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# One-Pot Reaction as an Efficient Method for Rigid Molecular Tweezers

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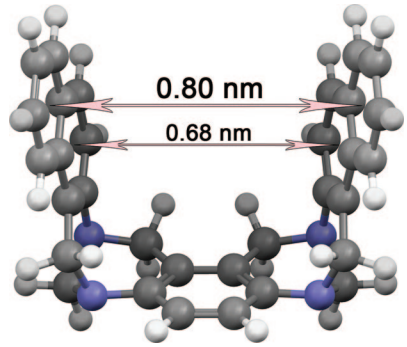
## ABSTRACT




**Rigid molecular tweezers are compounds of increasing scientific interest. As the structural requirements for such compounds are highly specific, few types of these tweezers are thus far known. The preparation of examples of rigid large-pincered molecular tweezers based on bis Tröger's bases derived from 1,4-benzenediamine is described. In addition, evidence is presented of the different binding abilities of the diastereoisomers of such compounds.**

Analogous to common tweezers, molecular tweezers are compounds which consist of two pincers able to bind a guest compound through the intermolecular interactions occurring on each side. The pincers are joined together by a tether, which keeps them more or less preorganized. Most studies of molecular tweezers are focused on rigid tweezers, i.e., molecules consisting of a rigid tether and reasonably large, electron-rich arenes ($\pi$-donor, D, host). Generally, the goal of such studies is to bind an electron-deficient arene ($\pi$-acceptor, A, guest) via the formation of a D-A-D $\pi$-sandwich.[1] To achieve this, the tether should maintain the pincers in parallel alignment at a distance of about 0.64 to 0.70 nm from each other.[1c] As many electron-deficient arenes have been shown to be important for both health and the environment, molecular tweezers have been studied intensively, both experimentally and using quantum chemical calculations.[2,3] The first examples of their potential use in medicine[3,4] and analytical applications[5] have recently been published.

As the concept of rigid molecular tweezers is quite young and the requirement of keeping parallel pincers at a proper distance from each other is very limiting, there are few known structural motifs for useful tethers. Until recently, rigid tweezers were based on derivatives of glycolurils,[6] Kagan's ethers,[7] or methanoanthracenes.[3,8] However, the

(1) The molecular tweezers idea: (a) Chen, C.-W.; Whitlock, H. W. *J. Am. Chem. Soc.* **1978**, *100*, 4921–4922. Reviews: (b) Zimmerman, S. C. *Bioorg. Chem. Front.* **1991**, *2*, 33–71. (c) Zimmerman, S. C. *Top. Curr. Chem.* **1993**, *165*, 71–102.

(2) (a) Klärner, F.-G.; Panitzky, J.; Preda, D.; Scott, L. T. *J. Mol. Model* **2000**, *6*, 318–327. (b) Chang, C.-E.; Gilson, M. K. *J. Am. Chem. Soc.* **2004**, *126*, 13156–13164.

(3) (a) Klärner, F.-G.; Kahlert, B.; Nellesen, A.; Zienau, J.; Ochsenfeld, C.; Schrader, T. *J. Am. Chem. Soc.* **2006**, *128*, 4831–4841. (b) Talbiersky, P.; Bastkowski, F.; Klärner, F.-G.; Schrader, T. *J. Am. Chem. Soc.* **2008**, *130*, 9824–9828.

(4) Weiss, S. T.; McIntyre, N. R.; McLaughlin, M. L.; Merkler, D. J. *Drug Discovery Today* **2006**, *11*, 819–824.

(5) Kamieth, M.; Burkert, U.; Corbin, P. S.; Dell, S. J.; Zimmerman, S. C.; Klärner, F.-G. *Eur. J. Org. Chem.* **1999**, 2741–2749.

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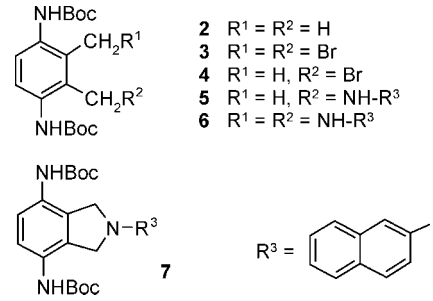
beginning of the 21st century saw the introduction of new molecular tweezers based on Tröger's base derivatives,[9] bisTB.[10,11] The unique property of bisTB, its ability to isomerize between tweezer diastereoisomers (*syn*-bisTB) and nontweezer diastereoisomers (*anti*-bisTB) in acid media,[12] has potential for future applications. The requirements for rigid molecular tweezers (vide supra) are best met by bisTB regioisomer **1** derived from 1,4-benzenediamine. However, until now, the preparation of bisTBs **1** with reasonably large pincers has not been successfully achieved.[13]

