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2-α-Hydroxybenzhydryl- and 2,7-di(α-hydroxybenzhydryl)-1,8-bis(dimethylamino)naphthalenes: the first examples of stabilization of in/out proton sponge conformers by intramolecular hydrogen bonding. The most flattened amino group ever participating in IHB

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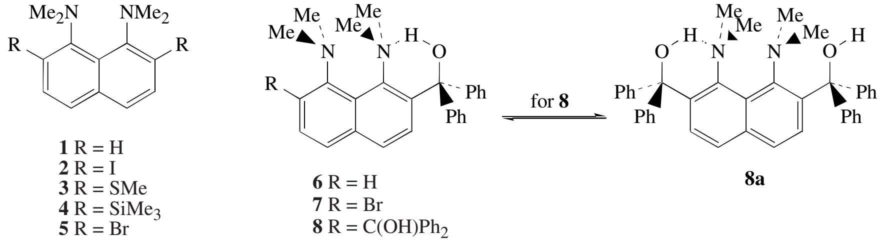
Abstract—2-(α-Hydroxybenzhydryl)- **6** and 2,7-di(α-hydroxybenzhydryl)-1,8-bis(dimethylamino)naphthalenes **8** have been shown to exist in crystals as *in/out* conformers stabilized by O–H···N intramolecular hydrogen bonding. In agreement with X-ray studies, the NMR data are also consistent with **7** retaining its *in/out* form in solution, whilst for **8** superimposed equilibrating *in/out–out/in* conformers are observed.

It is known that strong steric and electronic repulsion of *peri*-NMe_2 groups in 1,8-bis(dimethylamino)naphthalene (proton sponge) **1** (Scheme 1) results not only in exceptionally high basicity ($pK_a = 12.1$, H_2O, 25 °C) but also in severe distortion of the molecular structure.[1] Thus, the naphthalene ring in **1** loses its planarity and the NMe_2 groups adopt the *in/in* (*trans*) conformation shown in Scheme 2a.[2] Two specific features of this form are: (1) division of the *N*-methyl groups into two sorts, one lying approximately in the ring plane and the other perpendicular to it, and (2) orientation of the axes of the non-bonded electron pairs into the inter-nitrogen space and at opposite sides (*trans*) of the mean ring plane. This conformation is also typical for many other proton sponges.[1b,c]

Recently, we disclosed that dramatic structural changes take place in derivatives of compound **1** bearing bulky



Scheme 1.

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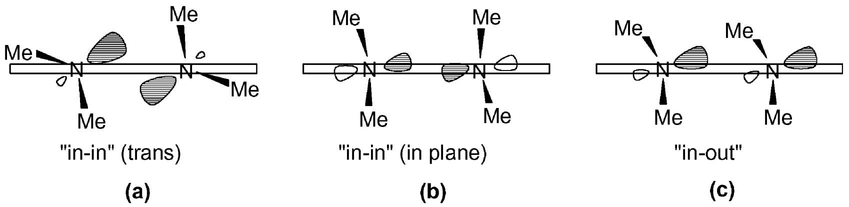


Scheme 2. Possible dimethylamino group conformations in naphthalene proton sponges (white rectangles stand for side view of the mean ring plane).

substituents in positions 2 and 7 (*ortho*).[3] For example, in diiodide **2** and di(sulfide) **3** both the nitrogen atoms are nearly planar and the NMe_2 groups are almost perpendicular to the ring plane which, unlike that in **1**, retains its planarity. This conformation was named *in*/*in* (*in plane*) since the nitrogen pyramids remain slightly directed towards each other and the almost pure p-orbitals of the unshared electron pairs lie in the ring plane (Scheme 2b). Even bigger changes occur in the 2,7-bis(trimethylsilyl) derivative **4** for which the *in*/*out* conformation was registered for the first time (Scheme 2c), though the 'out-ness' of the inverted NMe_2 group was relatively small (the sum of the valency angles at the 'inverted' nitrogen atom equals 355.3°).[3] Presumably, realization of the *in*/*out* form in the case of **4** is caused by spatial repulsion exerted by the extraordinary bulkiness of the trimethylsilyl group and by the relatively weak $n \rightarrow d$ interaction between the nitrogen and silicon atoms.

