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Binaphthyl substituted 1,8-bis(dimethylamino)naphthalenes, the first chiral, atropisomeric, proton sponges

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ABSTRACT

Atropisomeric naphthalene proton sponges (*R,S*)-**3** (*meso*), (*R,R* + *S,S*)-**3** (racemic) and (*S,S*)-**3** (enantiopure) were prepared by bis-N,N-dialkylation of 1,8-diaminonaphthalene, using both racemic (*R* + *S*)- and enantiopure (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl, respectively, as alkylating agents. The amino function of the corresponding mono-binaphthyl substituted tertiary/primary diamines (*R* + *S*)-**4** (racemic) and (*S*)-**4** (enantiopure), obtained as side products, was N,N-dimethylated to give the corresponding bis(tertiary) diamines (*R* + *S*)-**2** and (*S*)-**2**, respectively. Thermal isomerisation of the *meso* adduct (*R,S*)-**3** to the corresponding racemic adduct (*R,R* + *S,S*)-**3** occurred in the solid state. Reversible evolution of the ^{1}H NMR spectra of (*R,S*)-**3**, (*R,R* + *S,S*)-**3** and (*R* + *S*)-**2** in toluene-d_8 solution as a function of temperature was observed, showing conformational changes but no isomerisation of the binaphthyl skeleton. ^{1}H NMR of the protonated diamines showed the resonance of a single proton at very low field (18.7–20.2 ppm) in all cases.

The remarkable basicity of 1,8-bis(dimethylamino)naphthalene **1** (Fig. 1), first observed by Alder and coworkers in the late 1960s,[1] led to the name '*proton sponge*'. A general feature of proton sponges is the strong steric strain induced by the repulsion between two close basic nitrogen centres in the molecule, which have an orientation that allows the uptake of *one* proton to yield a stabilised $[N\cdots H\cdots N]^+$ intramolecular hydrogen bond. The diamine **1**, prototypical of the first generation of proton sponges, all having in common 'sluggish' behaviour (poor nucleophilicity and slow protonation/deprotonation) combined with exceptionally high basicity (pK_a values of ca. 12–17), was later followed by several naphthalene as well as non-naphthalene analogues.[2–11] Proton sponges and their complexes with mineral or organic acids have been the focus of intense research activity and continue to generate considerable interest in theoretical studies of factors responsible for enhanced basicity as well as in a variety of applications.[12,13] However, surprisingly, *chiral proton sponges* have seldom been considered, and to our knowledge, only unresolved *dl* forms of 1,8-bis(*N*-benzyl-*N*-methylamino)naphthalene[14] and of a resolved proton sponge-like bis-tetrahydroisoquinoleine,[15] both with asymmetric nitrogen atoms,[16] had been reported until the recent synthesis of 1,8-bis(dimethylamino)-2-(α-hydroxy-α-phenylethyl)naphthalene in both enantiomerically pure forms by Kostyanovsky, Pozharskii and co-workers.[17]

We were interested in applying to 1,8-bis(dimethylamino)naphthalene **1** the same concept of substitution by axially chiral binaphthyl units that we previously employed to render tetramethylethylenediamine (TMEDA) chiral,[18] and in this Letter, we wish to report the synthesis and characterisation of the binaphthyl-substituted 1,8-bis(dimethylamino)naphthalenes (*S*)-**2** and (*S,S*)-**3** (Fig. 1) in enantiopure state. These diamines represent unique, *chiral*, *atropisomeric*, naphthalene proton sponges.

Synthesis: the *gem*-dialkylation with exclusive formation of a seven-membered ring system in the reaction of primary or secondary amines with either 2,2′-bis(bromomethyl)-1,1′-binaphthyl or 2,2′-bis(bromomethyl)-1,1′-biphenyl was established in the 1950s,[19] and has often been exploited in the synthesis of a variety of catalysts.[18,20] Here, treatment of freshly sublimed 1,8-diaminonaphthalene with 2 M equiv of racemic 2,2′-bis(bromomethyl)-1,1′-binaphthyl and an excess of diisopropylethylamine (DIEA) in toluene–acetonitrile 1:1 at 110 °C for 40 h gave a mixture of the bis-binaphthyl substituted naphthalene proton sponges (*R,R* + *S,S*)-**3**[21] (racemic) (Fig. 2), sparingly soluble in usual organic solvents, which was easily isolated in 40% yield by fractional crystallisation, and (*R,S*)-**3** (*meso*)[21] which was obtained in 41% yield after repeated chromatography and crystallisation. Characterisation of the isomeric diamines (*R,R* + *S,S*)-**3** (racemic) and (*R,S*)-**3** (*meso*) by ^{1}H NMR in $CDCl_3$ (or toluene-d_8) solution at room temperature was straightforward, since completely different patterns were observed for their Ar-NCH_2(Ar) protons, an AB quartet and singlet for (*R,R* + *S,S*)-**3** and two AB quartets for (*R,S*)-**3** at room temperature (Table 1). The configurational attribution of the two isomers

