and hence the DMAN-glycine derivatives adopt *N*-chirality. This is in contrast to proton sponges with *N*-benzyl substituents, which are quite stereolabile in the NMR time-scale even in the form of salts.[20] The NMR picture is even more complex in the case of alanine derivatives **4b** and **6b**, which owing to two stereogenic centres, the N(1) and C(α) atoms, exist as a mixture of diastereomers.

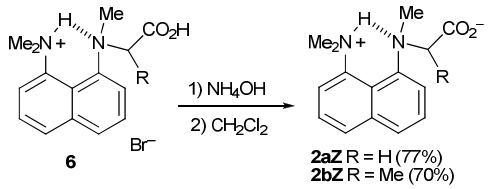
Hydrobromide **6a** was used to estimate the acid-base strength of proton sponge-based amino acids, as it is soluble in water and does not capture any solvent molecule even being recrystallized from aqueous alcohol. This salt was subjected to potentiometric titration (see the ESI for details) and the results presented in Scheme 3 (in water scale) are average of at least three runs.



Scheme 3 Protolytic equilibria constants between anionic **7** and cationic **6a** counterparts of amino acid **2a** given in the form of zwitterion **2aZ**.

As seen, the nitrogen basicity of the DMAN-glycine base (**2a**) (pK_a = 11.57) is somewhat lower than that of the parent DMAN (pK_a = 12.10) and is on the level of arginine (pK_a = 12.48) and creatine (pK_a = 10.57), the most basic natural amino acids. Noteworthy, the isoelectric point of **2a** lies near the physiological pH values and is almost equal to that of histidine (pH$_i$ = 7.60).[1,21]

It was rather intriguing to find out the real form (neutral **2** or zwitterionic **2Z**) the proton sponges extended by acidic groups adopt in different media. To do so, both amino acids **2a**,**b** were isolated using deprotonation of salts **6a**,**b** by aqueous ammonia as depicted in Scheme 4. Subsequent extraction with CH_2Cl_2 was quite fortunate owing to hydrophobic naphthyl and methyl substituents and gave high yields of pure amino acids. Compounds **2a**,**b** are hygroscopic, readily soluble in water and alcohols, while their insolubility in Et_2O and hydrocarbons provides a strong hint that DMAN-based amino acids possess zwitterionic structures **2Z** in the condensed state.

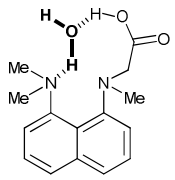


Scheme 4 Isolation of amino acids **2a**,**b**.

In fact, other spectroscopic techniques (IR and NMR) confirmed this conclusion. Thus, IR spectra recorded in KBr contain strong vibration bands of a carboxylate fragment near 1625–1626 and 1395–1398 cm^{-1}. The ^{1}H NMR spectra of **2a**,**b** (in DMSO-d$_6$, CD_3CN or $CDCl_3$) display the N–Me signals near or well above 3.0 ppm and a very low-field peak (δ 17.7–18.1 ppm) of the chelated [NHN]$^+$ proton, which are characteristic for the proton sponge cations.[14]

At the same time, gas phase EI-MS behaviour of **2a** and **2b** very close resembles much of the fragmentation mode of neutral DMAN **1**.[22] Some details of the fragmentation are given in the ESI (see Fig. S1). The main pathways being the loss of *N*-methylglycine and *N*-methylalanine or their *N*-deprotonated radicals to give *N*-methylbenz[*c*,*d*]indolium ion (*m*/*z* 168, 100%). Gas phase decarboxylation of amino acids **2a**,**b** is not a characteristic feature of these compounds and the probability of $[M - CO_2]^+$ fragmentation route does not exceed 17% in both cases.

DFT calculations undertaken to establish relative stability of the proton sponge-based amino acids (B3LYP/6-31G**, see Table S1 in the ESI) have shown that neutral **2a** is by 16.0 kcal/mol more stable in the gas phase over zwitterion **2aZ**, although solvation (DMSO) strongly minimize this difference (up to 2.3 kcal/mol) and even make **2aZ** by 2.3 kcal/mol more stable over **2a** in H_2O media. Although we did not try water clusters, one water molecule calculated to form H-bridged structures of type **2a-H_2O** (see the ESI for details) is also able to decrease the energy difference between **2a** and **2aZ** to a somewhat over 2 kcal/mol.



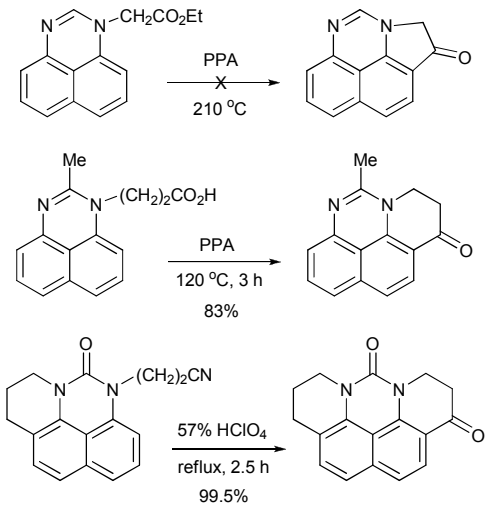
2a-H_2O

Interestingly that in the gas phase the NH proton in calculated zwitterion **2aZ**, obviously due to electrostatic attraction between the opposite charges, is shifted more to the N(1) nitrogen atom (Table S1). On the whole, these results are in line with the well-known fact that zwitterionic forms of the α-amino acids are less stable than their neutral counterparts in the gas phase, starting from glycine to the most basic arginine,[23] although there is a general trend of enhanced zwitterion stabilization with increasing basicity.[24]

Thermal behaviour, hydrolytic scission and oxidative transformations

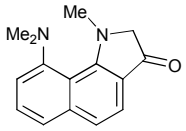
The first step to investigate any unusual reactivity the proton sponge moiety can bring to DMAN-based amino acids was an attempted intramolecular acylation in ester **5a**. There were some close

precedents in the literature, although much more successful for six-membered ring cyclisations (Scheme 5).[25]



Scheme 5 Literature examples of *ortho*-acylation.

