JOC Article

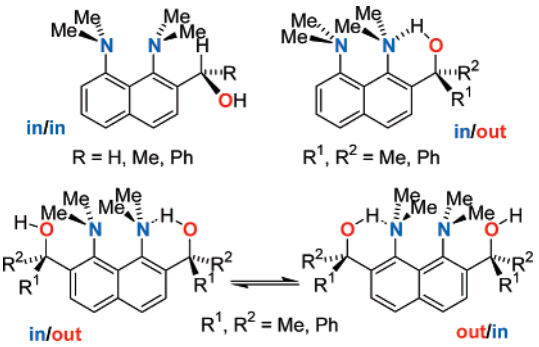
# 2-α-Hydroxyalkyl- and 2,7-Di(α-hydroxyalkyl)-1,8-bis(dimethylamino)naphthalenes: Stabilization of Nonconventional In/Out Conformers of "Proton Sponges" via N···H−O Intramolecular Hydrogen Bonding. A Remarkable Kind of Tandem Nitrogen Inversion

Alexander F. Pozharskii,*,† Alexander V. Degtyarev,† Oksana V. Ryabtsova,† Valery A. Ozeryanskii,† Mikhail E. Kletskii,† Zoya A. Starikova,‡ Lucjan Sobczyk,§ and Alexander Filarowski§

*Department of Organic Chemistry, Southern Federal University, Zorge 7, 344090 Rostov-on-Don, Russian Federation, A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilova 28, 119991 Moscow, Russian Federation, and Faculty of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50-383 Wroclaw, Poland*

*apozharskii@rsu.ru*

*Received December 28, 2006*




A regular set of 2-(α-hydroxymethyl)- and 2,7-di(α-hydroxymethyl)-1,8-bis(dimethylamino)naphthalenes has been prepared. Their X-ray, NMR, and IR studies have demonstrated that in tertiary mono-alcohols the orientation of free nitrogen electron pairs in crystals and solution corresponds to nonconventional in/out conformers stabilized by O−H···N intramolecular hydrogen bonding. For tertiary 2,7-dialcohols, the superimposed equilibrating in/out−out/in nitrogen invertomers are observed in solution. Unlike this, primary and secondary mono- and dialcohols commonly exist in the in/in form, which is typical for the parent proton sponge and the majority of its derivatives.

## Introduction

It is well known that the $NMe_2$ groups in 1,8-bis(dimethylamino)naphthalene ("proton sponge") **1** adopt the so-called in/in conformation with the nitrogen lone electron pairs pointing to each other and with the two pairs of approximately axial and equatorial methyl groups (Figure 1a).[1,2] Such orientation strongly favors *peri*-chelation, and indeed interaction of **1** with protic[3−5] and some Lewis[6] acids leads to cations of type **2** with locked in/in form. The situation is considerably changed upon introducing bulky substituents at positions 2 and 7 (ortho).[7] The $NMe_2$ groups in this case become strongly flattened and turn

* Corresponding author. Tel.: +7-863-297-5146.
† Southern Federal University.
‡ Russian Academy of Sciences.
§ University of Wroclaw.

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10.1021/jo062667v CCC: $37.00 
Published on Web 03/23/2007

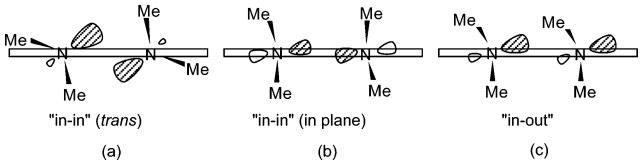
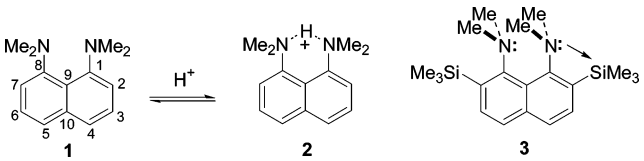
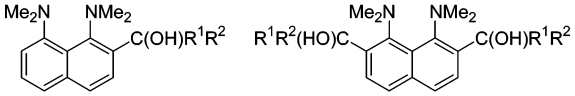



**FIGURE 1.** Possible conformations of $NMe_2$ groups in proton sponge molecules.

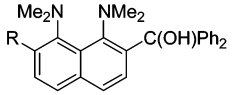
around the N−$C_{ar}$ bond almost perpendicular to the naphthalene ring plane (Figure 1b). In one instance, for the solid 1,8-bis-(dimethylamino)-2,7-bis(trimethylsilyl)naphthalene (**3**), we observed for the first time an in/out conformation with one inverted $NMe_2$ group (Figure 1c).[7] It was assumed that this inversion is caused by n,d-interaction between the free nitrogen electron pair and unoccupied d-orbital of the silicon atom. Following this observation, one could suggest that the in/out conformation might be also stabilized by other types of nonvalent interactions, for example, by intramolecular hydrogen bonding (IHB). To check this idea, in the present work we have prepared and studied a series of earlier unknown proton sponge alcohols **4**−**6** containing α-hydroxyalkyl groups in the ortho-positions.[8]




**4a** $R^1 = R^2 = H$
**4b** $R^1 = H$, $R^2 = Me$
**4c** $R^1 = H$, $R^2 = Ph$
**4d** $R^1 = R^2 = Me$
**4e** $R^1 = R^2 = Ph$
**4f** $R^1 = Me$, $R^2 = Ph$

**5a** $R^1 = R^2 = H$
**5b** $R^1 = H$, $R^2 = Me$
**5c** $R^1 = H$, $R^2 = Ph$
**5d** $R^1 = R^2 = Me$
**5e** $R^1 = R^2 = Ph$

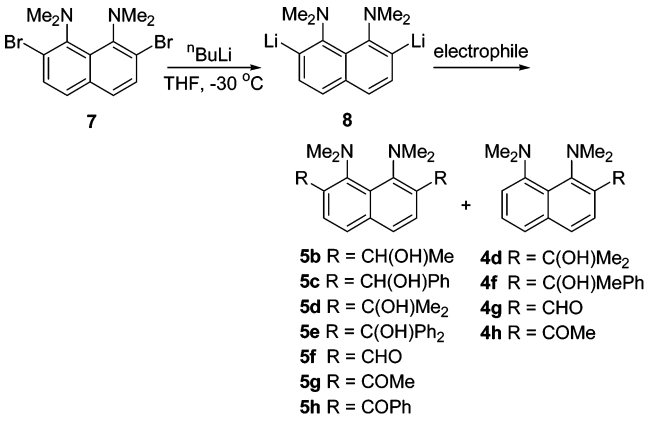



**6a** R = Br
**6b** R = $CH_2OH$
**6c** R = $C(OH)Me_2$

## Results and Discussion

**(1) Synthesis.** Easily accessible[9] *ortho*-dibromide **7** was used as a starting material in most preparations (Scheme 1). By addition of an excess of *n*-butyl lithium, the dibromide **7** was transformed into 2,7-dilithium derivative **8**, which after treatment with carbonyl-containing electrophiles gave 2,7-disubstituted proton sponges **5**, sometimes with an admixture of monosubstituted product **4** (Table 1). In those cases when electrophile

**SCHEME 1**




**5b** R = CH(OH)Me
**5c** R = CH(OH)Ph
**5d** R = $C(OH)Me_2$
**5e** R = $C(OH)Ph_2$
**5f** R = CHO
**5g** R = COMe
**5h** R = COPh

**4d** R = $C(OH)Me_2$
**4f** R = C(OH)MePh
**4g** R = CHO
**4h** R = COMe

**TABLE 1. Organometallic Synthesis of 2,7-Disubstituted and 2-Substituted 1,8-Bis(dimethylamino)naphthalenes**

| bromide | electrophile | product | 2(7)-substituents | yield (%) |
|---|---|---|---|---|
| **7** | MeCHO | **5b** | CH(OH)Me | 49 |
| **7** | PhCHO | **5c** | CH(OH)Ph | 80 |
| **7** | $Me_2CO$ | **5d** | $C(OH)Me_2$ | 11 |
| | | **4d** | | 49 |
| **7** | Ph(Me)CO | **4f** | C(OH)MePh | 21 |
| **7** | $Ph_2CO$ | **5e** | $C(OH)Ph_2$ | 68 |
| **7** | $Ph_2CO$ | **6a** | $C(OH)Ph_2$ | 80 |
| **7** | $HCO_2Me$ | **5f** | CHO | 40 |
| | | **4g** | | 10 |
| **7** | DMF | **5f** | CHO | 74 |
| | | **4g** | | 24 |
| **7** | MeCOCl | **5g** | COMe | 10 |
| | | **4h** | | 30 |
| **7** | PhCOCl | **5h** | COPh | 90 |
| **10** | DMF | **4g** | CHO | 93 |
| **10** | PhCOCl | **4i** | COPh | 74 |
| **10** | MeCHO | **4b** | CH(OH)Me | 52 |
| **10** | PhCHO | **4c** | CH(OH)Ph | 79 |
| **10** | $Ph_2CO$ | **4e** | $C(OH)Ph_2$ | 21 |
| **6a** | $Me_2CO$ | **6c** | $C(OH)Me_2$ | 21 |
| **6a** | $(EtO)_2CO$ | **6b** | $CH_2OH$[a] | 24 |

[a] After LAH reduction of the ester **6d**, which was not isolated.

was aldehyde or ketone, the reaction led to the formation of the corresponding alcohols in one preparative step. However, their yields were high enough only when using benzaldehyde and benzophenone. When the electrophile contained a CH-acidic methyl group (acetaldehyde, acetone, and especially acetophenone), the yields of alcohols considerably decreased, evidently due to protolysis of the dilithium compound **8**. In view of this, some alcohols were alternatively prepared by LAH reduction of certain aldehydes and ketones (Scheme 2).

For the preparation of *ortho*-monoalcohols and mixed 2,7-dialcohols, a different approach was also applied. Thus, 2,7-dibromide **7** was monolithiated to yield 2-bromo-7-lithium derivative **9**, which after quenching with water gave monobromide **10**, providing an alternative approach over the selective monobromination of the proton sponge.[10] Lithiation of **10** and subsequent treatment of the transient 2-lithium-1,8-bis(dimethylamino)naphthalene with electrophiles led to the corresponding 2-substituted derivatives **4** in moderate to good yields. Alternatively, after action of benzophenone, the bromolithium

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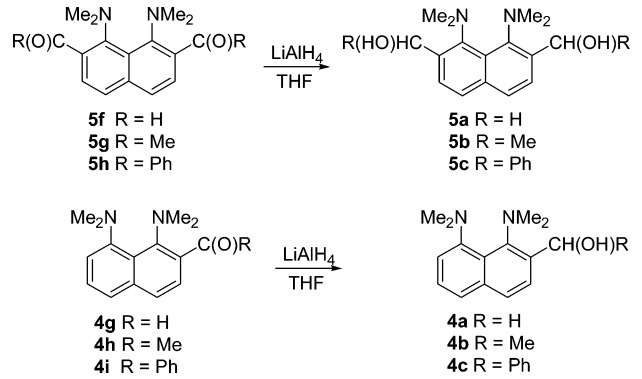
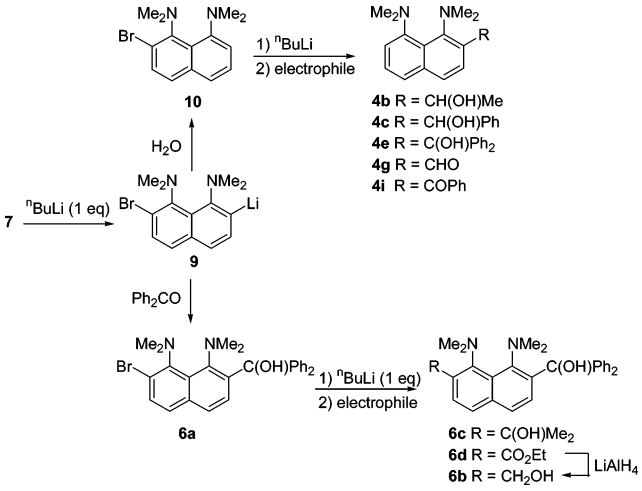
(10) In accordance with a recent report, the monobromide **10** can be also prepared by bromination of proton sponge **1** with 1 equiv of NBS in dry THF at −78 °C: Farrer, N. J.; McDonald, R.; McIndoe, J. S. *Dalton Trans.* **2006**, 4570−4579.