From the above, one could assume that the *in*/*out* conformation might be more strongly stabilized via other types of interactions, such as intramolecular hydrogen bonding (IHB) or charge-transfer complexes. To check this assumption, in the present work we have prepared and studied alcohols **6**–**8** containing α-hydroxybenzhydryl groups in the *ortho*-positions of the parent proton sponge **1**.

Alcohols **6**–**8** were obtained in good yields from the corresponding bromides (e.g., **5**), which were treated successively with *n*-butyllithium and benzophenone (see General procedure for details).[9] For alcohols **6** and **8**, single crystal X-ray measurements were conducted at 115 K.[10] As expected, both compounds exist in the solid state as *in*/*out* conformers fixed by O–H···N hydrogen bonding (Figs. 1 and 2).

The N···N distances (**6**: 2.921 Å; **8**: 2.915 Å) are very close to that of **4** (2.925 Å) and are significantly larger than in the parent sponge **1** (2.804 Å at 100 K[2b]). Undoubtedly, the methyls of the inverted nitrogen atom arranged between the amine nitrogens cause this enlargement. The IHB in molecules **6** and **8** has several peculiarities. Firstly, the sum of the valence angles at their inverted nitrogens lie in the range of 350–351° against 355° for compound **4**. This means that the 'out-ness' of the chelated NMe_2 group in **6** and **8** is somewhat higher and therefore the IHB provides a stronger stabilization of the *in*/*out* form than the n,d-interaction in **4**. Secondly, the IHB in **6** (∠O–H···N = 152.3°) and especially in diol **8** (∠O–H···N = 162.7°) tends to be more linear than in the aniline counterparts **9a**,**b** (∠O–H···N = 145.0° and 150.9°, respectively).[4] Obviously, this is caused by the enhanced planarity of the 1-NMe_2 groups in the proton sponge derivatives that provides better directionality of the lone

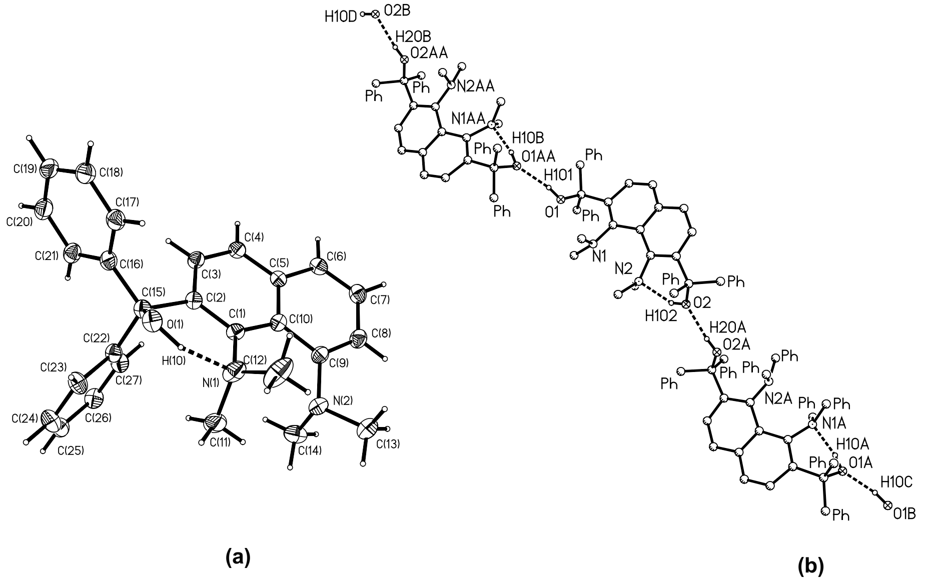


Figure 1. General view and atom numbering scheme for a molecule of alcohol **6** (a) and part of one of the endless chains along the *b* axis showing intra- and intermolecular H-bonding between molecules of **8** (b).