In our case, as compound **5a** is more flexible with its nitrogen atoms not involved in the pyrimidine ring, the *ortho*-cyclisation may lead to benzo[*g*]indolone derivative **8**.



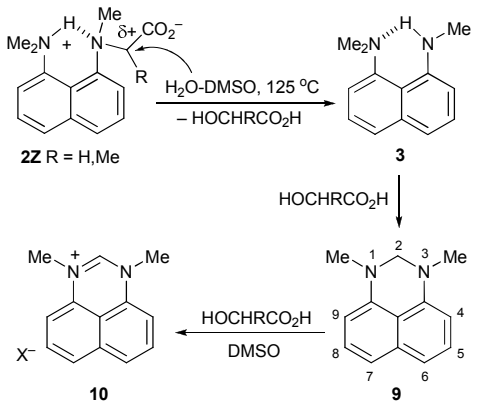
8

We have shown that compound **5a** on heating with 57% $HClO_4$ is completely destroyed, heating with conc. aqueous HCl gave only carboxylic acid **6a** as chloride, and heating in PPA at 110–120 °C for 4 h followed by KOH neutralisation and methylene chloride extraction gave nothing but anion **7**, which was isolated in 95% yield as hygroscopic potassium salt and fully characterised by spectral data.

Dissolution of ester **5a** together with one equivalent of Lewis acid $BF_3 \cdot Et_2O$ in anhydrous CH_2Cl_2 followed by layering with Et_2O and keeping the reaction mixture at –20 °C for 6 d resulted in diffusion crystallisation of the product, which, in fact, turned out to be the hydrogen tetrafluoroborate salt of **5a**, **5a**·HBF_4 (yield 19%), but not the expected difluoroborate complex; most of **5a** remained unchanged. A similar reaction was earlier observed for some heterocyclic

superbasic compounds,[26] and may be rationalise in light of the well-known tendency of strongly destabilised neutral proton sponges to remove electrostatic and steric strain, so the protonation is frequently the simplest way.[14]

Thermolysis of hydrobromide **6a** in DMSO-d_6 has proved this salt is stable below 130 °C, but a spontaneous decomposition occurred above 135 °C to yield complex mixture of unidentifiable products. From the other hand, potassium salt **7** was found unchanged in this solvent even at 150 °C for 30 h. Unlike its cationic and anionic forms, the amino acid **2a**, via transient diaminonaphthalene **3**, already at 120–125 °C gave 1,3-dimethyl-2,3-dihydroperimidine (**9**), which then gradually turned into other oxidation products; the main one being aromatic perimidinium salt **10**. Interestingly, DMAN-alanine amino acid **2b** produces the same reaction products (see Fig. S2 for a representative run) and, hence, the overall transformation may be described by Scheme 6.

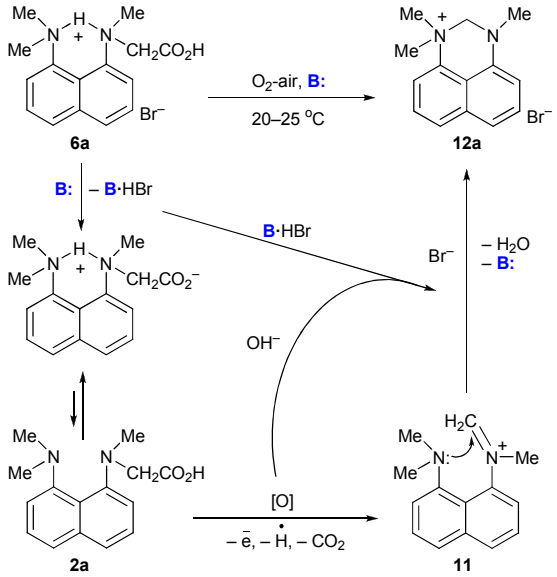


Scheme 6 Transformation of amino acids **2Z** on heating in wet DMSO.

Apparently, the reaction starts with hydrolytic cleavage of the amino acid side chain to give **3** and a corresponding hydroxyacid. In a separate experiment (heating with 1 equiv. of glycolic acid in DMSO-d_6), we have shown that diamine **3** is indeed oxidised into heterocyclic product **9** and then into **10**. No transformations of type **3** → **9** and **9** → **10** occur until glycolic or lactic acids are added to hot DMSO. In the ^{1}H NMR spectra, compounds **9** and **10** have very characteristic singlet peaks of the C(2)-protons at δ 4.14 and 9.0–9.2 ppm, respectively, which are easily identified and monitored. The X^- in **10** is glycolate or lactate anions and the yields of **3**, **9**, and **10** did not exceed 35%, 19%, and 65% at their maximum (see Table S2). It should also be stressed that

transformations **2** → **10** were never complete as oxyacids gradually turn amino acids **2** into more inert cationic forms **6** (there is raising in acidity in the reaction mass because the basicity of aromatic amines **3** and **9** is very low[7b,14]) thus providing inhibition.

