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Synthesis of a Protonated C_2-Symmetric *N,N*-Chiral "Proton Sponge"

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Abstract: The hydrogen iodide salt of 1,8-bis-(*N*-benzyl-*N*-methylamino)naphthalene was synthesised as an 89 / 11 ratio of diastereomers in good yield. The structure of the major (±)-(R_NR_N / S_NS_N) diastereomer was determined by single crystal X-ray diffraction. The minor diastereomer is shown to be the *meso*-(R_NS_N) form by performing ^{1}H NMR n.O.e studies on isotopically desymmetrized 1-(*N*-benzyl-*N*-[^{13}C]-methylamino)-8-(*N'*-benzyl-*N'*-methylamino)naphthalene (HI salt). The half-life of interconversion of *meso* and *dl* forms is less than 2 minutes in CD_2Cl_2 at ambient temperature.

The effect of strain on organic amines is well documented[1] and can result in large positive or negative deviations from "normal" thermodynamic and kinetic basicity. The gas-phase proton affinity of diamines able to form intramolecular hydrogen bridges [$^+$N-H···N] is larger than similarly polarisable monoamines. In these species, additional localised strain can result in "proximity" effects which destabilise the unprotonated form of the diamine and hence further increase their thermodynamic basicity. An example of such an effect can be found in *N,N,N',N'*-tetraalkylated derivatives of 1,8-diaminonaphthalene **1**. Such species, e.g. **2**, form the first generation of "proton-sponges".[2]

The proton-sponges[3] are characterised by their high pK_a values (*ca.* 12 - 17)[4] and "sluggish" behaviour: they are very poor nucleophiles and are protonated-deprotonated slowly.[5] Furthermore, once protonated (e.g. to form $[2H]^+$) they are very resistant to a second protonation ($\Delta[pKa_1\ pKa_2]$ ca. 20). These unusual and useful properties generate continued interest in the development of novel proton sponges.[6]

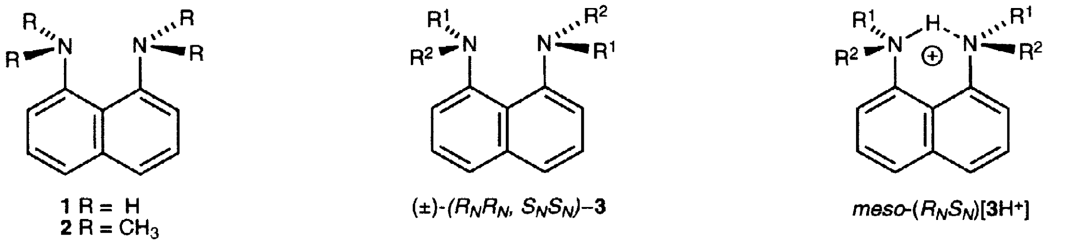

Figure 1 - Parent 1,8-diaminonaphthalene **1**, "proton sponge" **2**, generic *N,N*-chiral "proton sponges" chiral (R_NR_N/ S_NS_N)-**3** and *meso*-**3** in its protonated form in which the (R_N, S_N) stereogenic centres are "locked" through hydrogen bonding.

We are currently interested in the synthesis and stereodynamics of proton sponges that possesses C_2 symmetry and are chiral at nitrogen - this being typified by generic (R_NR_N/ S_NS_N)-**3** and *meso*-(R_NS_N)-**3**. The interconversion of (R_NR_N)-**3** and (S_NS_N)-**3** (automerisation) may involve *meso*-(R_NS_N)-**3** as an intermediate or, alternatively, a synchronous pathway involving correlated rotation may be possible. Barriers to pyramidal inversion at "normal" sp^3 nitrogen are typically less than 8 Kcal.mol^{-1} and thus amines which are stereogenic at