**SCHEME 2**




**SCHEME 3**




derivative **9** gave alcohol **6a** in 80% yield, which was converted into asymmetrical 2,7-dialcohols **6b**,**c** by similar procedures (Scheme 3, Table 1).

**(2) Structure.** All conclusions on fine structure of the alcohols obtained have been made using a combination of X-ray, NMR, and IR techniques. Some quantum chemical calculations have been also performed.

Structurally, all of the alcohols are clearly divided onto three categories: (1) primary and secondary mono- and dialcohols, existing in conventional in/in form, (2) tertiary monoalcohols and mixed primary−tertiary and secondary−tertiary diols for which nonconventional in/out conformation of the $NMe_2$ groups is typical, and (3) tertiary 2,7-diols rapidly interconverting in solution between two in/out−out/in forms. Let us consider them in the same order.

**Primary and Secondary Alcohols.** As one can see from Table 2, in the $^1$H NMR spectra of all primary and secondary alcohols in DMSO-$d_6$, the peak of hydroxy group appears at $\delta$ 5.0−5.8 ppm. In $CDCl_3$, the OH signal is invisible for primary (**4a** and **5a**) and most secondary alcohols, apparently due to their O−H···O association and rapid proton exchange inside associates. However, when the association is sterically hindered, the OH signal in nonpolar solvents arises at 2−3.5 ppm moving to a low-field by lowering the temperature. For example, in the spectra of diol **5c** in $CD_2Cl_2$ recorded at 25, −20, and −50 °C, the hydroxy protons resonate as a broadened peak at $\delta$ 2.75, 3.15, and 3.60 ppm, respectively. These values unambiguously testify an absence of the O−H···N chelation in the primary and secondary alcohols both in polar and in nonpolar media. For the alcohols with sufficient solubility in nonpolar solvents, this conclusion is supported by IR spectroscopy. Thus, in the IR spectra of 2-hydroxymethyl- and 2,7-di(hydroxymethyl)-1,8-bis(dimethylamino)naphthalenes **4a** and **5a** in $CHCl_3$, a sharp band of free OH groups is present at 3590 cm$^{-1}$ along with a broad band of associated hydroxyl in the range of 3500−3100 cm$^{-1}$. In the IR spectra of the solid samples, only the latter band is observed in this region.

In one instance, for the diol **5c**, we were able to obtain crystals suitable for X-ray measurements. Their results are shown in Figures 2 and 3 and in Table 4. One can see that the hydroxy groups in this diol are indeed nonchelated, and both participate in the intermolecular hydrogen bonding. The crystal structure thus formed consists of the tetramers with neighboring naphthalene rings approximately perpendicular to each other (Figure 3). Although the dimethylamino groups in the diol **5c** still retain the in/in conformation, they are essentially flattened and turned around the $C_{ar}$−N bonds as in many other 2,7-disubstituted proton sponges.[7] On average, the rotation angle is of 72°, and the sum of the angles at the nitrogen atoms reaches 353° (the corresponding values for the proton sponge **1** are 40° and 347°).[1,2] Stereochemistry of the ortho-substituents in **5c** deserves special comments. Two phenyls, as well as two hydroxyls, are located at different sides of the mean naphthalene ring plane, so that the diol **5c** consists of a racemic mixture of *R*,*R*- and *S*,*S*-enantiomers without any admixture of the meso-form.[11] At the same time, both the α-C−H and the $C_{ar}$−N bonds are partially eclipsed with the dihedral angle between the $N_1-C_1-C_2$ ("chemical" atom numbering is used throughout the text as depicted in structure **1**) and $C_2-C_\alpha$−H planes of ∼10° that minimizes steric repulsions (Figure 4, **A**). Yet, such repulsions remain significant as manifested in a shortening of the N···N distance to 2.747 Å as compared to 2.804 Å for diamine **1**. This is the smallest separation of the *peri*-nitrogen atoms among all known proton sponge bases. Similar proximity (2.749 Å) was earlier observed only for 2,7-dimethyl-1,8-bis(dimethylamino)naphthalene, in which, as in molecule **5c**, the α-C−H bonds of ortho-substituents are also in a neighborhood with the $NMe_2$ groups.[7]

**Tertiary Alcohols.** A remarkable peculiarity of all tertiary monoalcohols (**4d**−**f** and **6a**) is the appearance in their $^1$H NMR spectra in $CDCl_3$ a one-proton singlet at $\delta$ ca. 10.5 ppm exchanging with $D_2O$ (Table 3). Evidently, it can be assigned to the chelated hydroxy group that supports realization of the out conformation for the 1-$NMe_2$ group and the in/out conformation for the whole molecule (Scheme 4). Table 3 demonstrates that this chelation remains in DMSO-$d_6$ solution although in a weaker form. The weakening effect becomes smaller as the number of phenyl groups in the ortho-substituent increases. Thus, $\Delta\delta_{OH}$ value, representing the chemical shift difference for hydroxyl in $CDCl_3$ and DMSO-$d_6$, for monoalcohols **4d**, **4f**, and **4e** is equal to 2.24, 1.48, and 0.6 ppm, respectively. The strengthening of the intramolecular O−H···N bond by the side phenyl groups seems to result from the following changes[12] in the OH-acidity: **4e** > **4f** > **4d** (cf., data below for compound **6c**).

(11) Stereochemical induction actually observed at the synthesis of **5c** and the lowered stability of *meso*-form is apparently caused by steric hindrances from *peri*-$NMe_2$ groups. The energetic difference between trans (*R*,*R* or *S*,*S*)- and cis (*R*,*S* or *S*,*R*)-forms calculated by us with the DFT B3LYP/6-31G** approach is equal to ∼0.9 kcal mol$^{-1}$ in favor of the trans (see the Supporting Information for details). Although this value is rather small, one can assume that the difference in energies between the corresponding transition states is much more.

**TABLE 2. $^1$H NMR and IR Spectroscopic Characteristics of Hydroxymethyl and Dimethylamino Groups in Proton Sponge Alcohols Existing in In/In Form**

| | | δ (ppm) | | | | IR data[a] | |
|---|---|---|---|---|---|---|---|
| alcohol | solvent[b] | 1-$NMe_2$ | 8-$NMe_2$ | CH(*OH*)R | *CH*(OH)R | solvent[c] | $\nu_{OH}$ ($cm^{-1}$) |
| **4a** | $CDCl_3$ | 3.00 | 2.74 | | 4.87 (s) | Nujol | 3350 (br) |
| | DMSO-$d_6$ | 2.89 | 2.67 | 5.10 (t) | 4.62 (d) | $CHCl_3$ | 3590 (sh); 3330 (br) |
| **4b** | $CDCl_3$ | 2.99 | 2.63<br>2.78 | | 5.35 (q) | film | 3330 (br) |
| | DMSO-$d_6$ | 2.90 | 2.68 | 5.00 (d) | 5.20 (m) | | |
| **4c** | $CDCl_3$ | 2.85 | 2.65<br>2.72 | | 6.25 (br s) | film | 3370 (br) |
| | DMSO-$d_6$ | 2.85 | 2.61 | 5.75 (d) | 6.16 (d) | | |
| **5a** | $CDCl_3$ | 2.95 | 2.95 | | 4.85 (s) | Nujol | 3320 (br) |
| | DMSO-$d_6$ | 2.89 | 2.89 | 5.14 (t) | 4.64 (d) | $CHCl_3$ | 3590 (sh); 3350 (br) |
| **5b** | DMSO-$d_6$ | 2.90 | 2.90 | 5.01 (m) | 5.11 (m) | Nujol | 3330 (br) |
| **5c** | $CDCl_3$ | 2.96 | 2.96 | | 6.31 (s) | Nujol | 3350 (br) |
| | DMSO-$d_6$ | 2.93 | 2.93 | 5.79 (d) | 6.13 (d) | | |

[a] Designations: sh, sharp; br, broad; only the center of broad bands is indicated. [b] $c \approx 5 \times 10^{-2}$ M. [c] $c = 4 \times 10^{-2}$ M for $CHCl_3$ solutions.

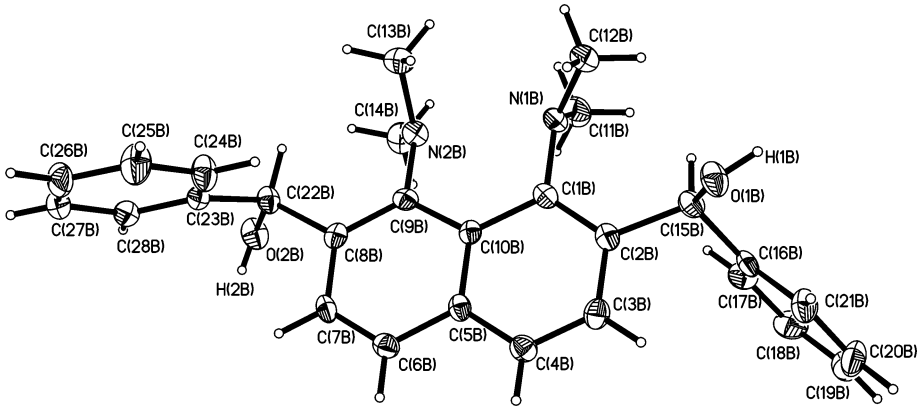



**FIGURE 2.** Molecular structure of diol **5c**.

As it follows from X-ray data for compounds **4e** and **4f** (Figures S1 and 5), the tertiary monoalcohols exist as in/out conformers also in the crystal state. The in/out form is also typical for symmetrical 2,7-diols **5d** and **5e** in the solid (Figures 6 and S2). Notably, along with IHB the intermolecular hydrogen bonds O−H···O are realized in their crystal lattice, in which the oxygen atom of the chelated OH group acts as a proton-acceptor and the nonchelated hydroxyl as a proton-donor (Figures 7 and S3). In all tertiary alcohols, the chelated cycle is not perfectly planar. Because the 1-$NMe_2$ group is somewhat turned around the $C_{ar}$−N bond, an axis of its free electron pair is directed under a certain angle to the mean naphthalene ring plane. To maintain the strength of the IHB, the α-hydroxyalkyl substituent also turns around the $C_2-C_\alpha$ bond. This turning is rather significant, and for alcohols **4d**, **5d**, and **5e** it ranges between 35° and 45°. As a result, the O−H bond gets off the $N_1C_1C_2C_\alpha$ plane (Figure 4, **B** and **B′** at R = R′), and the IHB thus formed crosses the average naphthalene ring plane under the angle of 9−13°; other geometrical parameters of the IHB are in Table 4.

If this picture worked for solutions, a nonequivalence of the $NMe_2$ and OH groups as well as the naphthalene *meta*- and *para*-protons would be observed in the NMR spectra of diols **5d**,**e**. In fact, their $^1$H and $^{13}$C NMR characteristics in $CDCl_3$ are very simple as one can expect for a symmetrical structure. Thus, the naphthalene protons appear as two doublets at δ 7.37 and 7.43 for **5d** and 6.63 and 7.25 ppm for **5e** with a spin−spin coupling constant $J_o$ = 8.7 Hz. The $NMe_2$ groups give one singlet at 2.91 and one singlet at 2.43 ppm, respectively. Besides, in the spectrum of **5d**, four methyls of two α-hydroxyisopropyl groups are equivalent, resonating at δ 1.76 ppm. All of this indicates that the symmetrical tertiary diols rapidly equilibrate in solution between a pair of degenerated in/out and out/in conformers (Scheme 4). Most clearly this is exhibited by the behavior of two hydroxyls, which interconvert between chelated or nonchelated states. In the $^1$H NMR spectra of diols **5d**,**e**, the OH hydrogen atoms give a two-proton singlet at δ 6.19 and 6.94 ppm, respectively. Actually, these values are the arithmetical mean of the chemical shifts for OH protons in the chelated alcohols **4d**,**e** and isomeric 4-alcohols **11a**,**b**, which can be considered as appropriate models for the nonchelated state.