Finally, another interesting transformation of amino acids **2a**,**b** was found, in which the amino acid side chain is now involved. To specify, hydrobromide **6a** is able to cyclize quantitatively into 2,3-dihydroperimidinium salt **12a** under air-oxygen in the presence of 1 equiv. or lesser of a mild base such as DMAN or pyridine (Scheme 7, Table 1).



Scheme 7 Proposed base-promoted oxidative mechanism of conversion **6a** → **12a**.

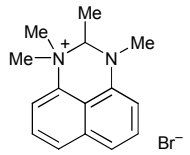
Table 1 Base-promoted oxidation of hydrobromide **6a** into perimidinium salt **12a**

Run	Solvent	Base	Time (d)	Degree of conversion (%)[a]
1	DMSO	DMAN	4[b]	4
2	DMSO	DMAN	2	24
3	DMSO	DMAN	6	42
4	Py	Py	1	30
5	Py	Py	4	100[c]

[a] Yields based on ^{1}H NMR. [b] Without air-bubbling. [c] Isolated yield 60%.

The reaction starts with the in situ generation of equilibrium amounts of **2a**, which then after oxidative decarboxylation produces methyleneiminium cation **11**, quickly cyclizing into 1,1,3-

trimethyl cation isolated as bromide **12a**. Earlier, cyclization of DMAN into 2,3-dihydroperimidinium salts was well documented under the action of different oxidants such as transition metal complexes,[27] carbonium centres in the ortho-position[28] or simple air-oxygen owing to strong electron-donating substituents in the aromatic ring.[29] Next, we have proved that methyl ester **4a**(**5a**) is inert in this reaction, which is evident that the decarboxylation step should precede the cyclization in accord with Scheme 7.[30] We also found that strong ionic bases such as KOH, generating only anion **7**, inhibit the process, and no reaction was observed without adding a base or keeping the reaction mass in an inert atmosphere. As seen from Table 1 (cf. runs 2 and 5), milder bases provide faster turnout, as the initially formed salt **B**·HBr has to take HBr off and let **B** enter the catalytic cycle back. Similarly to **6a**, the reaction of salt **6b** ends after six days of oxidation at room temperature in pyridine to give heterocyclic salt **12b** as the only isolable product.



12b

Structures of compounds **12a**,**b** were established using a set of analytical methods and, in the case of **12a**, X-ray diffraction data. Interestingly, bromide **12a** crystallises as dihydrate with the bromide anion and water molecules have been found to form endless uneven ribbons of alternating roughly five-membered H-bonded cycles, while the 2,3-dihydroperimidinium cations are situated at both sides of the ribbon with no appreciable interaction between them (Fig. 2). This type of water and anion arrangements is rarely observed in crystal engineering of organic molecules (cf. ref. 31).

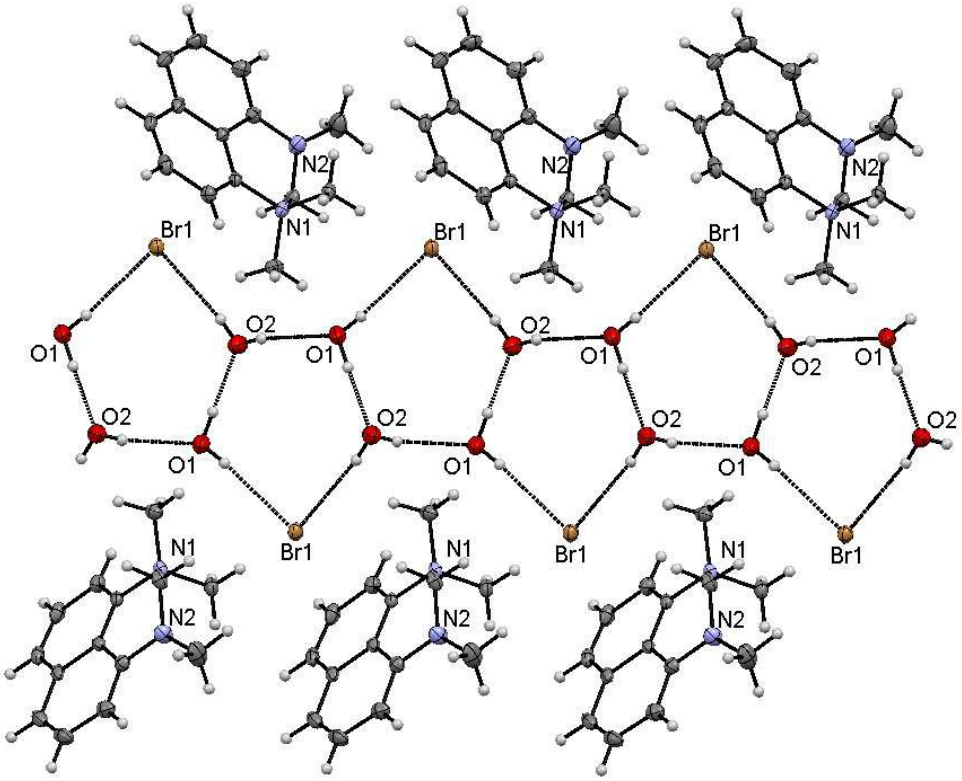


Fig. 2 ORTEP plot for X-ray crystal structure of **12a** with the ribbon-like H-bond network between bromide and water molecules (P = 50%, 120 K). Key lengths (Å) and angles (°): O(1)...Br(1) 3.319(2), O(2)–H...Br(1) 173(2), O(2)...Br(1) 3.361(2), O(2)–H...Br(1) 170(2), O(1)...O(2) 2.733(2), O(1)–H...O(2) 176(2), O(2)...O(1) 2.756(3), O(2)–H...O(1) 168(3).