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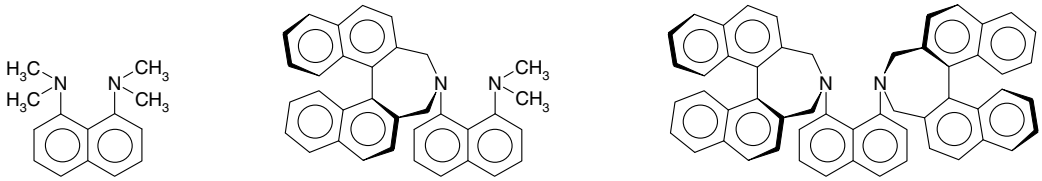

Figure 1. Chemical structures of 'proton-sponge' **1** and related binaphthyl-substituted 1,8-bis(dimethylamino)naphthalene (*S*)-**2** and (*S,S*)-**3**.

was unambiguous after isolation of the enantiopure diamine (*S,S*)-**3** (vide infra) with the same ^{1}H NMR spectrum as (*R,R* + *S,S*)-**3**. The isomeric bis-tertiary diamines **3** were accompanied to a minor extent by the primary–tertiary diamine (*R* + *S*)-**4**,[21] which was isolated in 10% yield after chromatography. In parallel, the use of enantiomerically pure (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl[18b,22] as the alkylating agent led to a mixture of enantiopure diamines (*S,S*)-**3**,[21] isolated in 86% yield after crystallisation/chromatography, and (*S*)-**4**[21] as a side product (8% yield). As expected, using a large excess (2 M equiv instead of half an equivalent) of 1,8-diaminonaphthalene over (*R* + *S*)- and (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl favoured the formation of the primary–tertiary diamines (*R* + *S*)-**4** and (*S*)-**4**, which were obtained in 44% and 59% yield, respectively. Methylation of (*R* + *S*)-**4** and (*S*)-**4** by treatment with sodium hydride and dimethylsulfate in refluxing THF (tetrahydrofuran) afforded the mono-binaphththyl substituted naphthalene proton sponges (*R* + *S*)-**2**[21] (78% yield) and (*S*)-**2**[21] (78% yield), respectively (Fig. 2).

Molecular stereodynamics: naphthalene proton sponges generally present reversible transitions between different conformations that can be observed by ^{1}H and ^{13}C NMR, due to the hindered rotation of the dialkylamino groups around the C_{Ar}–N bonds, distorted ring shape, and inversion of the nitrogen atoms.[6b] For 1,8-bis(dimethylamino)naphthalene **1** (Fig. 1) in CF_2Cl_2 solution, it has been reported that the unique singlet absorption for the *N*-methyl groups at room temperature broadens below −70 °C and splits to a 1:1 doublet below −120 °C, with a free energy of activation of 7.5 kcal mol^{-1} for the process. For the more sterically hindered 1-benzylmethylamino-8-dimethylamino-naphthalene, the $N(CH_3)_2$ and the $N(CH_2Ph)$ singlets observed at room temperature split at −38 °C to a doublet and an AB quartet, respectively, with coalescence temperatures of ca. −8 °C and −2 °C corresponding to a free energy of activation of 13.7 kcal mol^{-1} for the conformational process giving rise to these spectral changes.[3] In a similar manner, the ^{1}H NMR spectra of the binaphthyl substituted proton sponges (*R* + *S*)-**2** (or (*S*)-**2**), (*R,S*)-**3** (*meso*), and (*R,R* + *S,S*)-**3** (or (*S,S*)-**3**) in toluene-d_8 solution are temperature dependent in a reversible manner, but the spectral changes occur far above room temperature instead of below 0 °C, as these compounds are more sterically demanding than those reported above. For the mono-binaphthyl substituted proton sponge (*R* + *S*)-**2** (or (*S*)-**2**) (Fig. 3) two AB quartets for the *N*-methylene protons and two singlets for the *N*-methyl protons are present at room temperature (298 K), indicating an inequivalency of not only the *N*-methylene protons but also both the *N*-methylene and the *N*-methyl carbon atoms. This is confirmed by the ^{13}C NMR spectrum of (*R* + *S*)-**2** (or (*S*)-**2**) in $CDCl_3$ solution at room temperature, in which two singlets (58.2–52.9 ppm) for the *N*-methylene and two singlets (46.9–42.1 ppm) for the *N*-methyl carbon atoms are observed. Coalescence of the *N*-methyl proton singlets to a broad singlet occurs at about 318 K and coalescence of the *N*-methylene AB quartets to broad singlets (equivalency of the *N*-methylene protons) occurs at about 338 K. Further temperature increase results in the evolution of the *N*-methyl singlet to a sharp singlet at about 358 K (equivalency of the *N*-methyl carbon atoms), and in evolution of the two *N*-methylene broad singlets to one singlet at about 378 K, with a coalescence temperature of ca. 358 K, reflecting an equivalency of both the *N*-methylene protons and carbon atoms. The calculated[23] free energy of activation for the conformational processes giving rise to these spectral changes is ca. 15.6 ± 0.5 kcal mol^{-1} for the *N*-methyl carbon atoms and ca. 17.5 ± 0.5 kcal mol^{-1} for the *N*-methylene protons and carbon atoms.