In DMSO solution, the averaged chemical shift for the OH hydrogen atoms of diols **5d**,**e** is substantially higher ($\delta_{OH}$ 6.72 and 8.32 ppm, respectively). This results from the interference of a strong (>3 ppm) low-field displacement of the OH signal for the nonchelated hydroxyl (see **11a**,**b**) and lesser upfield shift for the chelated form (see Table 3 and the above discussion).

A more complex situation occurs for the unsymmetrical diol **6c** containing α-hydroxyisopropyl and α-hydroxydiphenylmethyl groups in positions 2 and 7. In its $^1$H NMR spectra in

(12) Hine, J.; Hine, M. *J. Am. Chem. Soc.* **1952**, *74*, 5266−5271.

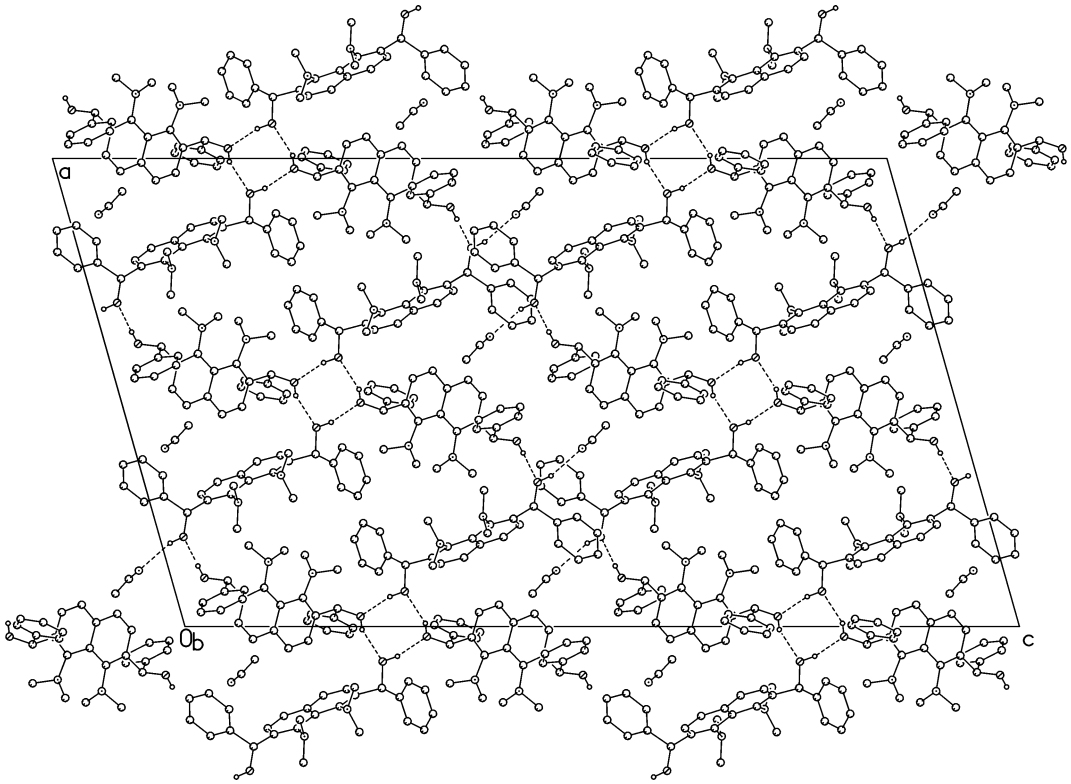



**FIGURE 3.** View along the *b*-axis on crystal packing of diol **5c** showing the intermolecular H-bonding.

**TABLE 3. $^1$H NMR and IR Characteristics of Hydroxymethyl and Dimethylamino Groups in Proton Sponge Alcohols Existing in In/Out Form**

| | | $\delta$ (ppm) | | | | |
|---|---|---|---|---|---|---|
| compd | solvent[a] | 1-$NMe_2$ | 8-$NMe_2$ | OH | solvent[b] | $\nu_{OH}$ ($cm^{-1}$) |
| **4d** | $CDCl_3$ | 2.94 | 2.67 | 10.70 | $CHCl_3$ | 3500−2500 |
| | | | | | film | 3500−2500 |
| | | | | | | 3400 (s, br) |
| | DMSO-$d_6$ | 2.84 | 2.64 | 8.46 | | |
| **4e** | $CDCl_3$ | 2.57[c] | 2.56[c] | 10.56 | Nujol | 3500−2500 |
| | DMSO-$d_6$ | 2.52[c] | 2.48[c] | 9.96 | | |
| **4f** | $CDCl_3$ | 2.83 (3H, sh) | 2.62 (3H, br) | 9.55 | $CHCl_3$ | 3500−2500 |
| | | 2.24 (3H, sh) | 2.40 (3H, br) | | | |
| | DMSO-$d_6$ | 2.67 (3H, sh) | 2.36 (6H, br) | 8.07 | | |
| | | 2.30 (3H, sh) | | | | |
| **5d** | $CDCl_3$ | 2.91 | 2.91 | 6.19 | Nujol | 3400−2500 |
| | | | | | | 3350 (s, br)[d] |
| | DMSO-$d_6$ | 2.82 | 2.82 | 6.72 | | |
| **5e** | $CDCl_3$ | 2.43 | 2.43 | 6.94 | $CCl_4$ | 3608 (sh, s)[e] |
| | | | | | Nujol | 3340 (s, br)[e] |
| | DMSO-$d_6$ | 2.34 | 2.34 | 8.32 | | |
| **6a** | $CDCl_3$ | 2.83 | 2.54 | 10.47 | $CHCl_3$ | 3500−2500 |
| **6c** | $CDCl_3$ | 2.55 | 2.79 | 7.83 | Nujol | 3330 (s, br)[e] |
| | | | | 5.13[f] | | |
| **6b** | $CDCl_3$ | 2.51 | 2.78 | 10.60[g] | Nujol | 3330 (s, br)[e] |
| | DMSO-$d_6$ | 2.42 | 2.69 | 10.17 | | |
| | | | | 5.29[h] | | |

[a] $c \approx 3.6 \times 10^{-2}$ M. [b] $c = 4 \times 10^{-2}$ M for $CHCl_3$ and $CCl_4$ solutions. [c] Arbitrarily assigned. [d] s, strong; for other designation, see footnote in Table 2. [e] No band of chelated OH group is visible. [f] Average positions for OH signals in $Ph_2C(OH)$ and $Me_2C(OH)$ groups. [g] OH signal in $Ph_2C(OH)$ group; hydroxyl proton of $CH_2OH$ is not seen. [h] OH signals for $Ph_2C(OH)$ and $CH_2OH$ groups, respectively.

$CDCl_3$, two peaks of the different OH groups are observed at $\delta$ 7.83 and 5.13 ppm. The latter can be assigned to the C(OH)-$Me_2$ group because of its considerable broadening in comparison with the normally sharp OH signal for the $C(OH)Ph_2$ group. The position of both signals, the average between that of chelated and nonchelated hydroxyls in model compounds, reveals a rapid equilibrium of two in/out conformers **6c** and **6c′** on the NMR time-scale. However, a considerable upfield shift of the OH peak for $C(OH)Me_2$ and low-field shift for $C(OH)Ph_2$ group as compared to symmetrical diols **5d** and **5e** demonstrates that the concentrations of both forms in this case are unequal. Using the corresponding chemical shift values and ordinary calculation scheme (see ref 13 for an example), we have estimated the **6c**/**6c′** ratio in the equilibrium mixture at

**TABLE 4. Selected X-ray Structural Characteristics of *ortho*-Hydroxymethyl Derivatives of Proton Sponges**

| | distances (Å) | | | angles (deg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| compd | N···N | O−H | N···H | ∑N(1)[a] | ∑N(8)[a] | 1-$NMe_2$ ring[b] | 8-$NMe_2$ ring[b] | N···H−O | *T* (K) |
| **4e** | 2.921(2) | 0.963 | 1.735 | 350.3[c] | 335.6 | 76 | 65 | 152 | 115 |
| **4f**[d] | 2.947(1) | 0.933 | 1.761 | 350.2[c] | 337.0 | 72 | 49 | 157 | 100 |
| | (2.980) | (0.985) | (1.781) | (351.0) | (359.0) | (76) | (54) | (150) | |
| **5c**[e] | 2.747(2) | –[f] | –[f] | 352.4 | 352.9 | 72 | 72 | –[f] | 100 |
| **5d** | 2.918(2) | 0.892 | 1.721 | 349.9[c] | 348.5 | 84 | 81 | 160 | 120 |
| **5e** | 2.916(3) | 0.840 | 1.799 | 350.8[c] | 349.9 | 76 | 69 | 163 | 115 |

[a] Sum of CNC-angles at nitrogen atoms. [b] Calculated on the basis of the torsion angles $C_2-C_1-N_1-C$ and $C_7-C_8-N_8-C$, respectively. [c] Chelated nitrogen. [d] Calculated data are given in parentheses. [e] Average data for two independent molecules. [f] No intramolecular H-bonding.

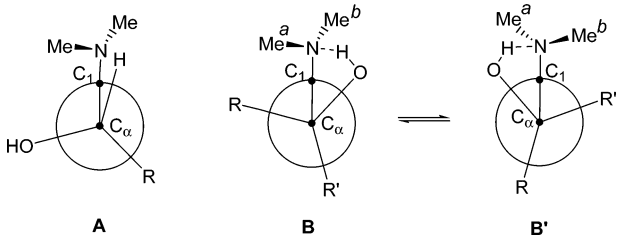



**FIGURE 4.** Relative orientation of 1-$NMe_2$ group and 2-substituent in proton sponge *ortho*-alcohols (schematic side view along the $C_\alpha-C_2$ bond): **A**, secondary alcohols (positions of R and OH group are arbitrary); **B**, **B′**, tertiary alcohols (two isoenergetic swinging conformations are shown).

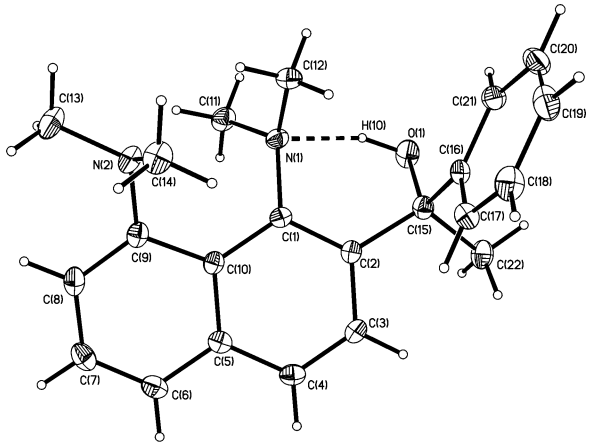
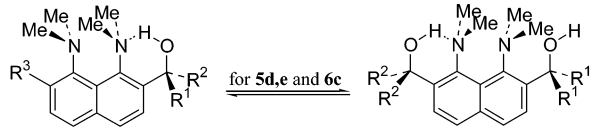


**FIGURE 5.** Molecular structure of compound **4f**.

**SCHEME 4**



**4d** $R^1 = R^2 = Me$, $R^3 = H$
**4e** $R^1 = R^2 = Ph$, $R^3 = H$
**4f** $R^1 = Ph$, $R^2 = Me$, $R^3 = H$
**5d** $R^1 = R^2 = Me$, $R^3 = C(OH)Me_2$
**5e** $R^1 = R^2 = Ph$, $R^3 = C(OH)Ph_2$
**6a** $R^1 = R^2 = Ph$, $R^3 = Br$
**6c** $R^1 = R^2 = Ph$, $R^3 = C(OH)Me_2$

**5d'** $R^1 = R^2 = Me$
**5e'** $R^1 = R^2 = Ph$
**6c'** $R^1 = Ph$, $R^2 = Me$

ambient temperature as equal to 63:37. The superiority of **6c** can be attributed to a higher acidity[12] of the $C(OH)Ph_2$ group strengthening the IHB. In accordance with expectation, the mixed primary−tertiary diol **6b** exists in $CDCl_3$ with the

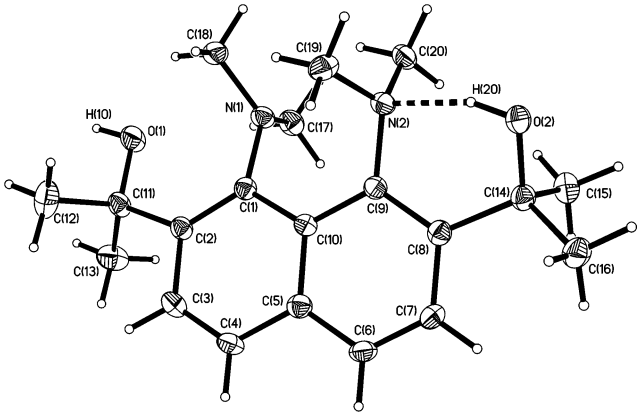
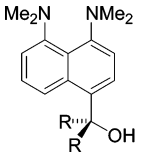


**FIGURE 6.** Molecular structure of diol **5d**.

chelated $C(OH)Ph_2$ and free $CH_2OH$ groups. This is confirmed by the similarity of $\delta_H$ of the OH groups in **6b** with those for reference alcohols **4e** and **4a** (for DMSO-$d_6$ solution).