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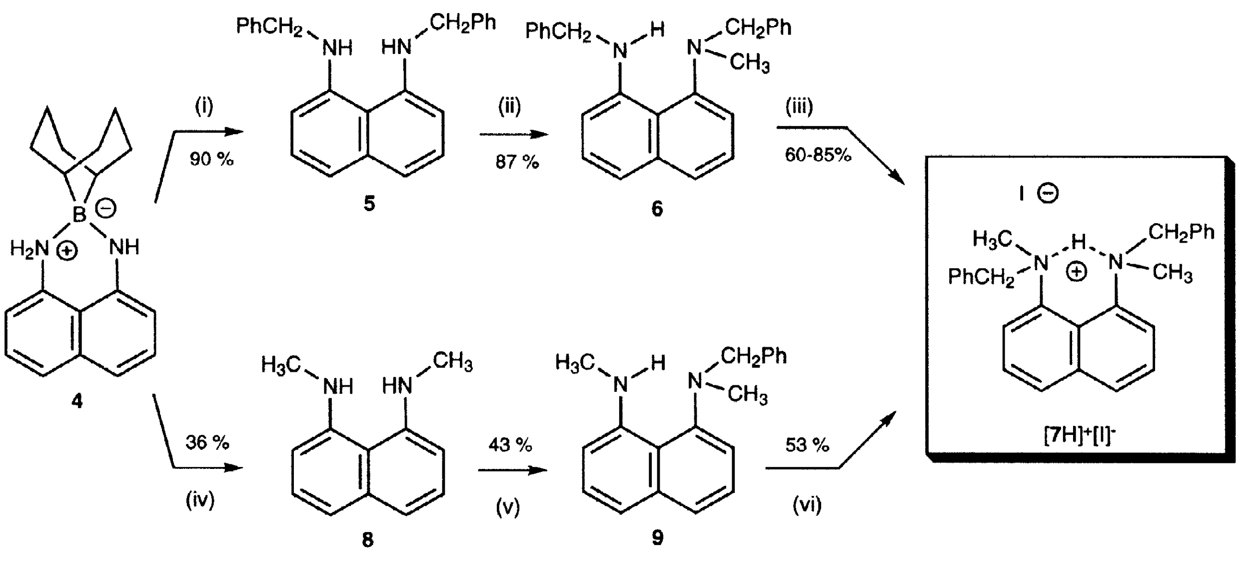
nitrogen have short half-lives towards racemisation or epimerisation at ambient temperatures.[7] However, in molecules such as **2** and **3** it is expected that the strain introduced by the proximity (peri-position) of the two amines in the naphthalene ring system will increase the energetic barriers to rotation-inversion.[8] If the barriers to automerisation of molecules of type **3** could be raised sufficiently then these compounds might become useful in asymmetric synthesis.

Herein we report our initial studies on $[7H]^+$ a molecule of type $[3H]^+$ in which R^1 = Me and R^2 = benzyl. Protonation has the interesting effect of "locking" the two amine stereogenic centres together through what is predicted to be a short strong hydrogen bond[9] and hence is expected to make both rotation-inversion and synchronous rotation much higher energy processes than in **7**. However, contrary to expectation, $[7H]^+$ is stereolabile in solution at ambient temperatures. The synthesis, stereolability and stereochemical assignment of the diastereoisomers of $[7H]^+$ form the subject of this *Letter*.

To prepare $[7H]^+$ we began by direct dibenzylation of unprotected **1** (2 eq. BnBr, NaH, THF) but this gave a complex mixture including **1**, the corresponding mono-, di- and tri-alkylated products (*N*-benzyl, *N,N*-dibenzyl and *N,N,N'*-tribenzyl) and only ca. 10% of desired **5**, Scheme 1.



Scheme 1 - reagents: (i) *t*-BuOK / BnBr then HCl(aq) - see reference 10. (ii) 2 eq. NaH, 2 eq. MeI, THF, reflux, 2 h. (iii) 34 eq. MeI (as solvent), 48 h. (iv) as for (i) but with MeI. (v) 2 eq. NaH, 2 eq. BnI, THF, reflux, 2 h. (vi) 34 eq. BnI (as solvent), 48 h.

However, the regioselective dialkylation of the 9-BBN-diaminonaphthalene compound **4**, as recently described by Kol *et al.*,[10] proved outstanding and afforded **5** in good yield and excellent purity. Reaction of **5** with excess MeI and NaH in refluxing THF afforded the monomethylated product **6**[11] in 80 - 87 % yields. The final methyl group required for **7** was introduced simply by dissolving **6** in MeI. After 12-48 h. at ambient temperature, pale yellow needles crystallised from the reaction mixture. Recrystallisation (CH_2Cl_2 / Et_2O) gave $[7H]^+[I]^-$ in analytically pure form in 60-85 % yields.[12]