For the *meso* diamine (*R,S*)-**3** in toluene-d_8 solution, two AB quartets are present at room temperature (295 K) for the *N*-methylene protons CH_A (δ 4.16 ppm)-CH_B (δ 3.60 ppm) and $C'H_A$ (δ 4.27 ppm)–$C'H_B$ (δ 3.87 ppm), reflecting an inequivalency of both *N*-methylene protons and carbon atoms. The latter is confirmed by ^{13}C NMR of (*R,S*)-**3** in $CDCl_3$ solution at room temperature, showing the presence of two singlets (58.2–56.0 ppm) for the *N*-methylene carbon atoms. Coalescence of firstly the two doublets relative to the CH_A–$C'H_A$ protons to a single broad doublet and secondly the two doublets relative to the CH_B–$C'H_B$ protons to a single broad doublet occurs at about 315 K and 335 K, respectively. The two broad doublets sharpen on further temperature increase, to give a typical AB quartet (4.23–3.85 ppm) at about 385 K (equivalency of the *N*-methylene carbon atoms). The calculated free energy of activation for the involved conformational processes is ca. 16.0 ± 0.5 kcal mol^{-1}. For the racemic diamine (*R,R* + *S,S*)-**3** (or the enantiomer (*S,S*)-**3**) in toluene-d_8 solution, no signal coalescence is observed in the temperature range 295–385 K, although

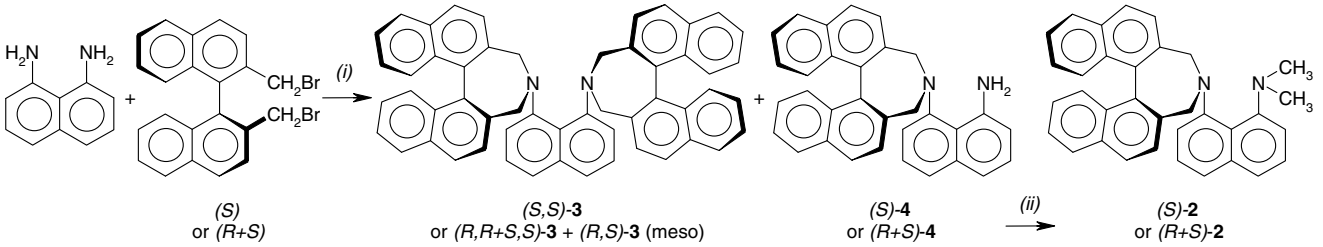

Figure 2. Synthesis of the diamines (*S,S*)-**3**, (*S*)-**4** and (*S*)-**2** from 1,8-diaminonaphthalene and enantiomerically pure (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl, and (not shown) the mixture of (*R,R* + *S,S*)-**3** (racemic) and (*R,S*)-**3** (*meso*) isomers, (*R* + *S*)-**4** and (*R* + *S*)-**2** from 1,8-diaminonaphthalene and racemic (*R* + *S*)-2,2′-bis(bromomethyl)-1,1′-binaphthyl. Reagents and conditions: (i) DIEA; toluene–acetonitrile 1:1; reflux; (ii) NaH; THF; $(CH_3)_2SO_4$; reflux.