In the infrared spectra of chelated monoalcohols, the O−H stretching vibrations produce a broad band at 3500−2500 $cm^{-1}$, which is much more diffuse than that of associated O−H groups and sometimes hardly visible. There are several reasons for such behavior. The first one is related to the fact that these bonds are markedly bent and the OH bonds are not collinear with the nitrogen n-electron axis. The second reason is connected with some coupling of proton and $\pi$-electron motion that was extensively discussed.[14] Finally, we have to take into account that the hydrogen-bonded rings are not rigid. There are several low-frequency librational modes that couple with the bridge vibrations. The IR spectra of the diols in Nujol show a strong and broad band of the associated O−H groups, usually centered at 3330 $cm^{-1}$, while in solution (**5e** in $CCl_4$), the "free" hydroxyl band is well seen at 3608 $cm^{-1}$.



| Compd. | R | Solvent | $\delta_H$(OH), ppm |
|---|---|---|---|
| **11a** | Me | $CDCl_3$ | 1.96 |
| **11b** | Ph | $CDCl_3$ | 3.42 |
| **11b** | Ph | DMSO-$d_6$ | 6.59 |

**Appearance of *peri*-$NMe_2$ Groups in NMR Spectra.** In general, an appearance of *peri*-$NMe_2$ groups in the $^1H$ NMR spectra of the *ortho*-alcohols is rather sensitive to the structural changes and conditions, providing valuable information about molecular conformation in solution (Figure 8). Let us take the parent proton sponge **1** as a reference compound. In $CDCl_3$ and

(13) Wofford, D. S.; Forkey, D. M.; Russel, J. G. *J. Org. Chem.* **1982**, *47*, 5132−5137.

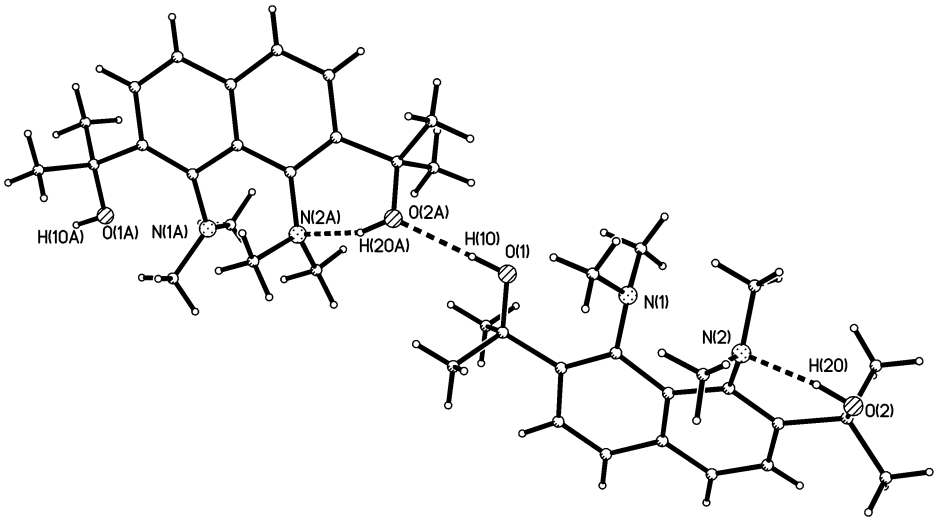



**FIGURE 7.** Fragment of crystal packing of diol **5d** showing the inter- and intramolecular H-bonding.

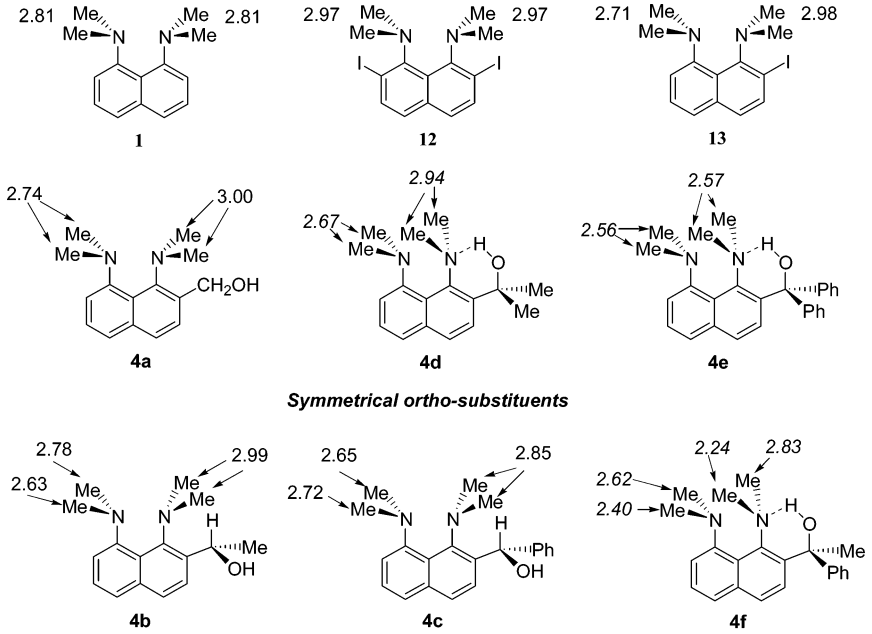



**FIGURE 8.** Chemical shifts of *peri*-$NMe_2$ groups in proton sponge *ortho*-monoalcohols and model compounds ($\delta_H$, $CDCl_3$).

temperatures above −100 °C,[15] all four methyl groups in **1** are magnetically equivalent, absorbing at $\delta$ 2.81 ppm. When bulky substituents are in the ortho-positions, the nitrogen atoms are markedly planarized, getting more $sp^2$-character. Thus, the sum of valent angles, $\sum N_{1(8)}$, in the 2,7-diiodide **12** is larger than that in molecule **1** by 10°.[7] Unsurprisingly, the $NMe_2$ signal in **12** moves downfield to 2.97 ppm.

In the case of mono-ortho-substituted derivatives, only the 1-$NMe_2$ group undergoes flattening; on the contrary, the 8-$NMe_2$ group due to a steric compression from its counterpart strongly pyramidalizes (Table 4). As a result, the signal of the 1-$NMe_2$ group is shifted downfield and that of the 8-$NMe_2$ group upfield (see Figure 8 for $\delta_{Me}$ values for 2-iodide **13**). The same is true for the monoalcohols with symmetrical ortho-substituent regardless of their existence in in/in, as **4a**, or in/out form, as **4d**,**e**.

A substantial upfield chemical shift for the *N*-methyl groups in α-hydroxybenzhydryl derivative **4e** can be attributed to a shielding of the methyl hydrogen atoms by the side phenyl rings. This view is supported by X-ray data for compound **4e** (Figures S1 and 9). The phenyl ring nearest to the 1-$NMe_2$ group is turned relative to the naphthalene system by an angle of 85° and faced one of the methyl groups. Its C−H vector points to the aromatic ring under the C−H···centroid angle of 146°. The resulting H···centroid distance of 2.87 Å normally should cause hydrogen atom shielding equal to ca. 0.5 ppm.[16] The observed $\delta_{Me}$ value for the 1-$NMe_2$ group in **4e** (2.56 ppm) as compared to that for compound **4d** (2.94 ppm) is in satisfactory agreement with this

(14) Sobczyk, L.; Grabowski, S. J.; Krygowski, T. M. *Chem. Rev.* **2005**, *105*, 3513−3560.

(15) Alder, R. W.; Anderson, J. E. *J. Chem. Soc., Perkin Trans.* **1973**, *2*, 2086−2088.

(16) Heigh, C. W.; Mallion, R. B. *Org. Magn. Res.* **1972**, *4*, 203.

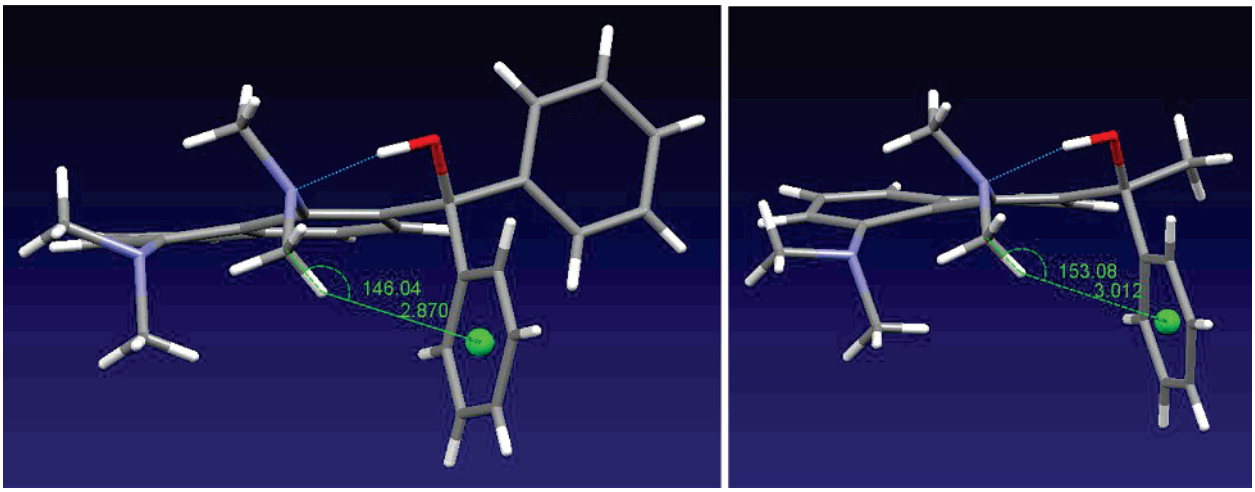



**FIGURE 9.** Representation of the shielding of the methyl hydrogen atoms in the 1-$NMe_2$ group of monoalcohols **4e** (left) and **4f** (right) (view along the mean naphthalene ring plane).