The ^1H NMR spectrum of $[7H]^+[I]^-$ in both $CDCl_3$ and CD_2Cl_2 at 25 °C indicated that one diastereomer of $[7H]^+[I]^-$ was present in excess (ratio 88.5 / 11.5) and that the stereochemistry had been efficiently "locked" at the NMR time-scale by protonation. In CD_2Cl_2, time-average localisation of the benzyl groups was apparent. In the major diastereomer one of the diastereotopic benzylic protons (H_A, Fig 2) displays a larger coupling (J = 3 Hz) with the hydrogen bonded proton (N-$\underline{H}_C$·N) than the other one (H_B, J =1.5 Hz) - presumably because the dihedral angle of the H_C-N-C-H_B unit approaches 90°. Both of the CH_3 groups couple with H_C (J = 3 Hz). By slow diffusion of Et_2O into a CH_2Cl_2 solution of $[7H]^+[I]^-$ we obtained pale yellow single crystals and X-ray diffraction studies (R_1 = 2.46 %) showed these to be the (R_NR_N / S_NS_N) diastereomer (Fig 2).

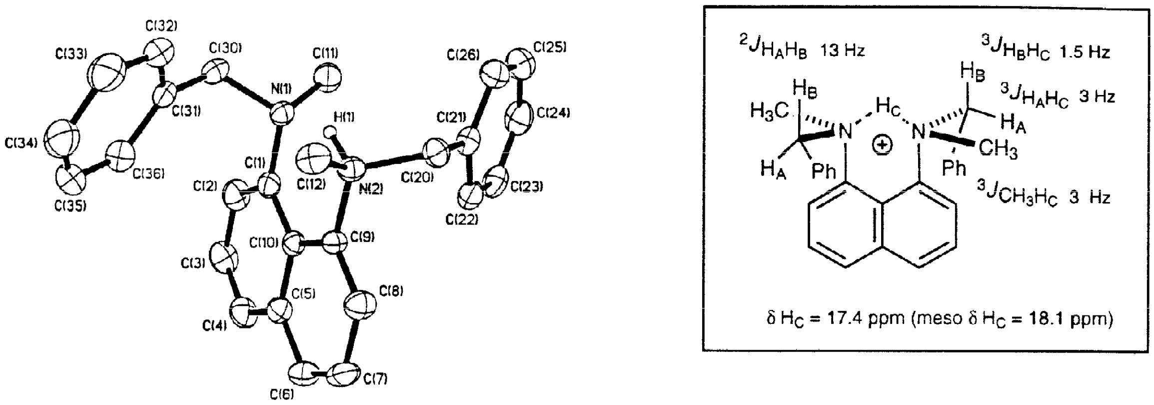
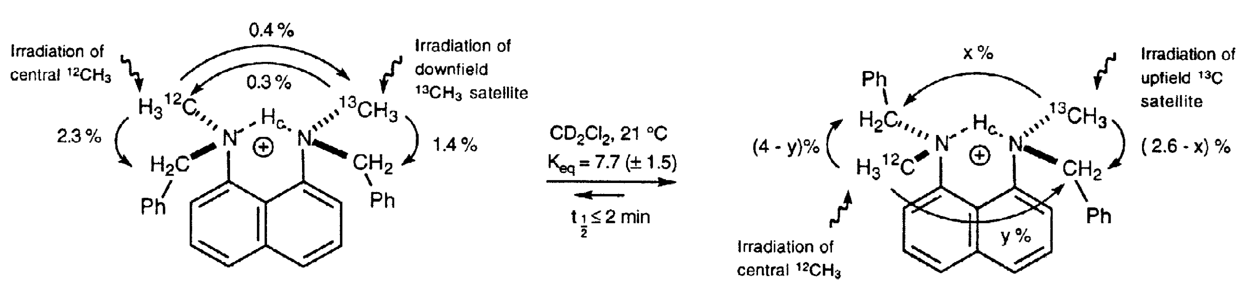


Figure 2 - X-ray crystal structure (R_1 = 2.46 %) of $[(R_NR_N / S_NS_N)\text{-}7H]^+[I]^-$ (the iodide ion is omitted for clarity). $[(R_NR_N / S_NS_N)\text{-}7H]^+[I]^-$ crystallises in space group $P2_1/c$. Four molecules occupy the centrosymmetric (racemic) unit cell. Inset shows selected ^1H coupling constants (J, Hz) for $(R_NR_N / S_NS_N)\text{-}[7H]^+$ (500 MHz, CD_2Cl_2). The depiction of the time-average conformation of the benzyl rotors in $(R_NR_N / S_NS_N)\text{-}[7H]^+$ is based on Karplus analysis of ^3J (H_A, H_B and CH_3 with H_C).