Unlike simple proton salts of DMAN and neutral DMAN **1**, DMAN-based amino acids and derivatives are all fluorescent in solutions when protonated to form $[N\text{-}H\text{-}N]^+$ bridges (compounds **2**, **4**, and **6**) but are not fluorescent when their nitrogen atoms are neutral (compounds **5** and **7**). This opens a simple possibility to introduce pH-sensitive fluorescent tags into supramolecular motifs and protein molecules.

Conclusions

In summary, we have for the first time obtained and studied proton sponges fused via nitrogen atoms with alanine and glycine residues. The proton sponge moiety renders to these hybrids high basicity and unusual reactivity, which depends on the form (anionic, neutral, or cationic) the DMAN-based amino acids treated. The most reactive form is neutral, which in fact zwitterionic in

condensed media. Unlike most amino acids, this form could be 'disassembled' on heating in wet DMSO to give 1-dimethylamino-8-methylaminonaphthalene and the corresponding oxyacid, while oxidation with air-oxygen, although slowly, gave 2,3-dihydroperimidinium salts as a result of decarboxylation and heterocyclization. Overall, these compounds may find an application, when redox-active and fluorescent amino acids are sought, combining the properties of strong but mild nitrogen bases.

Experimental

General. NMR spectra were recorded on a Bruker DPX-250 (250 MHz for ^{1}H, 62.9 MHz for ^{13}C) spectrometer with the solvent residual peaks as the internal standard (δ/ppm, *J*/Hz). IR spectra were measured on a FT FSM-1202 spectrometer. Mass spectra were obtained from a Finnigan MAT INCOS 50 instrument (electron impact, 70 eV). Thin layer chromatography was carried out on Al_2O_3 and on silica gel (70–230 mesh, Aldrich). The progress of reactions and the purity of products were monitored by TLC on Al_2O_3 and Silufol plates; development with iodine and bromine vapours. The melting points were measured in sealed capillaries and are uncorrected. The solvents were purified and dried by standard methods. 1-Dimethylamino-8-methylaminonaphthalene (**3**) was prepared as described previously.[18] Methyl 2-bromopropionate (97%) was purchased from Alfa Aesar.

Methyl *N*-methyl-*N*-(8-dimethylaminonaphth-1-yl)aminoacetate hydrobromide (4a). Methyl bromoacetate (1.04 mL, 1.1 mmol) was added to a solution of amine **3** (200 mg, 1.0 mmol) in dry toluene (7 mL) and acetonitrile (7 mL). The mixture was refluxed with $CaCl_2$-tube protection until the starting amine is consumed (~3 h, TLC control, Silufol plates, $CHCl_3$). The solvent was evaporated, the crude product was recrystallized from acetonitrile and washed with diethyl ether to afford **4a** (321 mg, 91%) as light grey crystals; mp 125–127 °C. ^{1}H NMR (DMSO-d_6): δ = 2.90 (s, 3H, 1-NMe), 3.29 and 3.45 (both d, *J* = 4.4 and *J* = 4.4, 6H, 8-NMe_2), 3.69 (s, 3H, OMe), 4.36 (ABq, *J* = 17.2, 2H, N–CH_2CO), 7.71 (t, *J* = 7.7, *J* = 8.1, 1H, 3-H), 7.77 (t, *J* = 7.7, *J* = 8.1, 1H, 6-

H), 7.99 (dd, *J* = 1.0, *J* = 7.7, 1H, 2-H), 8.07 (t, *J* = 1.7, *J* = 8.1, 1H, 4-H), 8.17 (d, *J* = 7.4, 1H, 5-H), 8.27 (dd, *J* = 1.0, *J* = 7.7, 1H, 7-H), 16.80 (br. s, 1H, NHN^+). ^{13}C NMR (DMSO-d_6): δ = 46.8 (1-NMe), 47.7 and 47.8 (8-NMe_2), 53.2 (OMe), 58.8 (N–CH_2), 120.9, 122.0, 124.6, 127.3, 128.3, 129.1, 131.1, 135.9, 142.3, 147.2, 171.5 (C=O). IR (Nujol) (ν/cm^{-1}): 3467, 3411; 1732 (C=O); 1630; 1608, 1524 (Ar); 1228, 1208 (C–O–C). $C_{16}H_{21}BrN_2O_2$ (353.25): calcd. C 54.40, H 5.99, N 7.93; found C 54.36, H 6.01, N 7.88. ^1H NMR (CD_3CN, data for HBF_4 salt; mp 137–139 °C): δ = 2.91 (s, 3H, 1-NMe), 3.27 and 3.40 (both d, both *J* = 4.7, both 3H, 8-NMe_2), 3.73 (s, 3H, OMe), 4.19 (s, 2H, N–CH_2CO), 7.67–7.83 (m, 3H), 7.97–8.04 (m, 2H), 8.12 (dd, *J* = 1.0, *J* = 8.4, 1H), 16.90 (br. s, 1H, NHN^+). MS (data for HBF_4 salt), *m*/*z* (*I* (%)): 273 $[M]^+$ (18), 272 (100), 213 (43), 199 (68), 198 (46), 197 (86), 184 (52), 183 (52), 182 (78), 170 (57), 169 (29), 168 (95), 167 (25), 154 (21), 127 (30), 99 (62), 91 (15), 49 (29), 42 (20).