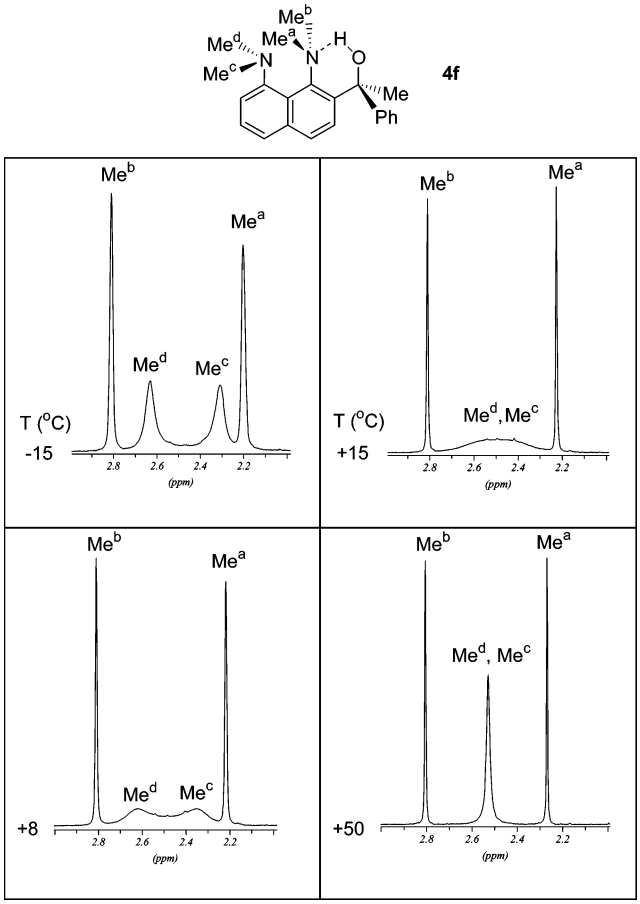



**FIGURE 10.** Temperature dependence of the *N*-methyl signals in the $^1H$ NMR spectra of **4f** (250 MHz, $CDCl_3$, $c = 5 \times 10^{-2}$ M).

estimation. A question can arise why both methyls of the 1-$NMe_2$ group in **4e** are magnetically equivalent? In our opinion, a logical explanation might consist of a rapid NMR time-scale swinging of the hydrogen-bonded cycle averaging $Me^a$ and $Me^b$ groups when R = R′ (Figure 4, **B** and **B′**).

The situation is complicated for monoalcohols with an asymmetrical ortho-substituent. For example, in the spectrum of compound **4f**, all four *N*-methyl groups display magnetic nonequivalence: in $CDCl_3$ at 8 °C, two of them give sharp signals at $\delta$ 2.2 and 2.8 ppm, while two others look like humps at $\delta$ 2.3 and 2.6 ppm (Figure 10). Obviously, such a picture is originated from asymmetry of the ortho-substituent in conjunction with the dynamic behavior of one of the $NMe_2$ groups. We believe that the upfield peak at 2.2 ppm belongs to the $Me^a$ group, shielded by the α-phenyl ring. Another sharp signal at 2.8 ppm can then be attributed to the $Me^b$ group. Both of these methyls are rotationally nonactive because the 1-$NMe_2$ group is fixed by IHB. It is noteworthy that the upfield displacement

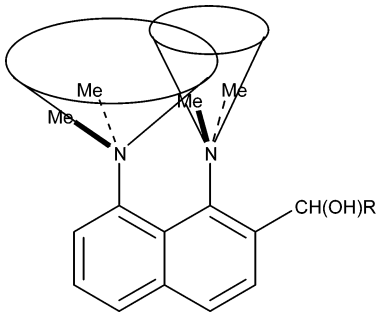



**FIGURE 11.** Schematic representation of the imaginary cones made by the rotating *peri*-dimethylamino groups in compounds **4b**,**c**.

of the Me[a] group in **4f** is the largest among all known naphthalene proton sponges. Although all of the details of this phenomenon are unclear, it should be noted that the C−H vector of the Me[a] group in **4f** points to the phenyl ring centroid more precisely (the C−H···centroid angle is 153°) than in the case of **4e** (Figure 9).

Apparently, an asymmetry of the 2-substituent in **4f** also exerts the nonequivalence of methyls of the 8-$NMe_2$ group although to a lesser extent. By a reason similar to the one mentioned above for the 1-$NMe_2$ group, the more upfield peak at 2.3 ppm can be assigned to the Me[c] group due to its larger proximity to the α-phenyl group than another methyl (Me[d]). Both Me[c] and Me[d] signals are strongly temperature dependent and they narrow at freezing, with coalescence at warming already at ca. 15 °C (Figure 10). In our opinion, the dynamic process, averaging the Me[c] and Me[d] groups in **4f**, can be attributed to rotation of the 8-$NMe_2$ group around the $C_8$−N bond.[17] Using an approximate relationship at the coalescence temperature (see ref 18 for an example), we estimated the barrier to rotation as equal to $\Delta G^{\ddagger} = 13.8$ kcal mol$^{-1}$.

Unlike alcohol **4f**, in the $^1$H NMR spectra of asymmetrical secondary monoalcohols **4b** and **4c** both methyls of the 1-$NMe_2$ group appear as a six-proton singlet. It is assumable that the nonchelated character and planarity of the 1-$NMe_2$ group for these compounds allows its fast rotation that makes the methyls magnetically equivalent in the NMR time-scale. In contrast, two methyls of the 8-$NMe_2$ group in **4b** and **4c**, similarly to **4f**, are magnetically different and temperature dependent (Figure S4). Their signals coalesce at 33 and 35 °C with $\Delta G^{\ddagger} = 15.7$ and 15.8 kcal mol$^{-1}$, respectively. The higher barrier to rotation of 8-$NMe_2$ group for **4b**,**c** in comparison with **4f** can be attributed to (1) lesser N···N distance in **4b**,**c** and (2) free rotation of 1-$NMe_2$ group in **4b**,**c** that restricts spatial possibility for rotation of the more pyramidalized 8-$NMe_2$ group (Figure 11). Notably, in DMSO-$d_6$ solution, the rotation of the 8-$NMe_2$ group is considerably relieved, and under ambient conditions both of its methyls in compounds **4b**,**c**,**f** become averaged (Tables 2 and 3).

An appearance of the $NMe_2$ groups in the $^1$H NMR spectra of the 2,7-diols with like alcohol functions **5a**−**e** is generally in accord with the above trends. As expected, all four methyl groups in compounds **5a**,**d**,**e** at temperatures from ambient up to −40 °C are magnetically equivalent, producing a 12-proton singlet at δ 2.95, 2.91, and 2.43 ppm, respectively. Somewhat complex is the spectral behavior of diols **5b** and **5c**. For example, $^1$H and $^{13}$C NMR spectra of **5c**, recorded in $CD_2Cl_2$, are evident of magnetic nonequivalence of four *N*-methyls, clearly divided into two pairs at room temperature. At −20 °C, the six-proton 2.98 ppm peak of **5c** moves to δ 2.86 ppm, while a singlet at 3.02 ppm splits into two three-proton signals located at 2.94 and 3.04 ppm. Lowering the temperature to −50 °C again gives two sharp peaks at 2.82 and 3.13 ppm. We believe that such behavior is caused by the asymmetrical nature of ortho-substituents in **5c** (**5b**) and their tendency to form intermolecular H-bonded associates on cooling (see above X-ray data for **5c**). Evidently, the molecule of **5c** becomes nonsymmetrical at −20 °C with regard to the axis passing through the C═C bond common for two benzene rings. Additionally, the sharp singlet of two C*H*(OH)Ph protons at 6.32 ppm separates into two one-proton peaks of two different CH(OH)Ph groups. On passing from $CD_2Cl_2$ to DMSO-$d_6$, the dipolar solvent prevents the intermolecular associates from being formed, coordinating with the hydroxyls of the ortho-substituents (cf., $\delta_{OH}$ of **5c** equal to ∼3.0 ppm in $CD_2Cl_2$ and 5.8 ppm in DMSO-$d_6$). This, in general, gives more freedom to the $NMe_2$ groups, so that all of the *N*-methyls of diols **5b** and **5c** appear in DMSO as one 12-proton peak.

**Theoretical Background.** The central point of the present study is: Why the primary and secondary proton sponge *ortho*-alcohols adopt the in/in conformation whereas for their tertiary counterparts the in/out form becomes highly preferable? To answer the question, consider first the parent compound **1**. Its existence in the gas phase as a mixture of more stable in/in and less stable in/out conformers has been recently claimed by Szemik-Hojniak and co-workers on the basis of fluorescence spectroscopy and ab initio calculations.[19] They estimated the energy difference between both forms as equal to 4.7 kcal mol$^{-1}$. Obviously, to reverse the situation in favor of the in/out form, this value should be overlapped at least twice. In general, there are two principal ways to achieve the goal. The first one is to further destabilize the already strained in/in form; the second approach is to stabilize the in/out form, most likely via organization of the attractive interactions between the $NMe_2$ groups and ortho-substituents.

A priori, placement of any substituent in the ortho-positions should raise the energy of the in/in conformer due to a steric compression on the adjacent $NMe_2$ group. Normally, this is accompanied by (1) shortening of the N···N distance, (2) flattening of the $NMe_2$ groups, and (3) their additional rotation around the $C_{ar}$−N bond. These changes are observed for the majority of 2,7-disubstituted proton sponges, for example, **14a**−**e** with OMe (2.756), $NMe_2$ (2.770), Cl (2.768), Br (2.775), and Me (2.749) groups (N···N distances are given in brackets, Å).[7] Notably, *ortho*-methyls, being the most bulky of all, cause the largest N···N shortening in **14e**.

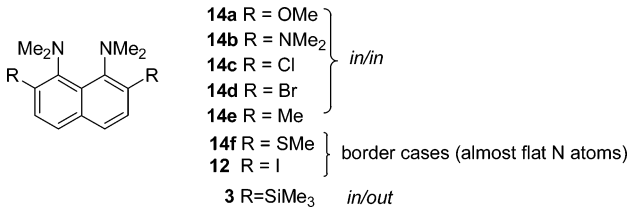
Surprisingly, introduction of more voluminous ortho-substituents, such as I and SMe in **12** and **14f**, and especially $SiMe_3$ in **3**, results in, instead of contraction, enlargement of the N···N distance to 2.82, 2.83, and 2.925 Å, respectively.[7] According to X-ray measurements, the $NMe_2$ groups in these cases become almost flat (I, SMe) or even out-inverted ($SiMe_3$), which requires more space between the nitrogen atoms and ultimately increases

(17) Of course, this does not exclude another type of dynamic activity, swinging of the hydrogen-bonded cycle as shown in Figure 4. However, such movements at R ≠ R′ cannot average the Me[a] and Me[b] groups.

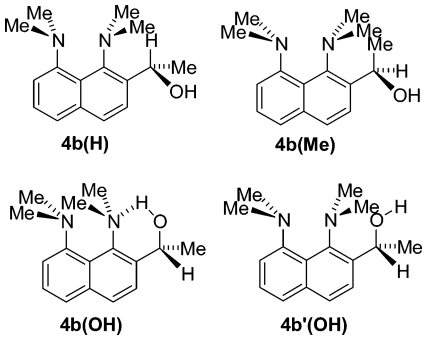
(18) Aganov, A. V.; Klochkov, V. V.; Samitov, Yu. *Russ. Chem. Rev.* **1985**, *54*, 931−947.

(19) Szemik-Hojniak, A.; Zwier, J. M.; Buma, W. J.; Bursi, R.; Van der Waals, J. H. *J. Am. Chem. Soc.* **1999**, *120*, 4840−4844.

the N···N distance. One can see that the above geometry distortions may induce the n → d interaction between the unshared electron pair of the $NMe_2$ group and the empty d-orbitals of a heavy α-atom of the nearest ortho-substituent. A possibility of such interaction is indirectly supported by the fact that the N···I, N···S, and N···Si distances in **12**, **14f**, and **3** are essentially less than the sum of the atomic van der Waals radii.[7] Hence, one can conclude that for compounds **3**, **12**, and **14f** along with the destabilization of the in/in form, the stabilization of the in/out form takes place. As a result, a pure in/out configuration is realized for molecule **3**, while **12** and **14f** stand for a border case between **3** and proton sponges **14a**−**e**.




Let us now turn to the alcohols under consideration. Among them, the secondary alcohols, for example, **4b**, seem to be the most common case. For **4b**, three distinct conformations are possible. They differ by a fragment of the ortho-substituent adjacent to the $NMe_2$ group: it is hydrogen atom for **4b**(**H**), methyl for **4b**(**Me**), and hydroxy group for **4b**(**OH**) [for the latter, both chelated and nonchelated forms **4b′**(**OH**) are instructive]. The **4b**(**H**) form structurally resembles the 2,7-dimethyl derivative **14e** and sterically is the most favorable. Unsurprisingly, there is a similarity between structures **5c** (close analogue of **4b**, see above) and **14e**. Respectively, their main characteristics are 2.749 and 2.747 Å (N···N distances), 352.6° and 352.5° (average sum of the valence angles at N atoms), and 72° and 70° (average rotational angle of the $NMe_2$ groups). Thus, the α-C−H bonds in the neighborhood with the $NMe_2$ groups are only able to compress the N···N distance to 2.75 Å, leaving their in/in orientation principally intact.