Table 1
Patterns and chemical shifts of the $ArCH_2$–N and $(CH_3)_2$–N signals in ^1H NMR of the diamines (*R* + *S*)-**2** (or (*S*)-**2**), (*R*,*S*)-**3** and (*R*,*R* + *S*,*S*)-**3** (or (*S*,*S*)-**3**) in $CDCl_3$ solution as a function of the molar fraction of added TFA

		$CDCl_3$	$CDCl_3$ + TFA (0.5 equiv)	$CDCl_3$ + TFA (1 equiv)	$CDCl_3$ + TFA (2 equiv)
(*R* + *S*)-**2**	*N*-Methyl	2.72–2.64 (s)	3.58–3.31 (s)[a]	3.48–3.21 (s)	3.39[c]–3.13[c] (s)
	N-Methylene	4.13–3.94 (AB)	4.50–3.80 (m, br)[b]	4.40–4.16 (AB)	4.43[c]–4.18 (AB)
		4.06 (s)		4.29–4.23 (AB)	4.28[c] (s)
	N···H^+···N	—	18.70 (s)	19.00 (s)	19.39 (s)
(*R*,*R* + *S*,*S*)-**3**	*N*-Methylene	3.96 (s)	4.71–4.53 (AB)[a]	4.70[c]–4.48 (AB)	4.71[c]–4.38 (AB)
		3.90–3.81 (AB)	4.50–4.31 (AB)[a]	4.43–4.31[c] (AB)	4.35–4.29[c] (AB)
	N···H^+···N	—	20.20 (s)	20.22 (s)	20.22 (s)
(*R*,*S*)-**3**	*N*-Methylene	4.47–4.09 (AB)	5.18–3.69 (m, br)[b]	5.03–4.33 (AB)	4.73–4.40[c] (AB)
		4.34–3.68 (AB)		4.36–4.26 (AB)	4.31–4.27 (AB)
	N···H^+···N	—	18.94 (s)	18.92 (s)	18.94 (s)

[a] Signals of the unprotonated diamine (left column) seen apart in a ca. 1:1 ratio.
[b] Signals of the unprotonated diamine (left column) not distinguished.
[c] Additional splitting of ca. 2–5 Hz attributed to coupling with a single proton.

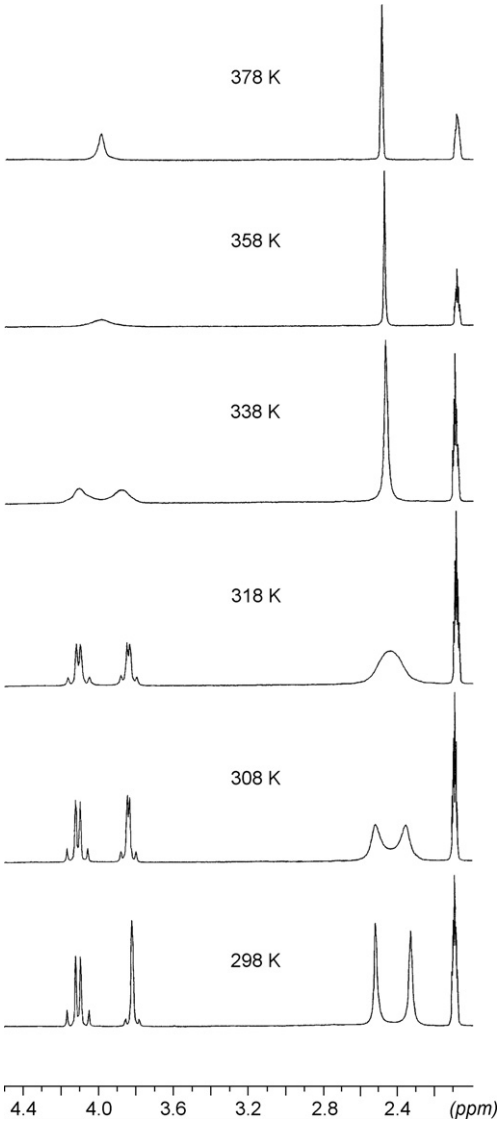

Figure 3. Patterns of the $ArCH_2$–N (3.7–4.1 ppm) and $(CH_3)_2$–N (2.2–2.6 ppm) signals as a function of temperature in ^1H NMR of the diamine (*R* + *S*)-**2** (or (*S*)-**2**) in toluene-d_8 solution.

spectral changes occur, from an AB quartet and singlet (ca. 295–335 K), to two AB quartets (ca. 355–370 K) to two singlet-like AB quartets at about 385 K, consistent with variations of the methylene proton environments and persistent inequivalency of the methylene carbon atoms (two singlets at 58.1–52.0 ppm observed in ^{13}C NMR of (*R*,*R* + *S*,*S*)-**3** in $CDCl_3$ solution at room temperature).