It rapidly became evident that thermodynamic equilibration of $[7H]^+[I]^-$ occurs on dissolution in $CDCl_3$ or CD_2Cl_2.[13] Assignment of the major and minor diastereomers in solution by NMR is impeded by the symmetry of the molecules and we thus prepared the hydrogen iodide salt of 1-(*N*-benzyl-*N*-[^{13}C]-methylamino)-8-(*N'*-benzyl-*N'*-[^{12}C]-methylamino)naphthalene by employing $^{13}CH_3I$ to convert **5** to [$^{13}C_1$]-**6**. The ^{13}C label in $[^{13}C_1]\text{-}[7H]^+[I]^-$ results in isotopic desymmetrization of both diastereomers.



$[^{13}C_1]\text{-}[(meso)\text{-}(R_NS_N)\text{-}7H]^+[I]^-$ $[^{13}C_1]\text{-}[(\pm)\text{-}(R_NR_N ; S_NS_N)\text{-}7H]^+[I]^-$

Figure 3 - Assignment of diastereoisomers based on nOe difference experiments at 500 MHz in CD_2Cl_2 on an equilibrium mixture of ^{13}C-labelled *meso* and $(R_NR_N / S_NS_N)\text{-}[7H]^+$ (91.4 % ^{13}C).

The diastereomers were assigned by ^1H n.O.e difference experiments at 500 MHz (Fig 3). Irradiation of the downfield ^{13}C satellite ($^1J_{CH}$ = 141 Hz) of the ^1H signal of the labelled methyl group in the minor isomer (11%) resulted in an enhancement in both the unlabelled methyl group (0.3 %, center of satellite) and the benzylic protons (1.4 %). This isomer was then assignable as the *meso* form. On irradiation of the labelled methyl group in the major isomer (89 %) an enhancement was observed at the benzyl protons (≤ 2.6 %) but not at the unlabelled methyl group. The major isomer was then assignable as the (±)-(R_NR_N / S_NS_N) diastereomer. Irradiation of the unlabelled methyl groups (center of ^{13}C satellites) in both diastereomers gave complimentary results and confirmed the assignments.

An equally selective synthesis of $[7H]^+[I]^-$ was achieved when the alkylation sequence was reversed, Scheme 1. Monobenzylation of **8** gave **9** which dissolved in benzyl iodide[14] to afford an 89 / 11 mixture of (±)-$[(R_NR_N / S_NS_N)$-7H$]^+[I]^-$ and *meso*-(R_NS_N)-$[7H]^+[I]^-$.

In conclusion, we have prepared the protonated form of a C_2-symmetric *N,N*-chiral proton sponge $[7H]^+$ in good yield (up to 67 % from **1**) by selective sequential alkylations. The diastereomers of $[7H]^+$ interconvert slower than the NMR time-scale but faster than the laboratory time-scale. NMR studies (n.O.e) demonstrate that the thermodynamically favoured diastereomer in solution $[K_{eq} = 7.7\ (\pm\ 1.5)]$ is the chiral (±)-(R_NR_N / S_NS_N) form. The structure of this diastereomer in the solid state was obtained by single crystal X-ray diffraction. The stereodynamics of $[7H]^+$ and its free-base (**7**) will be reported, in full, in due course.

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11. Distinct resonances arising from the diastereotopic benzylic protons of both the $[PhCH_2$-NH]- and $[PhCH_2$-$NCH_3]$- units in the ^1H NMR (300 MHz, C_6D_6) spectrum of **6** indicates that all automerisation processes are slower than the NMR time-scale. For the $[PhC\underline{H}_2$-N-H]- unit, $\Delta\delta_H \approx 18$ Hz and thus $\Delta G_{298} \geq 16$ $kcal.mol^{-1}$. Clearly, the N-$\underline{H}$ group acts as some form of stereochemical lock.
12. **6**, **9** And $[7H]^+[I]^-$ have been characterised by IR, ^1H-NMR, ^{13}C-NMR, (HR)MS and elemental analysis. Full experimental details will be reported in due course.
13. Large single crystals of $[7H]^+[I]^-$ dissolved in CD_2Cl_2 at 21 °C, reproducibly gave an 88.5 / 11.5 ratio of diastereomers.
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