To date, bisTBs **1** have been prepared entirely via the troegeration[14] of corresponding amine intermediates prepared exclusively by the reduction of equivalent amides. The TB units can be constructed simultaneously in one reaction step[11] or in separate steps.[10] The one-step simultaneous formation of both TB units from the corresponding tetraamine is obviously the shortest way of preparing symmetrical bisTBs. However, we recently discovered that the preparation of the corresponding amides is problematic. Furthermore, due to their instability in relation to reduction agents, we found it impossible to reduce the matching amides derived from large-arene-amines.[15] Another approach involves the mixed troegeration of 1,4-benzenediamine and an arylamine. However, the scope of this reaction is unknown (having only been described with 4-methoxyaniline[12]), and the isolation of the bisTB from the complex reaction mixture is highly problematic. In this article, we present synthetic pathways for the preparation of the first examples of the rigid large-pincered molecular tweezers, *syn*-**1b** and *syn*-**1c**, as well as the first evidence of the different binding abilities of *syn*-**1b** and *anti*-**1b**.

First, we tried to prepare bisTB **1** using a method similar to the successful preparation of bisTBs derived from 1,3-benzenediamine.[15] Correspondingly (Scheme 1), the starting bis(BocNH)xylene **2** (Boc = *t*-butoxycarbonyl) was prepared from commercially available 2,3-dimethylaniline in five steps (overall yield 29%). However, the subsequent bromination resulted in only partial conversion, the expected dibromide

**Scheme 1**




**3** being followed by monobromide **4** (6:5). (The use of longer reaction times and/or higher amounts of bromination agent led to even more complex mixtures.) The treatment of the mixture with an excess of methyl 6-amino-2-naphthoate (brom to amine 1:4.7, temp 75 °C, time 5 h) converted monobromide **4** into monoarylamine **5** as expected,[16] but dibromide **3** produced no desired disubstitution product **6** but cyclic amine **7** only. In contrast, the treatment of hexakis(bromomethyl)benzene in neat aniline has been shown to give a hexasubstitution product in a preparative yield of 47% (bromine to amine 1:18, temp 150 °C, time 27 h), wherein no cyclic products were reported.[17]

The aim of our second approach was to bypass the intramolecular attack (leading to cyclic amine **7**) via the treatment of dibromide **3** with the sodium salt of amine. However, we were aware that such an approach would inevitably lead to acid−base equilibrium with protons of the BocNH groups and, thereby, complicate the reaction. Therefore, we protected the BocNH groups by additional Boc groups (Scheme 2).

In accordance with the known methods,[18] the treatment of bis(BocNH)xylene **2** with $Boc_2O$ (di-*t*-butyl dicarbonate) gave bis($Boc_2N$)xylene **8**. Contrary to the bromination of bis(BocNH)xylene **2** (vide supra), the bromination of bis($Boc_2N$)xylene **8** gave the expected pure dibromide **9**. The obtained dibromide was subsequently treated with sodium salt of the corresponding arylamine, resulting in a mixture of products. NMR analysis showed that some protection groups were lost[18,19] but that the expected substitution took place, meaning that partially deprotected tetraamines **10** were formed. As the protection of amino groups is not required for the subsequent troegeration steps, we used the obtained mixture without purification. The obtained mixture contained both diastereoisomers of the expected bisTB **1**. The new compounds, syn and anti diastereoisomers of the naphthalene bisTB derivatives **1b**,**c**, were isolated in good yields by

(6) (a) Smeets, J. W. H.; Sijbesma, R. P.; Niele, F. G. M.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 928–929. (b) Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *Acc. Chem. Res.* **1999**, *32*, 995–1006.

(7) Klärner, F.-G.; Kahlert, B. *Acc. Chem. Res.* **2003**, *36*, 919–932.

(8) Harmata, M. *Acc. Chem. Res.* **2004**, *37*, 862–873.

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(10) Pardo, C.; Sesmilo, E.; Gutierrez-Puebla, E.; Monge, A.; Elguero, J.; Fruchier, A. *J. Org. Chem.* **2001**, *66*, 1607–1611.

(11) Valík, M.; Dolenský, B.; Petříčková, H.; Král, V. *Collect. Czech. Chem. Commun.* **2002**, *67*, 609–621.

(12) (a) Dolenský, B.; Valík, M.; Matějka, P.; Herdtweck, E.; Král, V. *Collect. Czech. Chem. Commun.* **2006**, *71*, 1278–1302. Preparations of different oligoTB derivatives by mixed troegeration were published recently. (b) Dolenský, B.; Valík, M.; Sýkora, D.; Král, V. *Org. Lett.* **2005**, *7*, 67–70. (c) Valík, M.; Čejka, J.; Havlík, M.; Král, V.; Dolenský, B. *Chem. Commun.* **2007**, *37*, 3835–3837.