Methyl 2-[*N*-methyl-*N*-(8-dimethylaminonaphth-1-yl)amino]propionate hydrobromide (4b). Methyl 2-bromopropionate (0.70 mL, 6.25 mmol) was added to a solution of diaminonaphthalene **3** (250 mg, 1.25 mmol) in dry ethyl acetate (15 mL). The mixture was refluxed for 100–130 h with $CaCl_2$-tube and light protection until the starting amine is consumed (TLC control, Silufol plates, $CHCl_3$). The solvent was evaporated and the residue was recrystallized from acetonitrile to afford **4b** (357 mg, 78%) as light yellow crystals with mp 186–188 °C (decomp.). ^1H NMR (CD_3CN): δ = 1.05 (d, *J* = 7.0, 2.3H), 1.70 (d, *J* = 6.7, 0.9H), 2.91 (s, 2.3H), 2.98 (s, 1H), 3.18 (d, *J* = 2.4, 0.25H), 3.30 (d, *J* = 4.5, 2.4H), 3.40–3.47 (m, 5.2H, 8-NMe_2), 3.89 (s, 2H), 4.17–4.25 (m, 0.7H, N–CH), 4.29–4.37 (m, 0.3H, N–CH), 7.62–7.87 (m, 2.8H), 7.97–8.19 (m, 3H), 16.83 (br. s, 0.3H, NHN^+), 17.57 (br. s, 0.7H, NHN^+). ^{13}C NMR (CD_3CN): δ = 16.2, 17.2, 42.0, 45.3, 45.7, 46.2, 47.0, 47.8, 52.2, 53.0, 63.2 and 64.2 (N–CH), 120.6, 120.7, 121.1, 121.5, 123.8, 125.6, 126.5, 126.7, 127.4, 127.5, 128.6, 128.8, 130.5, 130.7, 135.5, 135.6, 140.9, 141.3, 142.1, 146.2, 173.3 and 174.7 (C=O). $C_{17}H_{23}BrN_2O_2$ (367.28): calcd. C 55.59, H 6.31, N 7.63; found C 55.48, H 6.44, N 7.59.

Methyl *N*-methyl-*N*-(8-dimethylaminonaphth-1-yl)aminoacetate (5a). 10% aqueous KOH (15 mL) was added to a solution of hydrobromide **4a** (300 mg, 0.85 mmol) in acetonitrile (3 mL). The

mixture was shaken and extracted with *n*-hexane (3 × 10 mL). The extract was dried with anhydrous Na_2SO_4. The crude product obtained after solvent evaporation was purified by column chromatography (silica gel, ethyl acetate) to afford **5a** (171 mg, 74%) as light brown oil. ^{1}H NMR ($CDCl_3$): δ = 2.65 (br. s, 6H, 8-NMe_2), 3.10 (s, 3H, 1-NMe), 3.47 and 3.76 (both br. s, 2H, N–CH_2CO), 3.69 (s, 3H, OMe), 6.95 (dd, *J* = 1.3, *J* = 7.3, 1H, 2-H), 7.04 (dd, *J* = 1.3, *J* = 7.3, 1H, 7-H), 7.26–7.33 (m, 2H, 6-H, 3-H), 7.34–7.40 (m, 2H, 5-H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 40.3 (1-NMe), 42.2 and 47.5 (8-NMe_2), 51.5 (OMe), 59.7 (N–CH_2), 113.6, 113.8, 120.2, 122.8, 122.9, 125.8, 126.0, 138.3, 149.4, 150.8, 172.1 (C=O). IR (liquid film) (ν/cm^{-1}): 3051, 2993, 2950, 2864, 2828, 2785 (C–H); 1751 (C=O); 1607, 1575, 1504 (Ar); 1247, 1225, 1202, 1174, 1140 (C–O–C). $C_{16}H_{20}N_2O_2$ (272.34): calcd. C 70.56, H 7.40, N 10.29; found C 70.50, H 7.42, N 10.36.

Methyl 2-[*N*-methyl-*N*-(8-dimethylaminonaphth-1-yl)amino]propionate (5b). The compound was prepared from hydrobromide **4b** (367 mg, 1 mmol) similarly to **5a**. The crude product obtained after solvent evaporation was purified by column chromatography (silica gel, EtOAc) to afford **5b** (260 mg, 91%) as colourless oil. ^{1}H NMR ($CDCl_3$): δ = 0.86–0.91 (m, 1H), 1.06 (br. d, *J* = 7.2, 2H), 1.27 (br. s, 1.4H), 1.51 (br. d, *J* = 6.4, 0.9H), 2.56 (s, 2H), 2.65 (s, 2.8H), 2.87 (br. s, 0.9H), 3.04 (br. s, 0.9H), 3.10 (s, 1.8H), 3.38 (br. s, 0.7H), 3.74 (s, 1.7H), 3.97–4.12 (m, 0.7H, N–CH), 6.92–7.02 (m, 1.5H), 7.16 (br. d, *J* = 6.6, 0.3H), 7.25–7.41 (m, 3.2H). MS, *m*/*z* (*I* (%)): 286 [M]$^+$ (63), 227 (33), 199 (100), 198 (34), 197 (35), 184 (48), 168 (30). $C_{17}H_{22}N_2O_2$ (286.37): calcd. C 71.30, H 7.74, N 9.78; found C 71.36, H 7.70, N 9.71.