The conformation **4b**(**Me**) looks sterically very unfavorable, and the molecule can hardly exist as such keeping its in/in form; also, the corresponding in/out conformer (unlike, for example, **3**) cannot be stabilized by any attractive interactions. Because of a steric and electrostatic repulsion between the oxygen and nitrogen atoms, the same may be true for the open non-hydrogen-bonded conformer **4b′**(**OH**). Concerning the **4b**(**OH**) form, a question arises whether its IHB stabilization can compete with the structure **4b**(**H**)? For a deeper insight into the problem, we have conducted the DFT calculations on the B3LYP/6-31G** level of theory with inclusion of zero-point energy vibrations (ZPE) using the Gaussian 98 program complex.[20] For the method of gas-phase calculations of all potential energy minima, see ref 21. The theoretical analysis has been carried out at $T = 0$ K for rotational isomers of **4b** differing by the dihedral angle $C_3-C_2-C_\alpha-O$ (denoted as $\varphi$), and the results obtained are presented in Figure 12 and in Table 5.

All conformers that are being discussed below correspond to minima on the potential energy surface. At the same time, no minimum was found for the **4b**(**Me**), which confirms the above speculations concerning instability of this form. As expected, the conformer **4b**(**H**) is the most stable, and its total energy has been conveniently chosen as reference one ($E_{rel}$ = 0.0 kcal mol$^{-1}$). Some characteristic features of the optimized structure **4b**(**H**) are (1) the 1-$NMe_2$ group adjacent to the CH(OH)Me substituent is ideally planar and turned relatively mean to the naphthalene ring plane on ∼40°; in contrast, the 8-$NMe_2$ group being also acoplanar to the ring plane keeps a significant extent of the pyramidality (Table 5); (2) the $N_1$ nitrogen atom and the hydrogen of the hydroxyl group are eclipsed, and both come out of the $C_3-C_2-C_\alpha$ plane on ∼12° in the same direction; and (3) the oxygen atom also lies out of the plane and the dihedral angle $\varphi$ = 41° (Figure 12).

As rotation around the $C_2-C_\alpha$ bond starts and the atoms $N_1$ and O are approaching, the energy of the conformers increases and reaches its maximum (8.2 kcal mol$^{-1}$) for the structure **4b$_{2'}$**(**OH**). Obviously, this destabilization is caused by repulsion of the N and O atoms and by absence of the IHB between them. Indeed, a transition to the hydrogen-bonded conformers **4b$_1$**(**OH**) and **4b$_2$**(**OH**) via rotation around the $C_\alpha-OH$ bond (angle $\gamma$ in Figure 12) is accompanied by nitrogen inversion for the 1-$NMe_2$ group and leads to a considerable decrease in energy.

One can assume that the energy difference of 7.2 kcal mol$^{-1}$ between the forms **4b$_2$**(**OH**) and **4b$_{2'}$**(**OH**) reasonably reflects the strength of the IHB in the former.[22] However, because the calculated energy difference between the **4b$_2$**(**OH**) and **4b**(**H**) conformers does not exceed 1 kcal mol$^{-1}$ (the latter is slightly more preferable), this is not enough for effective stabilization of the chelated in/out form for **4b** and most likely for all other secondary and primary proton sponge *ortho*-alcohols. Notably, the calculated geometry parameters of IHB for the form **4b$_2$**(**OH**) (N···H 1.782, O−H 0.982 Å, −N···H−O 152°) are generally in satisfactory agreement with those determined experimentally for the in/out conformers of alcohols **4e**, **4f**, **5d**, and **5e** (Table 4).

Unlike the primary and secondary *ortho*-alcohols, their tertiary analogues cannot exist in the forms like **4b**(**H**) and hence are much more adapted for the N···OH chelation. As it has been

(20) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrewski, V. G.; Montgomery, J. A., Jr.; Stramann, R. E.; Buran, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Peterson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liaschenko, A.; Piskorz, P.; Komaromi, I.; Gomprets, R.; Martin, R. L.; Fox, D. L.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanaykkara, A.; Challacombe, M.; Gill, P. M. W.; Jonson, B.; Chen, W.; Wong, M. W.; Anders, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(21) Ozeryanskii, V. A.; Milov, A. A.; Minkin, V. I.; Pozharskii, A. F. *Agnew. Chem., Int. Ed.* **2006**, *45*, 1453−1456.

(22) The value of 7.2 kcal mol$^{-1}$ excellently agrees with commonly accepted Δ*H* values for O−H···N bonds: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; p 173.

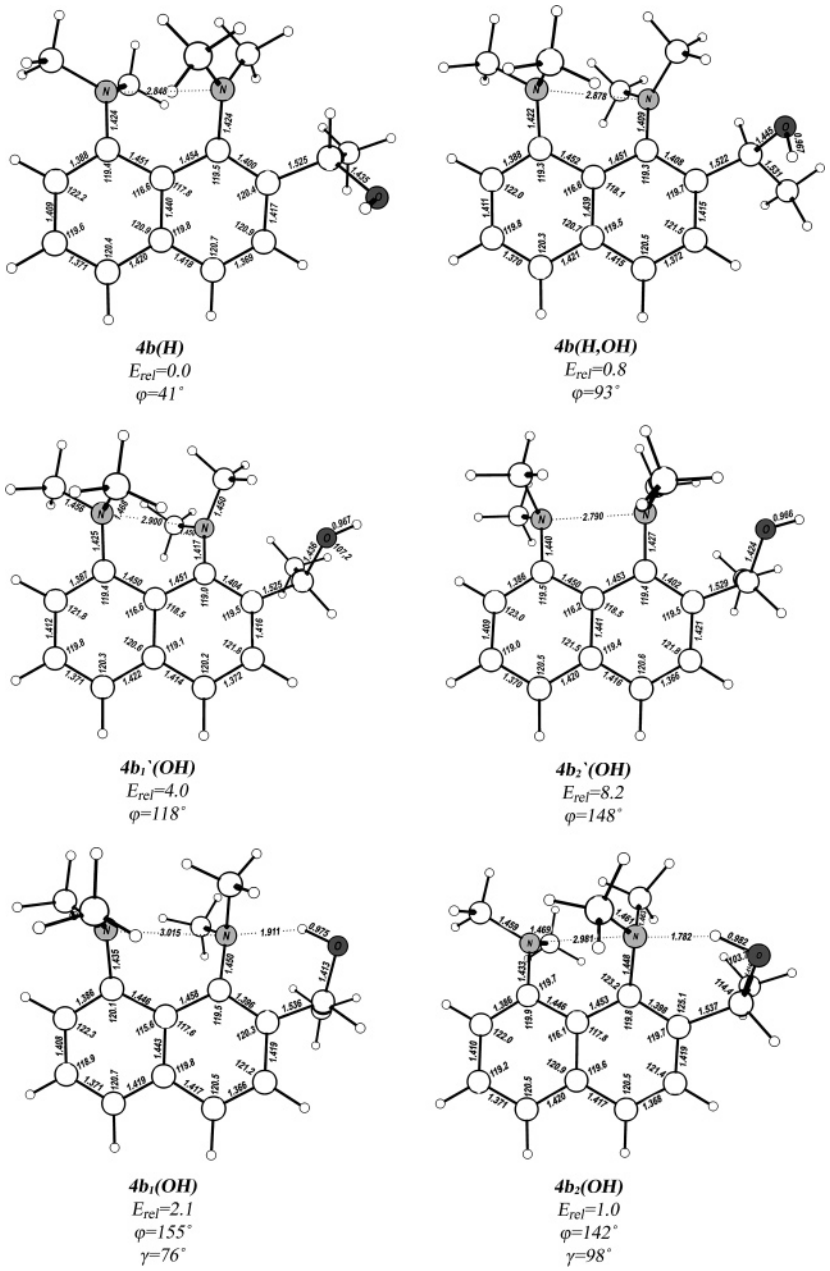



**FIGURE 12.** Calculated geometry (bond lengths and distances in Å, angles in deg) and relative energies (in kcal mol$^{-1}$) for the rotational conformers of alcohol **4b**.

**TABLE 5. Calculated N···N and O−H Distances, Selected Valence Angles, Sum of Valence Angles at Nitrogen Atoms, ∑N, and Total Energies, *E* + ZPE, for All Stable Conformers of Alcohol 4b**

| | conformer | | | | | |
|---|---|---|---|---|---|---|
| parameter | **4b(H)** | **4b(H,OH)** | **4b$_1$′(OH)** | **4b$_2$′(OH)** | **4b$_1$(OH)** | **4b$_2$(OH)** |
| N···N (Å) | 2.848 | 2.878 | 2.900 | 2.790 | 3.015 | 2.981 |
| O−H (Å) | 0.967 | 0.967 | 0.967 | 0.966 | 0.975 | 0.982 |
| ∠N$_1$−C$_1$−C$_2$ | 119.5 | 119.6 | 119.7 | 123.2 | 115.9 | 116.4 |
| ∠N$_8$−C$_8$−C$_7$ | 120.0 | 120.4 | 120.8 | 117.9 | 119.4 | 120,2 |
| ∑N$_1$ | 360.0 (in) | 359.7 (in) | 357.3 (in) | 356.2 (in) | 349.9 (out) | 351.4 (out) |
| ∑N$_8$ | 341.6 (in) | 341.6 (in) | 334.3 (in) | 340.3 (in) | 337.8 (in) | 338.1 (in) |
| *E* + ZPE, au | −807.31699 | −807.31575 | −807.31084 | −807.30431 | −807.31377 | −807.31543 |

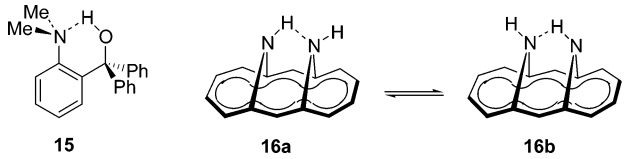
already mentioned, the transition from in/in to in/out conformers should be accompanied with a strong enlargement of the N···N distance. The X-ray data (Table 4) for the in/out proton sponges **3**, **4e**, **4f**, **5e**, and **5d** confirm this and reveal a surprising closeness of the N···N distances in their molecules (2.92−2.95 Å). Taking molecule **4f** as an example, we have shown that

there is quite a good agreement between experimentally observed and calculated structures for the chelated alcohols (see Table 4 and Supporting Information Figure S5).

Two main mechanisms appear to be responsible for the enlargement of the N···N distance in chelated alcohols. The first one operating for monoalcohols is based on the so-called[23] "leaning effect". Thus, in molecule **4e**, the chelated 1-$NMe_2$ group moves toward the 2-substituent that considerably decreases the $N_1-C_1-C_2$ angle (116°), while the 8-$NMe_2$ group does not move ($-N_8-C_8-C_9 = 120°$) [cf., above similar calculation results for conformers **4b$_1$(OH)** and **4b$_2$(OH)**].

