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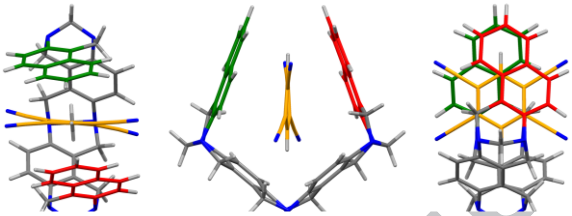

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Synthesis and characterisation of a new naphthalene tris-Tröger's base derivative – a chiral molecular clip

Bohumil Dolenský[a,] ∗ , Jiří Kessler[a] , Milan Jakubek[a] , Martin Havlík[a] , Jan Čejka[b] , Jana Novotná[a], Vladimír Král[a]

[a]*Department of Analytical Chemistry, Institute of Chemical Technology Prague, Technická 5, Praha 16628, Czech Republic*
[b]*Department of Solid State Chemistry, Institute of Chemical Technology Prague, Technická 5, Praha 16628, Czech Republic*

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ABSTRACT

Serial tris-Tröger's base derivatives (trisTBs) are members of a recently introduced family of chiral molecular clips. Naphthalene tris-Tröger's base is prepared via both stepwise and one-pot approaches. All three diastereoisomers are isolated and unambiguously identified, and their NMR spectra, enantioseparation and binding ability are studied. The *syn,syn*-trisTB diastereoisomer, a molecular clip, is found to be a potential molecular receptor of electron-deficient cyanobenzenes. For the first time, racemic *syn,syn*-trisTB is resolved via preparative HPLC (chiral column) and the absolute configurations are assigned by comparison of experimental and calculated ECD spectra. General dependencies on the oligoTB stability in acid media and potential anion binding are suggested.

Serial tris-Tröger's base derivatives (trisTBs) are members of the recently introduced family of various molecular scaffolds based on fused Tröger's base derivatives (oligoTBs).[1-3] A common Tröger's base (TB) derivative[4] consists of two arenes (AR) linked via [*b*,*f*] annelation to a 1,5-diazabicyclo-[3.3.1]nonane (TB unit; TBU), figuratively AR^1-TBU-AR^2. A serial trisTB consists of two TBs linked via [*b*,*f*] annelation to another TBU, figuratively AR^1-TBU-AR^2-TBU-AR^3-TBU-AR^4. As TBU is a chiral structural element constraining the attached arenes about a perpendicular position (rigid V-shape, 80-114°),[4] a serial trisTB has four diastereoisomers (*anti,anti*-trisTB, *anti,syn*-trisTB, *syn,anti*-trisTB and *syn,syn*-trisTB). To date, only five symmetrical (AR^1 = AR^4 and AR^2 = AR^3; *anti,syn*-trisTB ≡ *syn,anti*-trisTB) serial trisTBs are known (Figure 1).[5-9] The *syn,syn*-trisTBs were recently proposed as inherently chiral molecular clips.

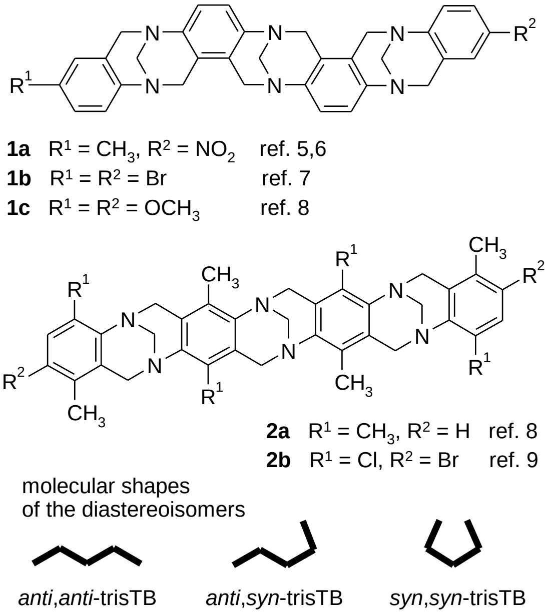

Figure 1. Known serial trisTBs and the profile shapes of their diastereoisomers.