The above-described conformational changes may be rationalised by the occurrence of 'narcissistic' processes (represented in Fig. 4 for the diamine (*S*)-**2**) involving interconversion of object and mirror image through a planar transition state (or high energy intermediate), as proposed by Alder and co-workers,[3] in which ring distortion and bond rotation may combine in order to minimise the lone-pair–lone-pair repulsion imposed by the sterically demanding dialkylamino groups. In the twisted conformations of lower energy, both *N*-methyl and *N*-methylene carbon atoms are inequivalent as reflected in the ^1H and ^{13}C NMR spectra of all diamines at room temperature, in which the signals at lower field are tentatively attributed to the *N*-methyl and *N*-methylene protons and carbon atoms of the $NC'H_3$ and $NC'H_AH_B$ groups located in the deshielding zone of the naphthalene ring current, and the signals at higher field to the NCH_3 and NCH_AH_B groups located out of the plane of the naphthalene ring.[3]

Configurational stability: remarkably, as opposed to the facile *meso*-to-DL interconversion involving asymmetric nitrogen atoms reported for the 1,8-bis(*N*-benzyl-*N*-methylamino)naphthalene proton sponges,[14] the above mentioned temperature-dependent conformational changes in solution do not involve any racemisation of the binaphthyl moiety, as demonstrated by (i) the lack of formation of the *meso* isomer (*R*,*S*)-**3** from (*R*,*R* + *S*,*S*)-**3** (or (*S*,*S*)-**3**) and reciprocally of racemic (*R*,*R* + *S*,*S*)-**3** from *meso* (*R*,*S*)-**3** in toluene-d_8 solution at 385 K (by ^1H NMR, vide supra), and (ii) the identical optical rotation of the diamine (*S*)-**2** before and after refluxing in toluene solution at 120 °C for 24 h. However, when the *crystalline meso* diamine (*R*,*S*)-**3** was heated at 245 °C under vacuum (ca. 0.1 mm) for 2.5 h, neither sublimation nor melting occurred, but *total isomerisation to the racemic diamine* (*R*,*R* + *S*,*S*)-**3** (with no trace of the initial *meso* isomer) was observed by ^1H NMR. This result is surprising (even unique to our knowledge) as 2,2′-bis(methylene)-1,1′-binaphthyl derivatives are generally reported to have very high enantiomeric stability.[20a,24] We believe that the driving force for this complete thermal isomerisation is related to the much higher crystallinity (and melting point) of the racemic than the *meso* isomer. Indeed, melting of (*R*,*S*)-**3** could possibly occur at the microscopic level (although in an apparently persistent solid state) at 245 °C and be accompanied by configurational inversion of a 1,1′-binaphthyl moiety (allowed rotation along the C^1—$C^{1'}$ bond) followed by crystallisation of (*R*,*R* + *S*,*S*)-**3** at that temperature. In a control experiment, we demonstrated that when the optically pure isomer (*S*,*S*)-**3** was heated under vacuum in the same