(13) Havlík, M.; Král, V.; Dolenský, B. *Org. Lett.* **2006**, *8*, 4867–4870.

(14) Troegeration is defined as any treatment of an arylamine derivative with a source of formaldehyde (e.g., aqueous solution, paraformaldehyde, hexamethylenetetraamine, dimethoxymethane, trioxane) in acidic condition (e.g., HCl, TFA) that leads to a Tröger's base derivative, at least in the case of troegerable arylamine derivatives (i.e., arylamine derivative giving a Tröger's base derivative under troegeration).

(15) Havlík, M.; Král, V.; Dolenský, B. *Collect. Czech. Chem. Commun.* **2007**, *72*, 392–402.

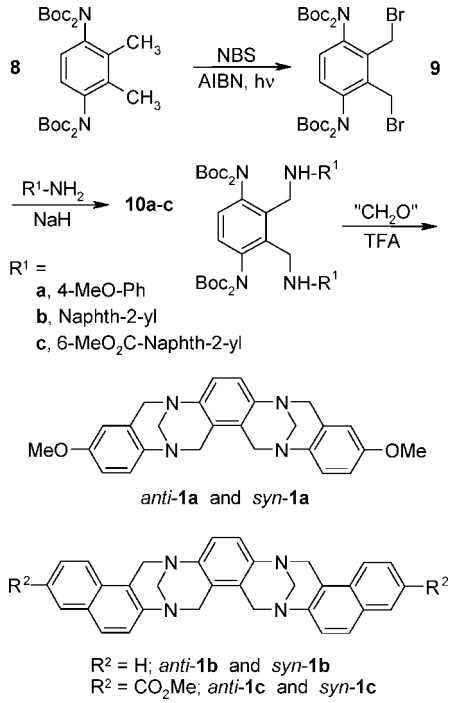
(16) Note that troegeration of monoarylamine **5** gave an unidentified compound consisting of one TB unit.

(17) Hardy, A. D. U.; MacNicol, D. D.; Wilson, D. R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1011–1019.

(18) (a) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997**, *119*, 311–325. (b) Dambrough, S.; Mervic, M.; Condon, S. M.; Burns, C. J. *Synth. Commun.* **2001**, *31*, 3273–3280.

(19) $Boc_2N$ groups are unstable in basic condition, e.g.: (a) Herzig, S.; Kritter, S.; Lübbers, T.; Marquardt, N.; Peters, J.-U.; Weber, S. *Synlett* **2005**, 3107–3108. (b) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand., Ser. B* **1987**, *41*, 18–23.

**Scheme 2**




column chromatography (16% *anti*-**1b**, 10% *syn*-**1b**, 13% *anti*-**1c**, 5% *syn*-**1c**).

For our third approach, we attempted one-pot mixed troegeration. 1,4-Benzenediamine, hexamethylenetetraamine, and arylamine **a**−**c** (in the molar ratio 10:19:28) were treated in TFA at room temperature for five days. With bisTB **1** standards in hand, repeated column chromatography was used to isolate the expected bisTB compounds from the corresponding complex reaction mixtures. Thus, 4-methoxyaniline yielded 5% of *anti*-**1a** and 3% of *syn*-**1a**; naphthyl-2-amine gave 9% of *anti*-**1b** and 4% of *syn*-**1b**; and methyl 6-amino-2-naphthoate produced 4% of *anti*-**1c** and 2% of *syn*-**1c**.

In all cases, diastereoisomers (*anti*-**1** and *syn*-**1**) were formed in a ratio of approximately 2:1. The difference in the chemical shifts of N−$CH_2$−N protons (measured in $CDCl_3$) was twice as great ($\Delta\delta = 0.09 - 0.13$ ppm) for the isomers with higher $R_f$ values (silica, $CH_2Cl_2/CH_3OH$ 95:5) than for the isomers with lower $R_f$ values ($\Delta\delta = 0.04 - 0.05$ ppm). Since the stereostructures of both *anti*-**1a** and *syn*-**1a** diastereoisomers are known from X-ray diffraction,[12] we assume that the isomers with higher $R_f$ values are the anti diastereoisomers, and those with lower $R_f$ values are the syn diastereoisomers.

In conclusion, we have described two synthetic pathways for the preparation of new bisTB **1** derivatives. Although both step-by-step and one-pot preparations should be further optimized, a preliminary comparison can be made. