Proton sponge analogue of the Troger's base: a compound with remarkable enantiomeric stability
Proton Sponge Analogue of the Tröger’s Base: A Compound with Remarkable Enantiomeric Stability

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Abstract. Proton sponge analogue of the Tröger’s base (4) has been obtained upon treatment of 1-amino-4,5-bis(dimethylamino)naphthalene with paraformaldehyde. It was found that in contrast to classical Tröger’s base 1, protonation of 4 occurs, at least thermodynamically, exclusively on peri-NMe2 groups producing a dication with two chelated [NHN]⁺ hydrogen bonds. This prevents the protonation of the bridge nitrogen atoms, which is responsible for rather easy racemization of 1. Indeed, two enantiomers of 4 were resolved by chiral chromatography and their much higher stability in acidic media as compared to 1 has been confirmed. Some other properties of base 4 including structure, basicity, dynamic NMR behavior, host-guest interactions and reactions with electrophiles are also discussed.

Introduction
The classical Tröger’s base, tertiary aromatic diamine (±)-1 (TB), was initially obtained in 1887 on interaction of p-toluidine with methylal in aqueous HCl.[1] Its molecular structure, rather far from obvious, was proposed only in 1935[2] and finally confirmed by X-ray in 1986.[3]
The distinctive features of the TB molecule are the V-shape and the presence of two kinds of methylene bridges which fix both nitrogen atoms in a rigid pyramidal form. Because of this hindered inversion of the bridgehead nitrogen atoms, TB is chiral and can exist in two enantiomeric forms, \( R,R \) and \( S,S \) (Figure 1). They were first resolved in 1944 by Prelog,\(^4\) who has also found that TB undergoes racemization in diluted acids. The suggested mechanism of the process involves a cleavage of the \( \text{CH}_2 \) bridge in the corresponding monocation leading to the formation of iminium salt followed by recyclization (Scheme 1).\(^5\)

![Scheme 1. Mechanism of racemization of TB in acidic media.](image)

Easy availability and the cleft-shaped chiral structure made TB \( \mathbf{1} \) an attractive object for supramolecular and chiral studies. However, its rather low basicity (even compared to anilines: \( \text{pK}_a = 3.2, \text{H}_2\text{O–EtOH, 1:1, v/v} \))\(^6\) and the above-mentioned tendency to racemization somewhat limit such possibilities. In this context, a lot of efforts have been undertaken to obtain various analogues of TB, which have been recently reviewed.\(^7\) The objective of our work was to design a TB analogue which would be stable towards racemization. To this end, we prepared and studied the
proton sponge modification of TB. We reasoned that high basicity of the parent proton sponge 2 \( \text{pK}_a = 12.1 \) (H₂O)\[^8\], 7.5 (DMSO)\[^9\]) together with its other specific properties\[^10\] should result in protonation of new TB analogue mostly onto the peri-NMe₂ groups thus preventing protonation of the Tröger’s base bridgehead nitrogen atoms and therefore hampering racemization in acidic media following the mechanism discussed in Scheme 1.

Results and Discussion

Synthesis, Structure and Chemical Behavior

The racemic (±)-4 was synthesized in high yield as a single product by reacting easily available 1-amino-4,5-bis(dimethylamino)naphthalene (3)\[^11\] with paraformaldehyde in trifluoroacetic acid (Scheme 2) by analogy with reported procedures.\[^12\] The structure of (±)-4 was confirmed by XRD analysis (see below) and spectral data. In particular, in the \(^1\)H NMR spectrum of (±)-4, it is evidenced by the presence of a singlet at δ 6.39 ppm obviously belonging to 6-H proton (Figure S4, Supporting Information). This would not occur if the electrophilic substitution (hydroxymethylation in our case) proceeded at the second peri-position of the naphthalene nuclei what is much more typical for proton sponges.\[^10\] Clearly the higher reactivity of position 2 in molecule 3 is resulted from the electron-donating effect of the NH₂ group.

Scheme 2. Synthesis of proton sponge TB analogue 4.

Compound (±)-4 crystallizes from ethyl acetate in two polymorphic forms: needles and prisms melting at nearly the same temperature (mp. 275–277 °C). For a prismatic crystals obtained by evaporation of the racemate solution the X-ray analysis was performed (Figure S1, SI). The crystal structure is formed by 2 different molecules demonstrating the inclusion phenomenon: under these
conditions the (±)-4 crystallizes as a solvate C₃₁H₃₈N₆·0.25EtOAc, in which disordered ethyl acetate molecule is enclosed in a cavity between two enantiomers of (±)-4 to form a typical clathrate (Figures S1 and 2). This inclusion is accompanied by decreasing dihedral angle between the planes of the two naphthalene systems in compound 4 from 104° in "free" molecules 4 to 92° in those of the clathrate shell. Apparently, such host-guest interaction in the clathrate may be caused by attraction of the ethyl acetate dipole (μ = 1.8 D) to the proton sponge residues acting as strong π-donors.¹³ Unlike prismatic crystals, the needle form according to the ¹H NMR spectrum does not contain ethyl acetate. Although the cavity diameter in structure (±)-4·0.25EtOAc is of 7.5–8.0 Å, no inclusion compounds are formed on crystallization of (±)-4 from ethanol or aqueous acetonitrile (Figure S2, SI).

Figure 2. X-ray structure of clathrate C₃₁H₃₈N₆·0.25EtOAc (hydrogen atoms are omitted for clarity; the ethyl acetate molecule is disordered over two positions), 100 K.

As we expected, protonation of (±)-4, unlike classical Tröger’s base, occurs exclusively at peri-NMe₂ groups producing, independently on the quantity of the added acid, a dication with two asymmetrical intramolecular hydrogen bonds (Scheme 3). Thus, on treatment of (±)-4 with 1–10 equiv. of HClO₄ in CD₃CN only diperchlorate (±)-4·2HClO₄ was isolated. Its ¹H NMR spectrum contains a low-field peak at δ 18.69 ppm belonging to two chelated NHN protons what is typical for the cations of all proton sponges (Figure S6, SI).¹⁰ Further protonation of isolated (±)-4·2HClO₄ with 1 or 3 equivs of HClO₄ in CD₃CN displayed no signs for the formation of non-symmetrical structures of type (±)-4·3H⁺, probably due to a fast proton exchange with the media, but the shift of the N–CH₂–N bridge signal from 4.60 ppm to 5.28 and 5.33 ppm gave some evidence for the
protonation of the heterocyclic nitrogen atoms (Figure S7, SI). Therefore, it could not be excluded that certain equilibrium quantity of trication (±)-4·3H⁺ is present in solution (see also below).

Scheme 3. Diperchlorate (isolated) and trication (nonisolated) of 4.

No dynamic changes were observed by ¹H NMR upon 120 °C on heating of (±)-4 in CDCl₂CDCl₂, as well as upon 75 °C on heating it with a 10:1 CD₃CN/HBF₄ mixture. We reasoned that based on this observation, base (±)-4 will retain its structural integrity in a wide range of conditions.

For diperchlorate (±)-4·2HClO₄, X-ray measurements were performed (Figure S3, SI). The salt crystallizes from acetonitrile as solvate with two independent dications 4·2H⁺; both dications and anions are strongly disordered. In spite of this, the most interesting feature of the whole structure is clearly seen, and again the inclusion phenomenon is realized (Figure 3).
Figure 3. X-ray structure of clathrate \((\pm)-4 \cdot 2(\text{HClO}_4) \cdot 0.83(\text{MeCN})\) (the internal and external \text{ClO}_4^- anions are disordered over two positions), 100 K.

In case of diperchlorate \((\pm)-4 \cdot 2\text{HClO}_4\) the cavity is much more expanded (up to 10 Å in diameter) to involve both the disordered anion and the solvent molecule. The cavity itself is build up with the help of two additional elements, \text{ClO}_4^- anions, allowing two positively charged ends of the V-shaped molecules to electrostatically interact with the anions (including long H-bonds).

The first ionization constant, \(pK_a^1\), of \((\pm)-4\) estimated by means of competitive \(^1\text{H}\) NMR experiment between equimolar amounts of \(2 \cdot \text{HClO}_4\) and \((\pm)-4\) in a 2:1 (v/v) mixture of DMSO-\(d_6\) and CDCl₃ is equal to 7.5. This is very close to the basicity of the parent proton sponge 2 and, hence, 1,5-diazocine fragment of compound 4 adds virtually nothing to the acid-base properties of the proton sponge residues.

Since along with the high basicity proton sponge 2 displays very low nitrogen nucleophilicity\(^{10}\) it was rather interesting to shed some light on reactivity of 4. One could expect that electrophiles more bulky than a proton will attack preferably the bridge nitrogen atoms. However, heating \((\pm)-4\) with large excess of methyl iodide in chloroform or toluene resulted in the formation of dihydroiodide \((\pm)-4 \cdot 2\text{HI}\) only (the yield is near quantitative). This contrasts sharply with the behavior of TB, which is readily quaternized with alkylating agents.\(^{7\text{b}}\) At the same time, reaction of \((\pm)-4\) with paraformaldehyde in polyphosphoric acid (PPA) unexpectedly furnished \(N\)-formyl-\(N'\)-methyldiazoacine derivative 7 in 72% yield. The same compound in 64% yield was obtained on treatment of amine 3 with \((\text{CH}_2\text{O})_n/\text{PPA}\) mixture. We believe that the process proceeds through the small equilibrium amount of the triprotonated form of 4 and includes the formation of methyleniminium salt 5, hydroxymethylation of the second bridge nitrogen and hydride transfer in intermediate 6 (Scheme 4). We have found no reports in the literature on such type of reactivity for Tröger’s base or its analogues.\(^{15}\)
Enantioseparation of (±)-4 and Kinetics of Racemization

High performance liquid chromatography on chiral stationary phases appears very attractive enantioseparation method for functionalized TB analogues.\(^7\) Since the hybrid base 4 contains highly basic fragments, the separation was carried out with the addition of Et\(_2\)NH. By changing the composition of the eluent and the amount of Et\(_2\)NH we determined the optimal conditions for separation (a 98:2 mixture of \(n\)-hexane and \(i\)-PrOH with addition of 0.2% Et\(_2\)NH). Separation of enantiomers of 4 was achieved using CHIRALPAK IC column [based upon cellulose tris(3,5-dichlorophenylcarbamate)polymer immobilized on silica using proprietary techniques] and gave the selectivity factor \(\alpha = 2.36\) with retention factors of the two enantiomers \(k_1 = 0.33, k_2 = 0.78\). Figure 4 shows the chromatogram of (±)-4 (CD-detection). The first eluting enantiomer displayed the negative CD signal \([-(-)-CD_{254}-4]\) and the second one was positive in sign \([+-(+)-CD_{254}-4]\).
The enantiomeric purity of the obtained enantiomers was confirmed by their chromatograms (UV-detection). Unfortunately, due to the separation on very small scale, we were not able to reliably measure the optical rotation sign, and refer to the individual enantiomers as (–)-CD$_{254}$ or (+)-CD$_{254}$, based on the sign of their CD signal at 254 nm wavelength.

Spectra of circular dichroism were measured for individual enantiomers of 4 and compared with the spectra of enantiomers of TB. The CD-spectrum of 4 has more absorption bands compared to TB due to more expanded aromatic chromophore (Figure 6a). Taking the advantage of the multiple transitions in CD spectra of 4, we assigned the absolute configurations of (–)-CD$_{254}$-4 and (+)-CD$_{254}$-4 using the comparison of the experimental and calculated CD spectra (TD-DFT calculations were performed at the cam-B3LYP/6-311++G(d,p) level). For details of calculations and optimized
geometries, see Experimental Section in the Supporting Information. The calculated spectra were blue-shift corrected by 10 nm to compensate for the typical underestimation of transition energies by TD-DFT (Figure 6b). Based on the good agreement between the calculated and experimental spectra, the absolute configuration of (−)-CD254-4 and (+)-CD254-4 was reliably assigned to (S,S)-(−)-CD254-4 and (R,R)-(+)−CD254-4, respectively.

![Figure 6](image_url)

Figure 6. CD spectrum of 4 in isopropanol (a) and calculated ECD spectrum (b) for the (R,R)-4 (black solid line) and (S,S)-4 enantiomers (dashed red line).

In addition, we investigated racemization of proton sponge TB analogue 4 in comparison with classical TB 1, which showed much higher stability of 4 to racemization (Table 1). Kinetics of racemization at 100 °C as a function of ee vs. time is presented in Figure 7.

<table>
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<tr>
<th>Entry</th>
<th>T [°C]</th>
<th>Ratio of enantiomers for 1</th>
<th>Ratio of enantiomers for 4</th>
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<tr>
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<td>21</td>
<td>60:40</td>
<td>100:0</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>50:50</td>
<td>100:0</td>
</tr>
</tbody>
</table>
3  80  50:50  86:14
4  90  50:50  78:22
5 100  50:50  61:39

Figure 7. Analysis of the racemization kinetics for 4 in 0.1 M CF₃SO₃H in isopropanol at 100 °C.

The pseudo-first order rate constants for racemization, $k_{rac}$, were derived by linear regression of the data according to the first-order kinetic law. Analyzing the obtained data one can see that the proton sponge 4 is by about four orders of ten more stable in racemization reaction than compound 1 (extrapolated values $k_{rac} = 0.06–0.42$ s$^{-1}$ at 105 °C).[5b]

Conclusions
The first proton sponge analogue of the Troger’s base has been obtained and described in the present work. It was demonstrated that unlike classical TB its protonation occurs mostly at the peri-NMe₂ groups leaving almost untouched the bridge nitrogen atoms. This strongly slows down the process of acid-catalyzed racemization of the enantiomers providing chirality retention of potentially labile molecule.

Supporting Information: Experimental section; details of crystal packing of 4 (from ethyl acetate and ethanol or aq. acetonitrile) and 4·HClO₄, $^1$H and $^{13}$C NMR spectra of new compounds; equilibrium geometry of (R,R)-4.
Acknowledgements

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Keywords: basicity; chirality; host-guest interaction; proton sponge; Tröger’s base.

References and Notes


[14] As a result of hindered internal rotation of the CHO group around the amide C–N bond almost all signals in the proton and carbon NMR spectra of amide 7 are unevenly split (Figures S8 and S9, SI). The ratio of rotamers is 2:3 based on the integration in the CHO-region.


[16] There is only one report in the literature on TB's analogue with additional basic centers in the molecule observed to be stable in an acidic solution. Thus, bis(aminoacridine) substituted TB due to protonation on the acridine ring nitrogens is not racemize in 0.1 M HCl/DMF at 20 °C. Note also, that this molecule is much less basic and no temperature-dependent or kinetic experiments were done: A. Tatibouet, M. Demeunynck, C. Andraud, A. Collet, J. Lhomme, *Chem. Commun.* **1985**, 161–162.
Proton sponge residues account for unusual chemistry and both for sterical and chemical inhibition to racemization of new chiral base PSTB (proton sponge Tröger’s base). Both neutral as well as doubly-protonated forms of PSTB are prone to form host-guest compounds.