***N*-Methyl-*N*-(8-dimethylaminonaphth-1-yl)aminoacetic acid hydrobromide (6a).** A solution of methyl ester hydrobromide **4a** (200 mg, 0.56 mmol) in 45% aqueous HBr (4.4 mL) was heated on water bath at 100 °C for 1 h. The crude product obtained after evaporation of volatiles to dryness was washed with diethyl ether to afford **6a** (184 mg, 96%) as light brown crystals (fluorescent in solutions under UV-light); mp 236–238 ºC (decomp.). ^{1}H NMR (DMSO-d_6): δ = 2.90 (s, 3H, 1-NMe), 3.25 and 3.41 (both br. d, *J* = 4.1 and 3.8, 6H, 8-NMe_2), 4.25 (ABq, *J* = 17.1, 2H, N–CH_2), 7.67–7.78 (m, 2H, 6-H, 3-H), 7.97 (d, *J* = 7.3, 1H, 2-H), 8.06 (d, *J* = 7.9, 1H, 4-H), 8.16 (d, *J* = 8.2,

1H, 5-H), 8.24 (d, *J* = 7.6, 1H, 7-H), 13.14 (br. s, 1H, CO_2H), 17.07 (s, 1H, NHN^+). ^{13}C NMR (DMSO-d_6): δ = 46.6 (1-NMe), 47.5 and 47.6 (8-NMe_2), 59.1 (N–CH_2), 120.9, 121.9, 124.4, 127.2, 128.2, 128.9, 130.9, 135.8, 142.5, 147.3, 172.2 (C=O). MS, *m*/*z* (*I* (%)): 259 $[M]^+$ (8), 258 (49), 214 (30), 199 (70), 198 (27), 197 (56), 184 (67), 183 (82), 182 (70), 170 (66), 169 (28), 168 (100), 167 (25), 154 (21), 127 (32), 99 (48), 91 (16), 82 (23), 80 (24), 44 (28), 42 (23). $C_{15}H_{19}BrN_2O_2$ (339.23): calcd. C 53.11, H 5.65, N 8.26; found C 53.20, H 5.57, N 8.30.

2-[*N*-Methyl-*N*-(8-dimethylaminonaphth-1-yl)amino]propionic acid hydrobromide (6b). The compound was prepared from hydrobromide **4b** (150 mg, 6.6 mmol) as described above for **6a**. The residue obtained after solvent evaporation was recrystallized from acetonitrile to afford light grey crystals of compound **6b** (130 mg, 90%); mp 228–230 °C (decomp.). ^1H NMR (CD_3CN): δ = 1.16 (d, *J* = 7.0, 2.5H), 1.72 (d, *J* = 7.0, 1.4H), 2.94 (d, *J* = 1.0, 3.8H), 3.25 (d, *J* = 4.5, 2.8H), 3.32–3.40 (m, 4.5H), 4.14–4.23 (m, 0.8H), 4.30–4.40 (m, 0.3H), 7.65–7.78 (m, 2.7H), 7.86 (dd, *J* = 1.3, *J* = 7.4, 0.7H), 7.93–8.16 (m, 3H), 16.98 (br. s, 0.2H, NHN^+), 17.78 (br. s, 0.7H, NHN^+). ^{13}C NMR (DMCO-d_6): δ =17.1, 17.9, 42.5, 45.7, 45.9, 46.4, 47.3, 47.9, 63.0 and 64.0 (N–CH), 120.8, 212.2, 122.0, 124.2, 126.3, 126.8, 127.0, 127.7, 127.8, 128.6, 129.0, 130.5, 130.8, 135.3, 135.5, 141.6, 142.2, 142.7, 147.1, 174.5 and 175.8 (C=O). $C_{16}H_{21}BrN_2O_2$ (353.25): calcd. C 54.40, H 5.99, N 7.93; found: C 54.44, H 5.93, N 7.90.

***N*-Methyl-*N*-(8-dimethylaminonaphth-1-yl)aminoacetic acid, zwitterion (2aZ).** 25% aqueous ammonia (0.2 mL) was added to a solution of hydrobromide **6a** (100 mg, 0.3 mmol) in water (1.4 mL). The resulting mixture was evaporated to dryness and the solid residue was extracted with methylene chloride (5 × 20 mL). The crude product obtained after solvent evaporation was washed with diethyl ether to afford amino acid **2aZ** (58 mg, 77%) as brown hygroscopic caramel, quickly liquefying on air (fluorescent in solutions under UV-light); mp 63–65 ºC (decomp. with water loss then decomp. above 203–205 ºC). ^1H NMR ($CDCl_3$): δ = 2.94 (s, 3H, 1-NMe), 3.32 and 3.53 (both s, 6H, 8-NMe_2), 4.00 (ABq, *J* = 16.1, 2H, N–CH_2), 7.55–7.67 (m, 3H, 2-H, 3-H, 6-H), 7.83 (d, *J* = 7.7, 1H, 4-H), 7.90 (d, *J* = 8.2, 1H, 5-H), 8.19 (d, *J* = 7.5, 1H, 7-H), 17.67 (br. s, 1H,

