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Absolute configuration of a chiral proton sponge

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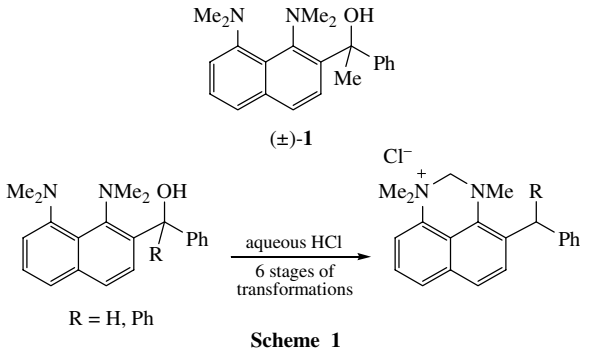
By the spontaneous resolution of racemic compound 1,8-bis(dimethylamino)-2-(α-hydroxy-α-phenylethyl)naphthalene (±)-1, enantiomer (–)-1 was obtained; its treatment with C_5H_5N·HBr resulted in the formation of proton sponge (–)-2; the absolute configurations of (*R*)-(–)-2 and, as a consequence, (*R*)-(–)-1 were determined by XRD analysis.

Recently, we carried out the spontaneous resolution of the enantiomers of proton sponge **1**[1] (Scheme 1). This work aims at determining the absolute configurations of the (+)- and (–)-enantiomers and their protonated forms $1H^+X^-$ containing a heavy anion X^- using XRD analysis. First, a method for the synthesis of (±)-**1**† was improved to afford a higher yield of the product than 21%.[2] An intriguing point was that no protonated form of **1** was obtained, and the analogues of **1**, under the action of aqueous HCl, undergo deep transformations resulted from the generation of a bis or tris(benzyl) type cation followed by hydride shift (Scheme 1).[3]

However, we developed a mild method for the protonation of chiral sponge **1** with the use of an equimolar quantity of pyridine hydrobromide† (Scheme 2).



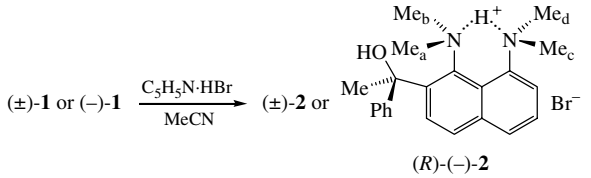
Scheme 1

The structures of salts (±)-**2** and (–)-**2** were confirmed by ^{1}H NMR spectroscopy.[4,5] Their characteristic features are the low-field shifts of the H signals from all of the MeN groups (with reference to the non-protonated precursor[1–3]) and noticeably greater non-equivalency of the protons of Me_a and Me_b in the groups approached closer to the asymmetric 2-substituent in comparison with the distant groups Me_c and Me_d (Figure 1, *cf*. ref. 2).

In aprotic solvents, the spin-coupling constants $^3J_{HCN\cdots H^+}$ for all the groups MeN differ in values† and disappear in the ^{1}H{H$^+$ at 20.2 ppm} NMR spectrum (Figure 1). In CD_3OD, these constants are not observed due to exchange between H^+ and D^+.

The structure of (–)-**2** was confirmed unambiguously by XRD analysis, and the absolute configuration (*R*) was established for both (–)-**2** and its precursor (–)-**1**.‡

Due to the protonation of the nitrogen atom in (–)-**2** instead of intramolecular O–H···N H-bond the intramolecular N–H···N one is formed (Figure 2). The parameters of the latter are close to the expected for proton sponges with the N(1)···N(2) distance equal to 2.544(1) Å. Note that the H-bond is asymmetric with



Scheme 2

† (±)-**1**: 0.63 ml (1 mmol) of Bu^{n}Li (1.6 M solution in *n*-hexane, Lancaster) was added to the solution of 300 mg (1 mmol) of 2-bromo-1,8-bis-(dimethylamino)naphthalene[4] in 5 ml of absolute diethyl ether under cooling (–20 °C) and stirring. In 15 min, 0.2 ml (2 mmol) of acetophenone was added to the light yellow solution of the formed 2-lithium derivative. The mixture was kept for 30 min at –20 °C, brought up to +20 °C and poured into 15 ml of H_2O. The diethyl ether layer was separated, the aqueous layer was extracted with diethyl ether (3×10 ml), and the combined diethyl ether layers were evaporated to dryness. The product was purified by preparative TLC using Al_2O_3 (III); eluent, $CHCl_3$. Yield, 175 mg (51%). All the physico-chemical and spectral data for the product as well as the chiroptic characteristics of its single crystals coincide with those reported previously.[1,2]

(±)-**2**. Solution of 7.2 mg (45 mmol) of C_5H_5N·HBr in 2 ml of MeCN was added to the suspension of 15 mg (45 mmol) of (±)-**1** in 1.5 ml of MeCN. The mixture was heated to 40 °C when it turned completely homogeneous and kept for 2 h at 20 °C and then for 12 h at –15 °C. The formed crystals were filtered off and dried *in vacuo*. 18.6 mg of the product was obtained (yield ~100%), mp 229–230 °C (decomp.).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H, MeC), 3.26 (d, 3H, Me_cN, ^3J 1.5 Hz), 3.33 (d, 3H, Me_dN, ^3J 1.3 Hz), 3.57 (d, 3H, Me_aN, ^3J 2.7 Hz), 3.77 (d, 3H, Me_bN, ^3J 3.1 Hz), 5.14 (br. s, 1H, HO), 7.15–7.70 (m, 10H, Ph, Naph), 20.2 (s, 1H, H$^+$). ^{1}H NMR (400 MHz, CD_3OD) δ: 2.24 (s, 3H, MeC), 3.16 (s, 6H, Me_2N), 3.52 (s, 3H, MeN), 3.57 (s, 3H, MeN), 7.22–7.98 (10H, Ph, Naph).

(*R*)-(–)-**2** was prepared from (–)-**1**[1] in a similar manner. Yield ~100%, mp 230–231 °C (decomp.), $[\alpha]_D^{20}$ –105.2 (*c* 0.4, MeOH). Its ^{1}H NMR spectrum is similar to those given for (±)-**2**. Analogously to (*R*)-(–)-**1**,[1] in the CD spectrum of (*R*)-(–)-**2** a negative Cotton effect at 307 nm was observed.

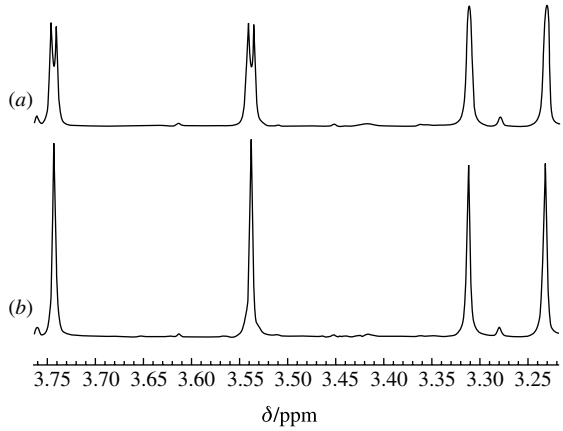


Figure 1 ^{1}H NMR spectra (600 MHz in [$^2H_6$]DMSO) of (±)-**2** Me groups protons: (*a*) normal and (*b*) under conditions of {H^+ at 20.2 ppm}.

the hydrogen atom located closer to N(2) [the N(1)···H(2N) and N(2)···H(2N) distances are equal to 1.52 and 1.06 Å, respectively, the N(2)H(2N)N(1) angle is 161°]. The hydroxyl group participates in the H-bond with the bromine anion, the Br(1)···O(1) distance is equal to 3.223(1) Å.

‡ *Crystallographic data.* Crystals of (–)-**2** ($C_{22}H_{27}BrN_2O$, M = 415.37) are monoclinic, space group $P2_1$, at 100 K: a = 6.9938(10), b = 13.0389(16) and c = 11.1748(16) Å, β = 91.469(5)°, V = 1018.7(2) Å^3, Z = 2 (Z' = 1), d_{calc} = 1.354 g cm^{-3}, μ(MoKα) = 20.30 cm^{-1}, F(000) = 432. Intensities of 5789 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$] and 4607 independent reflections [R_{int} = 0.020] were used in further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. Hydrogen atoms of OH and NH groups were located from the Fourier synthesis of the electron density. The H(C) atom positions were calculated. The absolute configuration was established based on the Flack parameter. For (–)-**2**, the refinement converged to wR_2 = 0.0780 and GOF = 0.873 for all independent reflections [R_1 = 0.0332 was calculated against F for 4075 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 655430 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

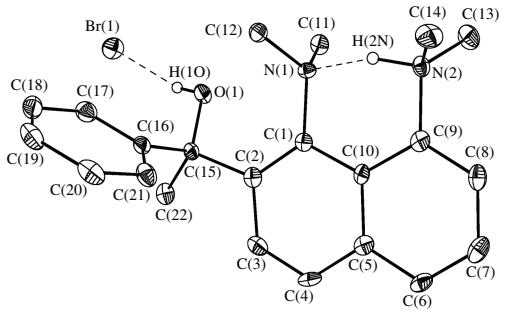


Figure 2 General view of compound (–)-**2** in representation of atoms *via* thermal ellipsoids at p = 50%.

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