In this communication, we present the preparation and characterisation of all three diastereoisomers of a new naphthalene trisTB derivative **3**, the first trisTB having

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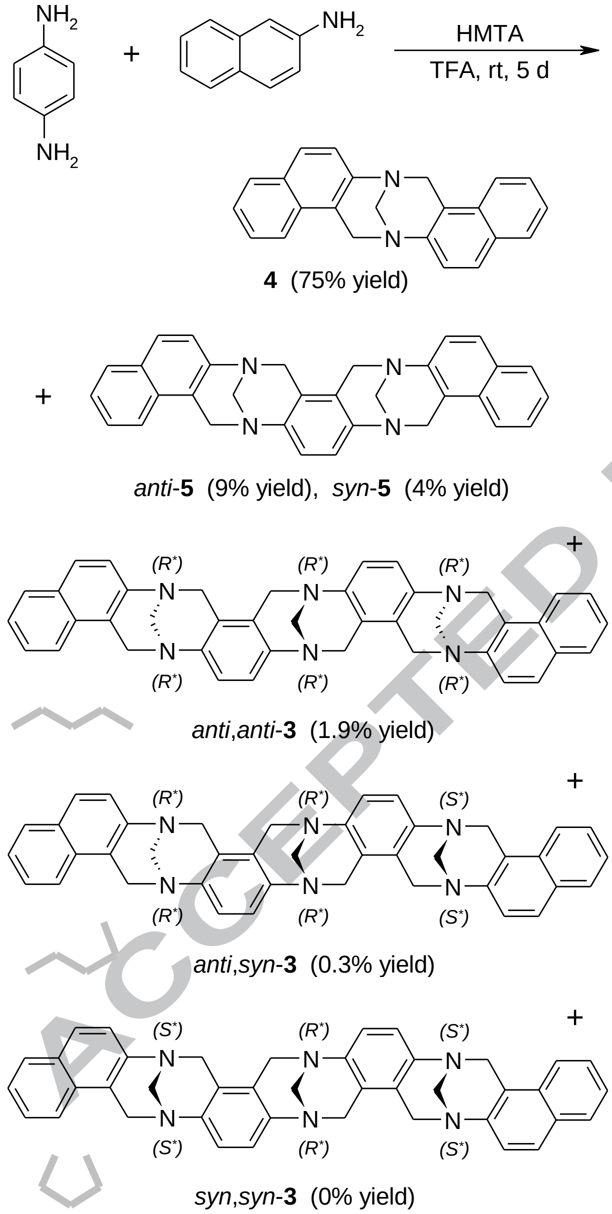
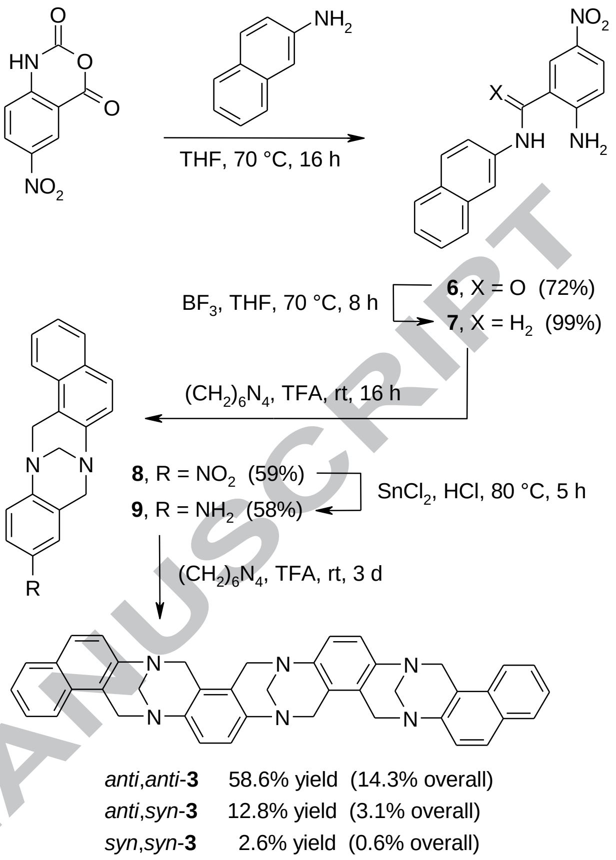
∗ Corresponding author. Tel.: +420-2-2044-4110; fax: +420-2-2044-4352; e-mail: Bohumil.Dolensky@vscht.cz naphthalene as the sidewall arenes (AR[1], AR[4]). In addition, we present the first evidence of binding abilities of each diastereoisomer, and the first resolution and characterisation of *syn*,*syn*-**3** enantiomers.

TrisTB **3** was prepared via one-step mixed troegeration,[8,10] i.e., by treatment of naphth-2-ylamine with phenylene-1,4-diamine and hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) at room temperature. While this method is simple and inexpensive, it provided low yields (1.9% of *anti*,*anti*-**3** and 0.3% of *anti*,*syn*-**3**; formation of *syn*,*syn*-**3** was not observed), and required a tedious isolation process due to formation of significant amounts of side-products, particularly, naphthalene TB **4** and bisTB **5** (Scheme 1).



Scheme 1. One-pot preparation of trisTB **3**.

As a better alternative, trisTB **3** was prepared in five steps (18% overall yield) via a known approach[7,8] (Scheme 2) through preparation of asymmetric amino-TB **9**, troegeration of which gave trisTB **3** in 74% yield as a mixture of all the possible diastereoisomers in overall yields of: 14.3% *anti*,*anti*-**3**, 3.1% *anti*,*syn*-**3**, and 0.6% *syn*,*syn*-**3**. TrisTB **3** was formed regioselectively, i.e., formation of no other isomers was observed. The structures of the diastereoisomers were identified via detailed analyses of NMR spectra supported by quantum chemical calculations, and confirmed by X-ray diffraction analyses of *anti*,*syn*-**3** and *syn*,*syn*-**3**.



Scheme 2. Stepwise preparation of trisTB **3**.

The single-crystal X-ray diffraction study of racemic *anti*,*syn*-**3** (CCDC 832257) shows that the *syn* part of the molecule resembles molecular tweezers (Figure 2); the opposite benzene cores are separated by 0.657(1) nm, and their planes form an angle of 29°. The crystal packing shows that two molecules having opposite absolute configurations are interlocked by the tweezers parts; the naphthalene planes are separated by approximately 0.36 nm and are entirely coplanar. This parallel displaced arene-arene interaction is supported by two simultaneous CH-π hydrogen bonds; the naphthalene hydrogen atom of one molecule points nearly to the middle of the benzene group of the second molecule and vice versa, and the hydrogen is approximately 0.25 nm from the plane of the central benzene.

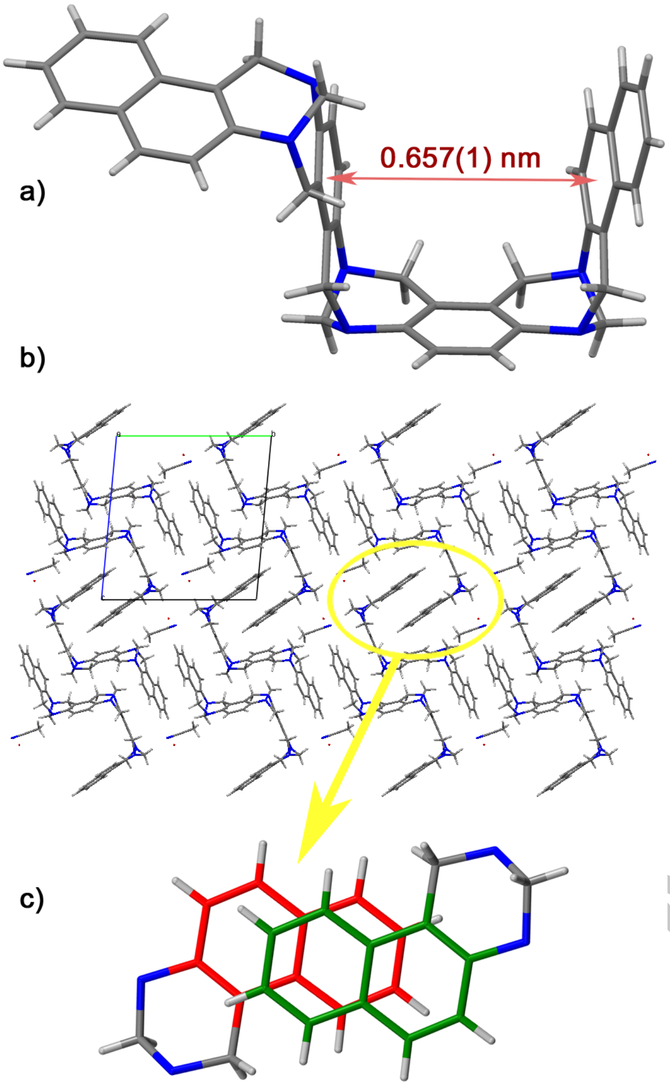


Figure 2. Single-crystal structure of racemic *anti*,*syn*-**3**: a) without solvent molecules; b) a view of the crystal packing along the *x* axis showing acetonitrile and water (the hydrogen atoms of the water molecules were not localised); c) a top view of the interacting naphthalene parts of the two molecules.

The single-crystal X-ray diffraction analysis of racemic *syn*,*syn*-**3** (CCDC 832258) shows the molecular clip shape and helical character of this molecule (Figure 3). The crystal packing indicates formation of homochiral double channels filled with heavily disordered solvent molecules; a similar packing mode was observed in both molecular clips *syn*,*syn*-**2b**[9] and methanoanthracene.[11]

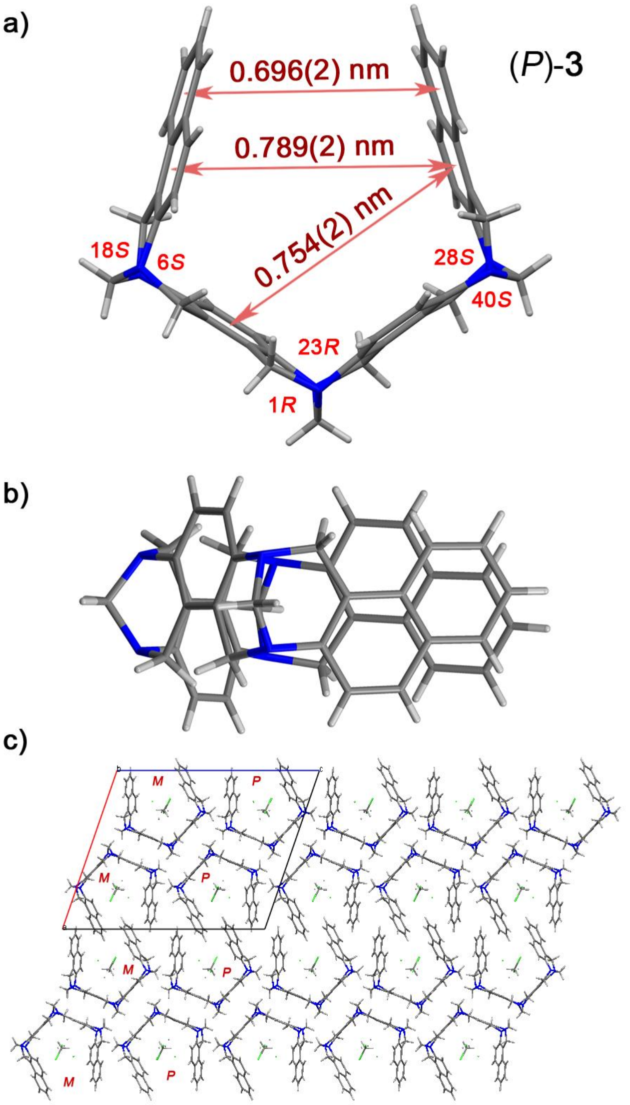


Figure 3. Structure of racemic *syn*,*syn*-**3**, as determined by X-ray diffraction analysis: a) front and b) side views without solvent molecules; c) view of the crystal packing along the *y* axis showing disordered CH_2Cl_2 molecules. The helicity descriptors *P* and *M* indicate the absolute configurations; (*P*)-*syn*,*syn*-**3** ≡ (1*R*,6*S*,18*S*,23*R*,28*S*,40*S*)-*syn*,*syn*-**3**, (*M*)-*syn*,*syn*-**3** ≡ (1*S*,6*R*,18*R*,23*S*,28*R*,40*R*)-*syn*,*syn*-**3**.

To increase the yield of *syn*,*syn*-**3**, acid-catalysed isomerisation of the major diastereoisomers was conducted. It was found that trisTB **3** was stable in TFA at 70 °C (at least for 16 h), and slowly isomerises at 130 °C to reach an equilibrium ratio 63:29:8 (*anti*,*anti*-**3** : *anti*,*syn*-**3** : *syn*,*syn*-**3**) in 2 days, which is, unfortunately, not far from the ratio reached in the stepwise preparation (79:17:4, TFA, rt). Furthermore, the addition of up to 3000 equivalents of nitrobenzene had a negligible effect.

Fortunately, we observed a high yield of the desired *syn*,*syn*-**3** by isomerisation in TFA with the addition of hydrochloric acid (1:1). The isomerisation takes place readily at 60 °C, reaching an equilibrium ratio of 12:41:47 in approximately 16 hours.

In contrast to trisTB **2b**, the high stability of trisTB **3** is surprising because trisTB **3** has no moieties in the *ortho* positions, which are known to hinder TBU isomerisation.[9,12] The following observations in TFA demonstrate that the nature of the side arene also plays a crucial role. 4-Methoxybenzene bisTB **10a** reached an equilibrium in TFA within one hour at rt, fluorene bisTB **10b** required a couple of hours at rt, while both naphthalene bisTB **10c** and anthracene bisTB **10d** required several days at 60 °C (Figure 4).

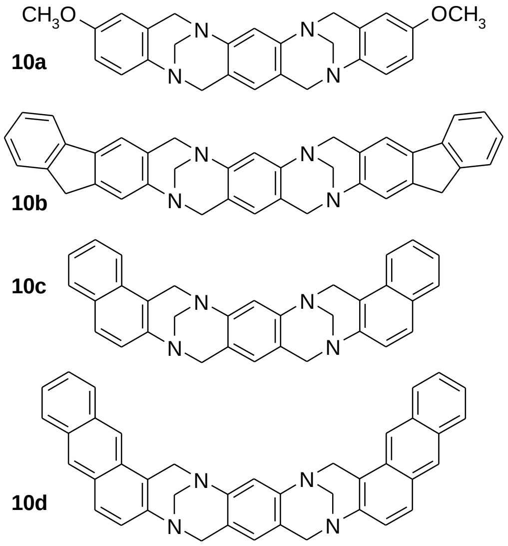


Figure 4. bisTB derivatives used in isomerization studies.

An increase in the yield of the *syn* diastereoisomer by isomerization in hydrochloric acid was observed previously in the case of a methoxybenzene bisTB derivative, where the *anti* to *syn* ratio of 64:36 was reached in TFA, and was 7:93 in neat hydrochloric acid.[13] Similarly, it was observed that a *syn*-bisTB derivative was not formed by reaction in TFA, but was obtained in 50% yield by isomerisation of the corresponding *anti*-bisTB isomer in ethanol with hydrochloric acid.[14] In addition, we recently found that the equilibrium composition of parallel tris-Tröger's base diastereoisomers can be affected by other acids. A 1:1 mixture of TFA with hydrochloric, hydrobromic, or phosphoric acid gave 24%, 71%, or 76% more of the *syn,syn*-diastereoisomer then in neat TFA, respectively.[3]

This evidence led us to assume that the anion plays an important role in the isomerization, which can be explained by the following deliberation. Since simple TB can be diprotonated,[15] an oligoTB derivative is expected to exist as an equilibrium mixture of multi-protonated species in a strong acid medium. Protonation of the nitrogen atoms will cause withdrawal of the electron density from the arenes, and make them electron-deficient, or even positively charged. Therefore, the *anti* diastereoisomers would be preferred due to repulsion of the charged arenes of the *syn* diastereoisomers. However, when a suitable anion is present, the *syn* diastereoisomers can be more stable due to tweezering (chelating) of the anion by the electron-deficient arenes. In addition, when the conditions are sufficient to cause isomerization, the system becomes a dynamic combinatorial library, i.e., the content of the species which forms a stable complex will increase.[16]

On the contrary, templating by the ammonium cation was suggested as the origin of the higher yield of the *syn,syn* diastereoisomer of trisTB **2b**, when NH_4Cl was added to the reaction mixture.[9] Based on the previous deliberation, that would be possible for reactions with a low degree of protonation. In that case, most arenes remain electron-rich, i.e., able to bind cations. In addition, it should be emphasised that the reaction proceeded under milder conditions than those required for isomerisation, therefore, an intermediate should be templated.

The binding ability of trisTB **3** was examined via titration experiments followed by ^1H NMR spectroscopy. This revealed that *syn,syn*-**3** binds 1,2,4,5-tetracyanobenzene (TCNB) with a binding constant 36-times higher than those of *syn,anti*-**3** or *anti,anti*-**3** ($K^{syn,syn}$ = 615 ± 68, $K^{anti,syn}$ = 17 ± 2, $K^{anti,anti}$ = 16 ± 2). The complexation-induced shift (CIS) of TCNB by *syn,syn*-**3** (3.9 ppm) is similar to the CIS obtained with the analogous methanoanthracene molecular clip (4.7 ppm),[11] while the CIS by *syn,anti*-**3** or *anti,anti*-**3** was approximately 50% less. The molecular model (B3LYP-D/6-31G**) of *syn,syn*-**3**•TCNB showed that TCNB was entirely in the middle of the molecular clip but not planar since the cyano groups were out of the benzene plane. The binding constants of *syn,syn*-**3** with both 1,4- and 1,3-dicyanobenzenes are approximately only 6, but the CIS values were similar to those measured for TCNB, suggesting the binding mode was similar. The binding of 1,2-dicyanobenzene was negligible.