NHN$^+$). ^{13}C NMR ($CDCl_3$): δ = 46.8 (1-NMe), 47.3 and 48.6 (8-NMe_2), 61.4 (N–CH_2), 120.0, 122, 123.7, 127.3, 127.7, 128.9, 130.4, 136.0, 142.5, 146.3, 172.6 (C=O). IR (ν/cm^{-1}), (KBr): 3432 (br. H_2O); 2938 (C–H); 1625 ($\nu_{as}CO_2^-$), 1395 ($\nu_sCO_2^-$); 1605, 1468 (Ar); 1034, 835, 773, 747. MS, *m*/*z* (*I* (%)): 258 [M]$^+$ (27), 226 [M – MeOH]$^+$ (29), 214 [M – CO_2]$^+$ (17), 199 [M – CH_2CO_2H]$^+$ (52), 198 [M – CH_3CO_2H]$^+$ (32), 197 [M – CH_3CO_2H – H]$^+$ (65), 184 [M – CH_2CO_2H – Me]$^+$ (57), 183 (72), 182 (73), 170 [M – N(Me)CH_2CO_2H]$^+$ (54), 169 [M – MeNHCH_2CO_2H]$^+$ (30), 168 [M – MeNHCH_2CO_2H – H]$^+$ (100), 167 (33), 154 (29), 140 (15), 128 (21), 127 (50), 126 (18), 115 (17), 99 (45), 91 (19), 82 (21), 80 (22), 77 (20), 44 (14), 42 (26). $C_{15}H_{18}N_2O_2$ (258.32): calcd. C 69.74, H 7.02, N 10.84; found C 69.81, H 6.95, N 10.93.

2-[*N*-Methyl-*N*-(8-dimethylaminonaphth-1-yl)amino]propionic acid, zwitterion (2bZ) was prepared similarly to **2aZ** from hydrobromide **6b** (28 mg, 0.079 mmol). The crude product obtained after solvent evaporation was washed with diethyl ether to afford brown caramel (15.4 mg, 70% yield), quickly liquefying on air (fluorescent in solutions under UV-light) with mp 80–82 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ = 1.20–1.14 (m, 3H), 2.84 (d, 1.7H), 3.02 (s, 0.9H), 3.08 (s, 3H), 3.30 (s, 3H), 3.36 (s, 3.3H), 3.54–3.62 (m, 0.6H), 3.96 (m, 4H), 7.42–7.48 (m, 1.1H), 7.55–7.68 (m, 3.6H), 7.88 (br. d, 1H), 7.91 (br. d, 1H), 8.09 (d, 1H), 18.10 (br. s, 1H, NHN$^+$). ^{13}C NMR ($CDCl_3$): δ = 9.2, 18.0, 29.9, 36.1, 44.5, 46.8, 47.2, 47.9, 48.3, 66.8 and 64.7 (N–CH), 118.0, 122.12, 122.15, 123.0, 124.6, 126.7, 126.8, 127.4, 127.7, 127.9, 129.7, 130.5, 136.5, 138.0, 142.7, 144.5, 147.0, 147.7, 175.9 and 176.6 (C=O). IR (ν/cm^{-1}), (KBr): 3430 (br. H_2O); 2956, 2924, 2854 (C–H); 1626 ($\nu_{as}CO_2^-$), 1398 ($\nu_sCO_2^-$); 1627, 1466 (Ar); 1034, 774. MS, *m*/*z* (*I* (%)): 272 [M]$^+$ (28), 228 (18), 213 (21), 199 (68), 198 (28), 197 (41), 185 (17), 184 (100), 183 (84), 182 (70), 170 (32), 169 (22), 168 (100), 167 (57), 154 (22), 127 (26), 44 (10), 42 (16), 29 (16), 28 (30), 27 (60), 18 (30), 14 (19). $C_{16}H_{20}N_2O_2$ (272.34): calcd. C 70.56, H 7.40, N 10.29; found C 70.60, H 7.45, N 10.21.

Potassium *N*-methyl-*N*-(8-dimethylaminonaphth-1-yl)aminoacetate (7). A solution of hydrobromide **6a** (50 mg, 0.14 mmol) in water (1 mL) was neutralized with 10% aqueous KOH to pH 8 and evaporated to dryness. The solid residue was extracted with methylene chloride (2 × 20

mL). After that, the solvent was evaporated to afford acetate **7** (41 mg, 95%) as brownish hygroscopic caramel, quickly liquefying on air; mp 128–130 °C (decomp). ^{1}H NMR ($CDCl_3$): δ = 2.83 (s, 6H, 8-NMe_2), 2.97 (s, 1H, 1-NMe), 3.65–3.72 (m, 2H, N–CH_2–CO), 7.19–7.26 (m, 1H, 7-H), 7.29–7.39 (m, 3H, 2-H, 3-H, 6-H), 7.47–7.54 (m, 2H, 4-H, 5-H). ^{1}H NMR (DMSO-d_6): δ = 2.66 (s, 6H, 8-NMe_2), 2.94 (s, 3H, 1-NMe), 3.47 (br. s, 2H, N–CH_2), 6.93 (dd, *J* = 7.5, *J* = 1.2, 1H), 6.99 (dd, *J* = 7.4, *J* = 1.2, 1H), 7.22–7.37 (m, 4H). ^{13}C NMR (DMSO-d_6): δ = 41.7 (1-NMe), 44.0 and 46.3 (8-NMe_2), 60.7, 114.8, 115.5, 120.0, 122.9, 123.4, 126.4, 126.5, 137.9, 149.3, 150.2, 172.9 (C=O). $C_{15}H_{17}KN_2O_2$ (296.41): calcd. C 60.78, H 5.78, N 9.45; found C 60.85, H 5.71, N 9.50.