Contrary to this, in diols **5d** and **5e** the leaning effect touches both $NMe_2$ groups, which are equally shifted in the same direction ($-N_1-C_1-C_2 = -N_8-C_8-C_9 = \sim 115°$). The N···N enlargement here occurs via another mechanism, enhanced ring distortion. As is known,[1,2] in the proton sponge molecule **1**, there occurs twisting along the central C═C bond resulting in the appearance of a torsion angle of 11° between two benzene moieties. This distortion enforces the $NMe_2$ groups to be more distant from each other, which decreases their repulsion. In monoalcohol **4e**, such twisting is the same as in **1**, but in diols **5d** and **5e** it is much more expressed (15° and 20°, respectively).[24]

Interestingly, the "out-ness" (sum of the valence angles at the nitrogen atom) of the inverted $NMe_2$ group for all tertiary alcohols also remains practically constant ($\sum N_1 = 350°$) and substantially exceeds that for compound **3** (355.3°). One can conclude therefore that stabilization of the in/out conformation via the IHB is much more effective than that based on the n → d interaction.[22]




**15** **16a** **16b**

Another remarkable outcome of the present work is the above-mentioned tandem nitrogen inversion existing in the tertiary proton sponge 2,7-dialcohols in solution (Scheme 4). To our knowledge, this is the first example of such a kind observed for aromatic amines. A somewhat related analogue of this phenomenon was reported earlier for *syn*-1,6:8,13-diimino[14]-annulene **16**.[25] Despite the stabilizing effect of the IHB in **16a** and **16b**, their exchange is very fast, and the inversion barrier, $\Delta G_{inv}^{\ddagger}$, does not exceed 6.5 kcal mol$^{-1}$. In our case, we still could not exactly estimate the $\Delta G_{inv}^{\ddagger}$ value. At cooling a solution of **5e** in $CD_2Cl_2$ to −40 °C, no decoalescence was noticed by means of NMR spectroscopy; further lowering the temperature was complicated by restricted solubility of the sample. Although we shall continue our efforts in this direction, even now it is possible to say that the *N*-inversion barrier for the tertiary proton sponge *ortho*-dialcohols is also rather low and apparently well below 10 kcal mol$^{-1}$ (see also ref 26).

The matter is that, while the out-$NMe_2$ group in the tertiary 2,7-dialcohols remains intramolecularly hydrogen bonded and somewhat stabilized, the in-$NMe_2$ group suffers from steric hindrance caused by the proximity of the second ortho-substituent. In the solid, this strain is compensated by the intermolecular hydrogen bonding (in addition to the IHB) and the formation of a tough crystal lattice. However, in solution, the factor of intermolecular association seems to be less important; the molecule in attempt to avoid the steric strain should actually choose between two equally nonfavorable conformations.

## Conclusions

In summary, it has been shown that placing any tertiary α-hydroxyalkyl substituent(s) in 2(7)-positions of the proton sponge molecule is an effective way for stabilization of its $NMe_2$ groups in nonconventional in/out conformation. This resulted from the formation of a rather strong intramolecular hydrogen bond of the O−H···N type, which overweighs energetic losses, caused by increasing steric repulsion of four N−Me groups in the in/out form and steric and electrostatic repulsions of the adjacent oxygen and nitrogen atoms. However, in the case of proton sponge derivatives with secondary and primary α-hydroxyalkyl groups in ortho-positions, there is realized an energetically more favorable in/in conformation without IHB but with the sterically less demanding α-C−H bonds close to the nitrogen atoms. Normally, retaining the in/in form in the ortho-disubstituted proton sponges due to internal sterical pressure is possible only at shortening of the N···N distance (from 2.80 in **1** to 2.75 Å), whereas transition to the in/out form is always accompanied by the strong increase of this parameter (up to 2.92−2.95 Å). The structural behavior of tertiary 2,7-diols depends on aggregate state. In the solid, their molecules are fixed in the in/out conformation, in which the nonchelated hydroxyl groups form hydrogen-bond chain associates with the oxygen atoms of the chelated OH groups. In solution, the tertiary 2,7-diols quickly equilibrate between two possible in/out forms. The driving force for this equilibration seems to be a sharp competition between hydrogen-bond stabilization of the out-inverted $NMe_2$ group and simultaneous steric destabilization of its in-inverted counterpart. This equilibration deserves further detailed study as a rare type of the tandem nitrogen inversion.

## Experimental Section

**1,8-Bis(dimethylamino)-2,7-dilithionaphthalene (8).** A solution of Bu$^n$Li (1.07 mL, 1.6 mmol) in *n*-hexane was added with stirring to a solution of dibromide **7**[9] (300 mg, 0.81 mmol) in $Et_2O$ (2 mL) under Ar at −20 °C. The resulting beige suspension of compound **8** was kept at −20 °C for 10 min and was used in subsequent reactions.

**1,8-Bis(dimethylamino)-2-bromonaphthalene (10).** A solution of Bu$^n$Li (0.43 mL, 0.69 mmol) in *n*-hexane was added with stirring to a solution of dibromide **7** (260 mg, 0.69 mmol) in $Et_2O$ (2 mL) under Ar at −20 °C. The resulting yellow solution of compound **9** was kept at −20 °C for 10 min, allowed to warm to rt, and poured into water. The ethereal layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The solvents were removed, and the residue was chromatographed with $CHCl_3$ as eluent. The

(23) Gallucci, J. C.; Hart, D. J.; Young, D. G. J. *Acta Crystallogr*. **1998**, *B54*, 73−81.

(24) It might be of interest that the main characteristics of IHB for alcohols **4e** and **5e** indicate that its strength markedly exceeds that for related benzene alcohol **15**. Thus, the IHB in **4e** and **5e** is more linear and shorter than that in **15**: −O−H···N = 152.3°, 162.7°, and 145.0°; O···N distances are 2.63, 2.61, and 2.66 Å, respectively. Al-Masri, H. T.; Sieler, J.; Lonnecke, P.; Blaurock, S.; Domasevitch, K.; Hey-Hawkins, E. *Tetrahedron* **2004**, *60*, 333−339.

(25) Destro, R.; Pilati, T.; Simonetta, M.; Vogel, E. *J. Am. Chem. Soc*. **1985**, *107*, 3185−3191.

(26) Mallpass, J. R.; Butler, D. N.; Johnston, M. R.; Hammond, M. L. A.; Warrener, R. N. *Org. Lett.* **2000**, *2*, 725−728.

first yellow fraction was bromide **10** eluted as yellowish oil, 191 mg (94%). The product has spectral properties identical to those reported in refs 7 and 10.

**General Procedures for Preparation of Ortho-mono- and -disubstituted 1,8-Bis(dimethylamino)naphthalenes 4a−i. (A) Organometallic Synthesis.** The corresponding electrophile was added to a solution of monolithium derivative prepared from 300 mg of **10** and Bu$^n$Li (0.64 mL, 1 mmol) under Ar and at −20 °C. The resulting mixture was kept at −20 °C for 30 min, allowed to warm to rt, and poured into water. The ethereal layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The combined organic extracts were evaporated, and the residue was purified by PTLC on $Al_2O_3$ to give the desired compounds with the yields indicated in Table 1.

**B. LAH Reduction of *ortho*-Aldehydes and *ortho*-Ketones.** An 8-fold excess of a powdered $LiAlH_4$ was added over a period of 15 min by small portions to a solution of the corresponding carbonyl derivative in dry $Et_2O$ or THF (10 mL). The mixture was stirred at rt for 12 h and then quenched with water (5 mL). The precipitate was filtered and washed with $Et_2O$ (3 × 5 mL). The solvent was removed, and the residue was purified by PTLC on $Al_2O_3$.

**1,8-Bis(dimethylamino)-2-hydroxymethylnaphthalene (4a).** Reduction of **4g** (method B) gave **4a** (90%) as light-yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.74 (6H, s), 3.0 (6H, s), 4.87 (2H, s), 7.13 (1H, dd, $J$ = 7.0, 0.8 Hz), 7.30 (1H, t, $J$ = 7.7 Hz), 7.39 (1H, d, $J$ = 8.4 Hz), 7.43 (1H, dd, $J$ = 7.6, 0.8 Hz), 7.52 (1H, d, $J$ = 8.4 Hz). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.67 (6H, s), 2.89 (6H, s), 4.62 (2H, d, $J$ = 5.6 Hz), 5.1 (1H, t, $J$ = 5.6 Hz), 7.01 (1H, d, $J$ = 7.3 Hz), 7.24 (1H, t, $J$ = 7.7 Hz), 7.38 (1H, d, $J$ = 7.9 Hz), 7.46 (1H, d, $J$ = 8.4 Hz), 7.51 (1H, d, $J$ = 8.5 Hz). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.78; H, 8.21; N, 11.35.

**1,8-Bis(dimethylamino)-2-(α-hydroxyethyl)naphthalene (4b).** Colorless crystalline powder with mp 54−56 °C (acetone). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.57 (3H, d, $J$ = 6.3 Hz), 2.63 (3H, s), 2.78 (3H, s), 2.99 (6H, s), 5.35 (1H, q, $J$ = 6.3), 7.19 (1H, d, $J$ = 7.3 Hz), 7.30 (1H, t, $J$ = 7.7 Hz), 7.46 (1H, d, $J$ = 7.7 Hz), 7.50 (1H, d, $J$ = 8.4 Hz), 7.57 (1H, d, $J$ = 8.4 Hz). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 1.33 (3H, d, $J$ = 6.5 Hz), 2.68 (6H, br s), 2.90 (6H, s), 5.00 (1H, d, $J$ = 3.9 Hz), 5.18 (1H, m), 7.12 (1H, d, $J$ = 6.8 Hz), 7.26 (1H, t, $J$ = 7.6 Hz), 7.42 (1H, d, $J$ = 6.8 Hz), 7.53 (1H, d, $J$ = 8.4 Hz), 7.57 (1H, d, $J$ = 8.4 Hz). Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.27; H, 8.51; N, 10.90.

LAH reduction of ketone **4h** (method B) gave 74% of alcohol **4b**, which was identical in properties to the pattern synthesized according to method A.

**1,8-Bis(dimethylamino)-2-(α-hydroxybenzyl)naphthalene (4c).** Brownish-yellow oil. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.65 (3H, s), 2.72 (3H, s), 2.85 (6H, s), 6.25 (1H, s), 7.16−7.54 (10H, m). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 2.61 (3H, s), 2.75 (3H, s), 2.85 (6H, s), 5.75 (1H, d, $J$ = 4.5 Hz), 6.16 (1H, d, $J$ = 4.5 Hz), 7.12−7.19 (2H, m), 7.25−7.32 (5H, m), 7.41−7.52 (3H, m). Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.79; H, 7.52; N, 8.67.

Reduction of ketone **4i** (method B) gave 71% of alcohol **4c**, which was identical in properties to the compound synthesized according to method A.

**1,8-Bis(dimethylamino)-2-(α-hydroxy-α-phenylethyl)naphthalene (4f).** Colorless crystals with mp 191−193 °C ($CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.93 (3H, s), 2.24 (3H, s), 2.4 (3H, s), 2.62 (3H, s), 2.83 (3H, s), 7.14−7.47 (7H, m), 7.57 (1H, dd, $J$ = 7.7, 1.5 Hz), 7.68 (2H, br s), 9.55 (1H, s). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 1.8 (3H, s), 2.3 (3H, s), 2.36 (6H, br s), 2.67 (3H, s), 7.10−7.41 (7H, m), 7.62 (1H, dd, $J$ = 7.5, 1.7 Hz), 7.72 (1H, d, $J$ = 8.6), 7.77 (1H, d, $J$ = 8.9 Hz), 8.07 (1H, s). Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.04; H, 7.78; N, 8.38. Found: C, 79.12; H, 7.71; N, 8.30.

**1,8-Bis(dimethylamino)-2-formylnaphthalene (4g).** Yellow oil. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.77 (6H, s), 3.22 (6H, s), 7.01 (1H, dd, $J$ = 7.3, 1.2 Hz), 7.35 (5H, m), 7.67 (1H, d, $J$ = 8.5 Hz), 10.22 (1H, d, $J$ = 0.8 Hz). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.36; H, 7.51; N, 11.58. Found: C, 74.42; H, 7.43; N, 11.52.

**2-Benzoyl-1,8-bis(dimethylamino)naphthalene (4i).** Brown-yellow oil. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.66 (6H, s), 2.75 (6H, s), 7.00 (1H, dd, $J$ = 6.4, 2.3 Hz), 7.25 (1H, d, $J$ = 8.5 Hz), 7.35−7.43 (5H, m), 7.52 (1H, t, $J$ = 6.6 Hz), 7.67 (2H, m). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.91; H, 7.86; N, 10.93. Found: C, 74.97; H, 7.82; N, 11.02.