Finally, HPLC [column Reprosil Chiral – NR (a Whelk O1 type)], which is efficient in resolving TB derivatives,[17] was used to separate the trisTB **3** diastereoisomers. On an analytical scale, both symmetric *anti,anti*-**3** and *syn,syn*-**3** were resolved regardless of the ratio of *i*PrOH : CH_2Cl_2 (2:8, 1:1, 8:2) used as the mobile phase; each sample of pure diastereoisomer gave two peaks of equal integral areas. Surprisingly, no resolution was observed in the case of unsymmetrical *anti,syn*-**3**, which suggests that this isomer behaves as an inner racemate.[17]

Thanks to the excellent separation, *syn,syn*-trisTB **3** was resolved on a preparative scale using the column (250 × 25 mm, isocratic elution by *i*PrOH : CH_2Cl_2 8:2). The pure enantiomers were characterised by optical rotation (OR). The less retained enantiomer (t_R' = 9.99 min) had a negative OR, $[\alpha]_D^{20}$ = -16.1 deg.cm^2.g^{-1}, the more retained enantiomer (t_R' = 15.41 min) had a positive OR, $[\alpha]_D^{20}$ = +61.1 deg.cm^2.g^{-1}. Based on comparison of the experimental and theoretical ECD (electronic circular dichroism) spectra (Figure 5), the *P* configuration (Figure 3) can be assigned to more retained enantiomer, *P*-(+)-*syn,syn*-**3**.

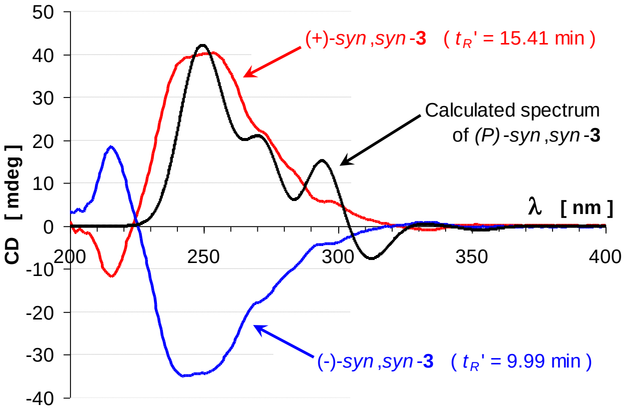


Figure 5. Experimental ECD spectra of *syn,syn*-**3** enantiomers (1.64 μmol.mL in CH_2Cl_2), and the calculated ECD spectrum of (*P*)-*syn,syn*-**3** (B3LYP/6-311+G**).

In conclusion, we have shown that a serial trisTB derivative with naphthalene as the side arenes can be prepared as the *syn,syn* diastereoisomer, and can be easily resolved into enantiomers on a chiral HPLC column. This compound represents a somewhat constricted and inherently chiral molecular clip. The crystal structure revealed that the molecular clips form a channel-like structure, thus the single-crystal can be considered as a potentially nanoporous material. For the first time, we have shown that the *syn,syn* diastereoisomer of a serial trisTB derivative has a significant ability to bind electron-deficient compounds, thus the serial *syn,syn*-trisTB derivatives have potential as chiral molecular clips in molecular and materials engineering.

In addition, we have demonstrated that the acid-catalysed isomerisation of Tröger's base derivatives depends considerably on the nature of the arenes. Based on several indirect forms of evidence we conclude that protonated oligoTBs can bind anions significantly. Thus, the isomerisation of oligoTBs should be perceived as a complex process, possessing the features of a dynamic combinatorial library.

Acknowledgements

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Supplementary Material

Detailed information about the preparation of all compounds; analyses of NMR spectra (and their copies) including an assignment of the signals and quantum chemical calculation, the binding studies, molecular modelling of the complex, analytical enantioseparation of trisTB **3** diastereoisomers, preparative enantioseparation of *syn*,*syn*-**3** and ECD spectra and their calculation, the crystallographic data on *syn*,*anti*-**3** and *syn*,*syn*-**3** are provided as a supplementary material. This material is available free of charge via the Internet at ...

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