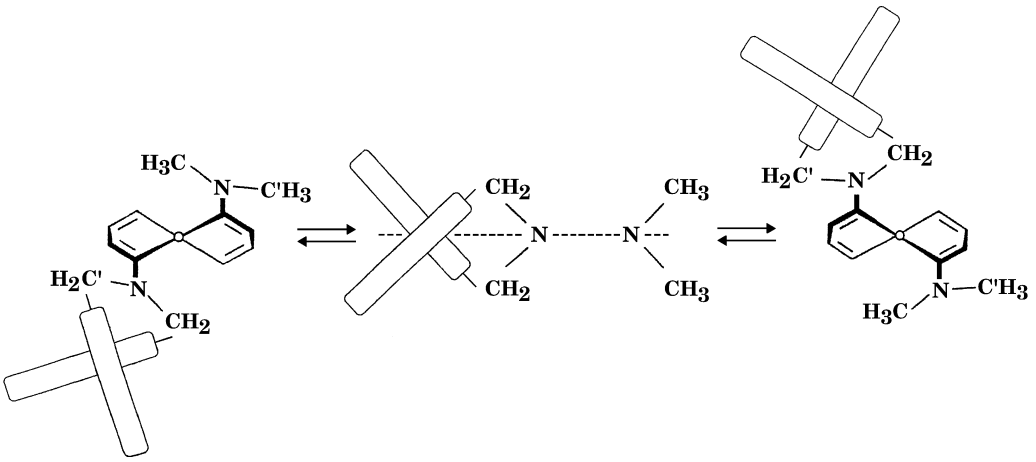

Figure 4. Postulated narcissistic pathway for the conformational changes of the diamine (*S*)-**2** (or (*R* + *S*)-**2**) in toluene-d_8 solution as a function of temperature.

conditions as above, it neither racemised to (*R*,*R* + *S*,*S*)-**3** nor isomerised to (*R*,*S*)-**3** to any extent.

Proton bonding: ^{1}H NMR analyses of the protonated diamines (*R* + *S*)-**2**, (*R*,*R* + *S*,*S*)-**3** and (*R*,*S*)-**3** were performed in $CDCl_3$ solutions containing various proportions of trifluoroacetic acid (TFA), respectively, ca. 0.5, 1 and 2 equiv (mol/mol) (Table 1). At a molar ratio TFA:(*R* + *S*)-**2** 0.5:1, two new singlets corresponding to the *N*-methyl groups of the protonated molecule are seen at far lower field (3.58 and 3.31 ppm) than the *N*-methyl singlets of the unprotonated form which appear as a broad signal at 2.70 ppm. According to the integration of these distinct signals, both protonated and unprotonated molecules are present in ca. 1:1 ratio. In a similar manner, for TFA:(*R*,*R* + *S*,*S*)-**3** 0.5:1, two AB quartets corresponding to the *N*-methylene signals of the protonated form are present at 4.71–4.53 ppm and 4.50–4.31 ppm, distinct from the *N*-methylene signals of the neutral form (Table 1). Therefore, for both (*R* + *S*)-**2** and (*R*,*R* + *S*,*S*)-**3**, it appears that the exchange between the protonated and unprotonated molecules is too slow to be observed by NMR at room temperature. For the *meso* diamine (*R*,*S*)-**3**, as well as for (*R* + *S*)-**2**, the *N*-methylene signals of the two forms appear as a complex broad multiplet and cannot be distinguished. Table 1 also shows that at a molar ratio TFA:diamine 1:1, sharp signals for both *N*-methyl and *N*-methylene protons are generally observed for all protonated molecules (*R* + *S*)-**2** (or (*S*)-**2**), (*R*,*S*)-**3** and (*R*,*R* + *S*,*S*)-**3** (or (*S*,*S*)-**3**), and this is also true at a molar ratio TFA:diamine 2:1, with only differences in signal patterns and chemical shifts. Finally, *in all cases and whatever the molar ratio TFA:diamine*, *resonance of a single proton is observed at very low field* (18.7–20.2 ppm), integration of which shows that it is bound to one diamine molecule. These features are very close to the ^{1}H NMR characteristics of protonated 1,8-bis(dialkyl)naphthalene proton sponges previously reported.[2b,4]

In summary, we prepared unique, chiral, atropisomeric, binaphthyl substituted 1,8-bis(dimethylamino)naphthalene derivatives in the racemic as well as enantiopure states. Reversible evolution of the ^{1}H NMR spectra of (*R*,*S*)-**3**, (*R*,*R* + *S*,*S*)-**3** and (*R* + *S*)-**2** in toluene-d_8 solution as a function of temperature was observed, showing conformational changes but no isomerisation of the binaphthyl skeleton. However, remarkably, thermal isomerisation of the meso adduct to the corresponding racemic adduct occurred in the solid state. ^{1}H NMR of the protonated diamines showed resonance of a single proton at very low field (18.7–20.2 ppm) in all cases, in agreement with proton sponge behaviour. This study constitutes a further insight into the synthesis of novel organic chiral superbases.[14] It also represents a first step towards the use of the present binaphthyl-substituted naphthalene proton sponges for enantioselective 'chiral proton'-catalysed reactions,[16] as well as for their exploitation as potential chiral shift reagents. Their conformationally labile analogues *biphenyl*-substituted 1,8-bis(dimethylamino)naphthalene derivatives will also be synthesised in our groups, and explored as potential new tools for assignment of the absolute configuration of amino acids through induced circular dichroism of the biphenyl moieties,[25] upon acid–base interaction.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.042.

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