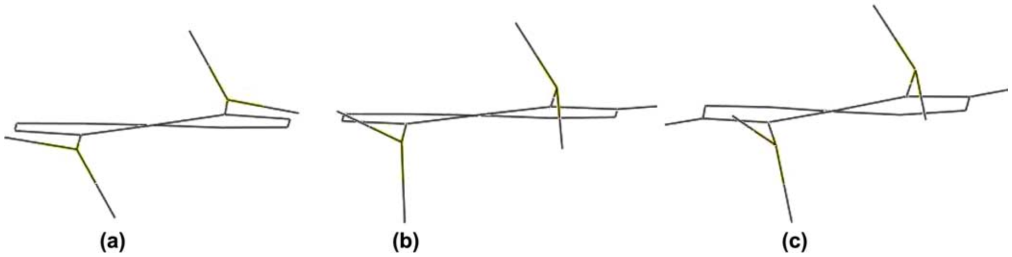
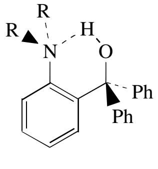
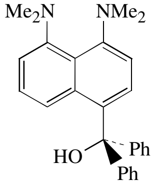


Figure 2. View of proton sponge molecules along the average ring plane with the amino groups closer to the viewer as wireframe CIF generated models (without 2,7-substituents and hydrogens): **1** (a), **6** (b), **8** (c).

nitrogen electron pair axis towards the hydroxylic hydrogen. Notably, the Cambridge Structural Database contains no information on any other amines with such planar amino groups involved in IHB of the O–H···N or N–H···N type. Finally, the N···O distances in compounds **6** and **8** are also shorter than in aniline alcohols **9a**,**b**, testifying the strength of IHB in the former.



9a R = Me
9b R = Et



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The intramolecular O–H···N hydrogen bonds in both **6** and **8** with participation of the inverted dimethylamino group are characterized by a broad IR band of low intensity in the region 2500–3000 cm^{-1} (solid state). The red shift of this band correlates with its length (2.626 Å for **6** and 2.613 and 2.599 Å for **8**—two independent molecules in the unit cell). The low intensity of the intramolecular ν(OH···N) IR band can be explained in terms of a geometrical effect:[5] in our case the hydrogen bond is markedly bent. Also one cannot exclude some coupling between the motion of the proton and the electrons as postulated by Witkowski[6] that seems to be common in the, so-called, resonance-assisted hydrogen bonds.[7] The intermolecular O–H···O hydrogen bonds in **8** (of 2.769 Å) show usual behaviour and are characterized by an intense IR band located at ca. 3330–3340 cm^{-1}. The formation of intramolecular O–H···N hydrogen bonds is also well evidenced by a drop in the intensity of the Bohlman bands of the ν(C–H) vibrations located at ca. 2780 and 2825 cm^{-1}.

It follows from ^{1}H and ^{13}C NMR spectra that compounds **6** and **7** also retain their *in*/*out* forms stabilized by IHB in solution. In fact, the OH-proton peak, in both alcohols, is situated near δ_H 10.5 ppm, whereas in the spectrum of 4-(α-hydroxybenzhydryl)-1,8-bis(dimethylamino)naphthalene **10**[8] where there is no possibility of forming IHB, the signal is much more upfield (δ 3.42 ppm). It should be emphasized that both the NMe_2 and $C(OH)Ph_2$ groups, as well as the meta- and para-protons of the naphthalene core of diol 8 are dynamically equivalent at 298 K in either ^{1}H or ^{13}C NMR spectra. One possible explanation would involve a fast (on the NMR time scale) equilibration of the two superimposed *in*/*out* conformers, **8** and **8a**, taking place in solution at ambient temperature (Scheme 1). Clear-cut evidence for this equilibration is the shift of the two-proton peak for the OH-groups to δ_H 6.94 ppm, that is, between the OH-signals for compounds **6** and **10**. However, there is another way to explain the equivalence of the two half-moieties of compound **8** based on the interconversion of the NMe_2 groups, which should be an extremely fast process. In such a case, both OH groups would be oriented towards the nitrogen atoms, but the lone electron pairs are engaged in hydrogen bond formation, either to one, or to another OH group. Full explanation of the process requires additional studies, which are presently underway.