**1,8-Bis(dimethylamino)-2,7-di(hydroxymethyl)naphthalene (5a).** Reduction of **5f** (method B) gave **5a** (90%) as yellow crystals, mp 113−114 °C (MeCN). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.95 (12H, s), 4.85 (4H, s), 7.44 (2H, d, $J$ = 8.4 Hz), 7.57 (2H, d, $J$ = 8.4 Hz). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 2.89 (12H, s), 4.63 (4H, d, $J$ = 5.6 Hz), 5.14 (2H, t, $J$ = 5.6 Hz), 7.51 (2H, d, $J$ = 8.5 Hz), 7.57 (2H, d, $J$ = 8.5 Hz). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.03; N, 10.22. Found: C, 70.13; H, 8.09; N, 10.14.

**1,8-Bis(dimethylamino)-2,7-di(α-hydroxyethyl)naphthalene (5b).** Pale-yellow crystals with mp 226−227 °C (acetone). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 1.38 (6H, m), 2.90 (12H, s), 5.01 (2H, m, $J$ = 4.4 Hz), 5.11 (2H, m), 7.51 (2H, d, $J$ = 8.4 Hz), 7.61 (2H, d, $J$ = 8.4 Hz). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.57; H, 8.72; N, 9.19.

Reduction of ketone **5g** (method B) gave 69% of alcohol **5b**, which was identical in its properties to the sample synthesized according to method A.

**1,8-Bis(dimethylamino)-2,7-di(α-hydroxybenzyl)naphthalene (5c).** Pale-yellow crystals with mp 190−191 °C (MeCN). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.96 (12H, s), 6.30 (2H, s), 7.29−7.40 (12H, m), 7.56 (2H, d, $J$ = 8.5 Hz). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 2.98 (12H, s), 5.79 (2H, d, $J$ = 4.5 Hz), 6.13 (2H, d, $J$ = 4.5 Hz), 7.21 (2H, d, $J$ = 8.4 Hz), 7.27−7.32 (10H, m), 7.56 (2H, d, $J$ = 8.4 Hz). Anal. Calcd for $C_{28}H_{30}N_2O_2 \cdot {}^1/_2$MeCN: C, 77.91; H, 7.10; N, 7.83. Found: C, 78.06; H, 7.12; N, 7.62.

Reduction of ketone **5h** (method B) gave 73% of alcohol **5c**, which had properties identical to those of the pattern synthesized according to method A.

**1,8-Bis(dimethylamino)-2,7-di(α-hydroxyisopropyl)naphthalene (5d).** Light-beige crystals with mp 123−125 °C (acetone). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.76 (12H, s), 2.91 (12H, s), 6.19 (2H, s), 7.37 (2H, d, $J$ = 8.7 Hz), 7.48 (2H, d, $J$ = 8.7 Hz). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 1.63 (12H, s), 2.82 (12H, s), 6.72 (2H, s), 7.45 (2H, d, $J$ = 8.6 Hz), 7.51 (2H, d, $J$ = 8.6 Hz). Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.73; H, 9.09; N, 8.48. Found: C, 72.79; H, 9.18; N, 8.40.

The second yellow fraction gave 1,8-bis(dimethylamino)-2-(α-hydroxyisopropyl)-naphthalene (**4d**) as a brownish-yellow oil. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.67 (6H, s), 2.67 (6H, s), 2.94 (6H, s), 7.32−7.43 (3H, m), 7.53−7.60 (2H, m), 10.72 (1H, s). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 1.59 (6H, s), 2.64 (6H, s), 2.84 (6H, s), 7.36−7.48 (2H, m), 7.56−7.71 (3H, m), 8.46 (1H, s). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 75.00; H, 8.83; N, 10.32.

**1,8-Bis(dimethylamino)-2,7-diformylnaphthalene (5f).** Orange-yellow crystals with mp 78−79 °C ($CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.17 (12H, s), 7.10 (2H, d, $J$ = 8.4 Hz), 7.67 (2H, d, $J$ = 8.4 Hz), 9.97 (2H, s). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.69; N, 10.38. Found: C, 71.03; H, 6.74; N, 10.36.

The second yellow fraction gave 1,8-bis(dimethylamino)-2-formylnaphthalene (**4g**) as a yellow oil, identical in properties to the aldehyde described above.

**2,7-Diacetyl-1,8-bis(dimethylamino)naphthalene (5g).** Pale-yellow crystals with mp 116−117 °C ($CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.52 (6H, s), 2.93 (12H, s), 7.23 (2H, d, $J$ = 8.3 Hz), 7.32 (2H, d, $J$ = 8.3 Hz). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.35; H, 7.49; N, 9.32.

**TABLE 6. Experimental Parameters and the Main Crystallographic Data for Alcohols 4f and 5c,d**

| | compound | | |
|---|---|---|---|
| | **4f** | **5c** | **5d** |
| empirical formula | $C_{22}H_{26}N_2O$ | $C_{28}H_{30}N_2O_2 \cdot {}^1/_2MeCN$ | $C_{20}H_{30}N_2O_2$ |
| formula weight | 334.45 | 447.07 | 330.46 |
| temperature (K) | 100(2) | 100(2) | 120(2) |
| crystal system | orthorhombic | monoclinic | orthorhombic |
| space group | $P2_12_12_1$ | $C2/c$ | $Pbca$ |
| $a$ (Å) | 10.5415(7) | 26.108(2) | 19.757(4) |
| $b$ (Å) | 12.4658(8) | 8.7845(6) | 8.955(2) |
| $c$ (Å) | 13.8618(9) | 44.836(3) | 21.234(4) |
| α (deg) | 90 | 90 | 90 |
| $\beta$ (deg) | 90 | 105.842(1) | 90 |
| $\gamma$ (deg) | 90 | 90 | 90 |
| $V$ (Å$^3$) | 1821.6(2) | 9892(1) | 3757(1) |
| $Z$ | 4 | 16 | 8 |
| $\lambda$ (Å) | 0.71073 | 0.71073 | 0.71073 |
| $D_{calcd}$ (g cm$^{-3}$) | 1.220 | 1.201 | 1.169 |
| $\mu$ (cm$^{-1}$) | 0.075 | 0.076 | 0.075 |
| reflections collected | 20 481 | 54 507 | 24 566 |
| reflections unique ($R_{int}$) | 4362 (0.0252) | 11 911 (0.0641) | 3760 (0.0545) |
| no. of parameters refined | 226 | 627 | 217 |
| reflections with $I > 2\sigma(I)$ | 4198 | 5681 | 2349 |
| $(2\theta)_{max}$ (deg) | 56 | 56 | 54 |
| $R_1$, w$R_2$ indices (all data) | 0.0358, 0.0890 | 0.0582, 0.0919 | 0.0863, 0.0982 |
| CCDC deposit no. | 631914 | 619601 | 619602 |

The second yellow fraction was 2-acetyl-1,8-bis(dimethylamino)-naphthalene (**4h**): brown-yellow oil. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.48 (3H, s), 2.78 (6H, s), 2.97 (6H, s), 7.00 (1H, dd, $J$ = 5.4, 3.3 Hz), 7.25−7.39 (4H, m). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.06; H, 7.81; N, 10.98.

**2,7-Dibenzoyl-1,8-bis(dimethylamino)naphthalene (5h).** Yellow crystals with mp 94−95 °C (*n*-hexane). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.71 (12H, s), 7.28 (2H, d, $J$ = 8.4 Hz), 7.44 (6H, m), 7.57 (2H, tt, $J$ = 7.3, 1.3 Hz), 7.78 (4H, dd, $J$ = 8.3, 1.5 Hz). Anal. Calcd for $C_{28}H_{26}N_2O_2$: C, 79.60; H, 6.20; N, 6.63. Found: C, 79.56; H, 6.14; N, 6.60.

**1,8-Bis(dimethylamino)-2-(α-hydroxybenzhydryl)-7-(α-hydroxyisopropyl)naphthalene (6c).** The compound was prepared from **6a**,[8] Bu$^n$Li, and acetone at −20 °C according to method A. Colorless crystals with mp 198−199 °C (acetone). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.76 (6H, s), 2.55 (6H, s), 2.79 (6H, s), 5.13 (1H, s), 6.69 (1H, d, $J$ = 8.6 Hz), 7.26−7.32 (11H, m), 7.38 (1H, d, $J$ = 8.8 Hz), 7.46 (1H, d, $J$ = 8.8 Hz), 7.83 (1H, s). Anal. Calcd for $C_{30}H_{34}N_2O_2$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.40; H, 7.47; N, 6.22.

The second yellow fraction gave 52% of 1,8-bis(dimethylamino)-2-(α-hydroxybenzhydryl)-naphthalene (**4e**), which has the same spectral data as does the compound obtained previously.[8]

**1,8-Bis(dimethylamino)-2-(α-hydroxybenzhydryl)-7-hydroxymethylnaphthalene (6b).** Diethyl carbonate (0.1 mL, 0.8 mmol) was added to a solution of lithium derivative [prepared from **6a** (363 mg, 0.8 mmol) and Bu$^n$Li (1 mL, 1.6 mmol)] at −20 °C. The reaction mixture was kept at −20 °C for 30 min, and then allowed to warm to rt and poured into water. The ethereal layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). After standard workup, the residue was chromatographed and yielded 151 mg (40%) of compound **6d** and 134 mg (42%) of compound **4e**.[8] Next, $LiAlH_4$ (100 mg, 2.6 mmol) was added over a period of 15 min by small portions to a solution of **6d** (150 mg, 0.32 mmol) in dry THF (10 mL). The mixture was stirred at rt for 12 h and then quenched with water (5 mL). The precipitate was filtered and washed with $Et_2O$ (3 × 5 mL). The combined organic extracts were evaporated, and the residue was purified by PTLC on $Al_2O_3$, yielding 80 mg (59%) of alcohol **6b** as light-beige crystals with mp 233−234 °C (acetone). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 2.51 (6H, s), 2.78 (6H, s), 4.90 (2H, s), 6.75 (1H, d, $J$ = 8.5 Hz), 7.28−7.39 (11H, m), 7.47 (1H, d, $J$ = 8.1 Hz), 7.58 (1H, d, $J$ = 8.5 Hz), 10.60 (1H, s). $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ 2.42 (6H, s), 2.69 (6H, s), 4.73 (2H, d, $J$ = 5.5 Hz), 5.29 (1H, t, $J$ = 5.5 Hz), 6.62 (1H, d, $J$ = 8.7 Hz), 7.23−7.36 (11H, m), 7.48 (1H, d, $J$ = 8.7), 7.62 (1H, m), 10.17 (1H, s). Anal. Calcd for $C_{28}H_{30}N_2O_2$: C, 78.87; H, 7.04; N, 6.57. Found: C, 78.80; H, 7.11; N, 6.54.

**X-ray measurements** for compounds **4f** and **5c**,**d** were carried out with Bruker SMART 1000 CCD area detector, using graphite monochromated Mo K$_\alpha$ radiation ($\lambda$ = 0.71073 Å, $\omega$-scans with a 0.3° step in $\omega$ and 10 s per frame exposure). The crystals of suitable quality were obtained from $CHCl_3$ (**4f**), MeCN (**5c**), or acetone (**5d**). The main crystallographic data and some experimental details are given in Table 6. Although compound **4f** crystallizes in a chiral space group $P2_12_12_1$, it was impossible to determine the absolute configuration due to the absence of heavy atoms in the molecule. Atomic coordinates, bond lengths, bond angles, and thermal parameters for **4f**, **5c**, and **5d** have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ; fax: +44 1223 335 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers.

**Acknowledgment.** This Article is dedicated to one of the leading Russian scientists in aromatic and dye chemistry, Prof. Michael V. Gorelik, State Scientific Center NIOPIK, on the occasion of his 75th birthday. This work was supported by the Russian Foundation for Basic Research (project no. 05-03-32110).

**Supporting Information Available:** General considerations; molecular structures of **4e** and **5e**; graphical representation of H-bonding in the crystal structure of **5e**; dynamic $^1$H NMR spectra of **4b** and **4c**; and calculated molecular geometries of **4f** and **5c** including total energies and atomic coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062667V