1,1,3-Trimethyl-2,3-dihydro-1*H*-perimidin-1-ium bromide (12a). Air was bubbled through a solution of hydrobromide **6a** (68 mg, 0.2 mmol) in pyridine (5 mL) for 4 days at room temperature. The solvent was evaporated and the crude oxidation product was washed with diethyl ether, the solid residue was dissolved in ethanol and purified with activated charcoal on boiling. After that the mixture was filtered and evaporated to dryness to afford light brown crystals of salt **12a** (35 mg, 60%) with mp 167–169 °C (decomp.). ^{1}H NMR (CD_3CN): δ = 3.33 (s, 3H, 3-NMe), 3.59 (br. s, 6.3H, 1-NMe_2), 5.05 (br. s, 2H, N–CH_2–N), 7.03 (dd, *J* = 1.1, *J* = 7.4, 0.9H, 4-H), 7.56 (dd, *J* = 1.1, *J* = 8.2, 1H, 6-H), 7.60–7.67 (m, 2H, 8-H, 5-H), 7.85 (d, *J* = 7.7, 1H, 9-H), 8.04 (dd, *J* = 0.5, *J* = 8.2, 1H, 7-H). ^{13}C ЯМР (CD_3CN): δ = 36.7 (1-NMe), 51.4 (8-NMe_2), 78.6 (NCH_2N), 108.2, 115.0, 119.1, 125.8, 128.4, 130.3, 134.7, 139.4, 139.9. $C_{14}H_{17}BrN_2 \cdot 2H_2O$ (329.23): calcd. C 51.07, H 6.43, N 8.51; found C 51.14, H 6.40, N 8.53.

1,1,2,3-Tetramethyl-2,3-dihydro-1*H*-perimidin-1-ium bromide (12b). Compound was prepared similarly to **12a** from hydrobromide **6b** (84 mg, 0.2 mmol) for 6 days. After boiling with activated charcoal and filtration, ethanol was evaporated to afford **12b** as light brown caramel (38 mg, 52%) with mp 78–80 °C (decomp.). ^{1}H NMR (CD_3CN): δ = 1.26 (br. d, *J* = 6.3, 1H, N–C(Me)–N), 3.22 (s, 3.1H, 3-NMe), 3.52 and 3.78 (both s, both 3H, 1-NMe_2), 5.68 (ABq, *J* = 6.2, 1H, N–CH–N), 6.98 (d, *J* = 7.6, 1H, 4-H), 7.55 (d, *J* = 7.9, 1H, 6-H), 7.61–7.70 (m, 2H, 5-H, 8-H), 7.86 (d, *J* = 7.9, 1H, 9-H), 8.06 (d, *J* = 8.5, 1H, 7-H). ^{13}C NMR (CD_3CN): δ = 11.9 (N–C*Me*–N), 36.8, 50.8, 57.6

(N–Me); 84.2 (N–CH–N); 110.1, 115.5, 117.4, 119.8, 127.1, 129.8, 131.4, 135.3, 137.3, 138.3. $C_{15}H_{19}BrN_2 \cdot 2H_2O$ (343.26): calcd. C 52.49, H 6.75, N 8.16; found C 52.41, H 6.84, N 8.10.

X-Ray diffraction analysis. Crystals suitable for X-ray studies were grown up by slow evaporation from solutions of compounds in appropriate solvents or solvent mixtures at room temperature: **6a** (MeOH), **12a** (Py–EtOH). The structures were solved by direct method and refined by the full-matrix least-squares against F^2 in anisotropic (for non-hydrogen atoms) approximation. All hydrogen atoms were placed in geometrically calculated positions and were refined in isotropic approximation in riding model with the $U_{iso}(H)$ parameters equal to $n \cdot U_{eq}(C_i)$ (n = 1.2 for CH and CH_2 groups and n = 1.5 for CH_3 groups), where $U(C_i)$ are respectively the equivalent thermal parameters of the atoms to which corresponding H atoms are bonded. The H(O) hydrogen atoms were found in the difference Fourier synthesis and refined in isotropic approximation without constrains. The main crystallographic data and some experimental details are given in Table S3. CCDC 1400689 and 1400690 contain the supplementary crystallographic data for this paper.

Acknowledgements

Financial support from the Russian Foundation for Basic Research (project RFBR 14-03-31301) is greatly acknowledged. The authors acknowledge the Scientific and Educational Laboratory of Resonance Spectroscopy (Department of Natural and High Molecular Compounds Chemistry of Southern Federal University) for NMR measurements. X-Ray experiments were performed by Drs. Zoya A. Starikova and K. Y. Suponitsky (A. N. Nesmeyanov Institute of Organoelement Compounds, Moscow, Russian Federation).

Electronic supplementary information (ESI) available: Details of potentiometric titration; main fragmentation pathways of $\mathbf{2a}^{+\cdot}$ under electron impact; DFT quantum-chemical calculations of amino acid **2a**; data for thermolysis of **2a**,**b**; copies of ^1H and ^{13}C NMR spectra; crystal data and structure refinement for compounds **6a** and **12a** (CCDC 1400689 and 1400690). For ESI see DOI:

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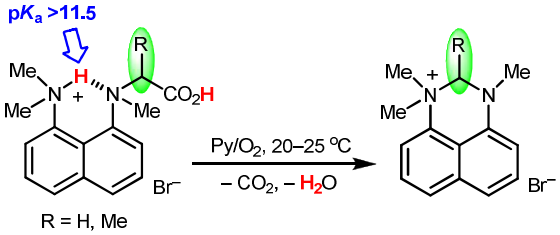
Table of contents entry



The first hybrid bases constructed of 1,8-bis(dimethylamino)naphthalene and glycine or alanine residues were synthesised, structurally characterised and unusual channels of their reactivity revealed.