Acknowledgements

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9. General procedure for the preparation of **6**–**8**. To a solution of dibromide **5** (0.200 g, 0.54 mmol) in dry ether (3 mL) cooled to −30 °C, a 1.6 M hexane solution of $Bu^{n}Li$ (0.34 mL, 0.54 mmol) was added. The solution of the monolithium derivative thus formed was treated with a

solution of benzophenone (0.098 g, 0.54 mmol) in dry ether (2 mL) at −30 °C. The reaction mixture was kept for 20 min at −30 °C and then for 40 min at 20 °C before being poured into water (10 mL). The organic layer was separated and the water layer was extracted with ether (3 × 3 mL). The combined organic extracts were dried over Na_2SO_4, evaporated to dryness and the residue was purified by PTLC on Al_2O_3 yielding 80% of bromoalcohol **7** as a yellowish oil.

This procedure was repeated with 2 equiv of *n*-BuLi to give 21% of **6** as pale-yellow crystals with mp 154.5–155.5 °C (from hexanes); with 2 equiv of both *n*-BuLi and benzophenone, a 15% yield of **8** was obtained as yellowish crystals with mp 273 °C (from $CHCl_3$). Compounds **6**–**8** gave analytical and spectral data consistent with their structures. The NMR and IR data are as follows.

2-(α-Hydroxybenzhydryl)-1,8-bis(dimethylamino)naphthalene (**6**): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ/ppm: 2.56 (s, 6H, NMe_2), 2.57 (s, 6H, NMe_2), 6.77–8.49 Hz (d, 1H, H-3), 7.22–7.37 (m, 12H, H-6, H-7, Ph), 7.40–8.48 (d, 1H, H-4), 7.49–8.10 and 1.16 (dd, 1H, H-5), 10.56 (s, 1H, OH, exchangeable with D_2O). ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C) δ/ppm: 43.40, 47.53, 83.71, 118.12, 125.56, 125.64, 126.14, 127.06, 127.89, 128.38, 128.57, 128.76, 136.96, 143.61, 146.06, 149.70, 152.66. IR (fluoroluble suspension) ν/cm^{-1}: 3082, 3058, 3018, 2995, 2980, 2928, 2854, 2827, 2783, 1595, 1582, 1551, 1503, 1478, 1459, 1444, 1433, 1372, 1350, 1334.

2-(α-Hydroxybenzhydryl)-7-bromo-1,8-bis(dimethylamino)-naphthalene (**7**): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ/ppm: 2.54 (s, 6H, NMe_2), 2.83 (s, 6H, NMe_2), 6.80–8.55 (d, 1H, H-3), 7.33–7.79 (m, 13H, H-4, H-5, H-6, Ph), 10.42 (s, 1H, OH).

2,7-Di(α-hydroxybenzhydryl)-1,8-bis(dimethylamino)naphthalene (**8**): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C) δ/ppm: 2.43 (s, 12H, NMe_2), 6.66–8.78 (d, 2H, H-3, H-6), 6.94 (s, 2H, OH, exchangeable with D_2O), 7.13–7.28 (m, 22H, H-4, H-5, Ph). ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C) δ/ppm: 44.95, 83.83, 124.10, 127.35, 128.05, 128.54, 129.81, 132.81, 136.47, 142.65, 147.80, 150.01. IR (fluoroluble suspension)ν/cm^{-1}: 3333, 3083, 3057, 3022, 3003, 2989, 2955, 2924, 2867, 2835, 2801, 2784, 1599, 1582, 1522, 1504, 1490, 1445, 1368, 1353. IR (CCl_4)ν/cm^{-1}: 3608, near 3100 (broad band), 3086, 3062, 3025, 2929, 2904, 2807, 1492, 1447, 1370, 1312, 1172, 1096, 1054, 1033, 1024, 931, 892, 654, 640, 596, 550. IR (CD_2Cl_2) ν/cm^{-1}: 3592, near 3050 (broad band), 3086, 3063, 3026, 2929, 1600, 1583, 1523, 1490, 1447, 1318, 1232, 1172, 1102, 840.

10. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 248980–248981. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].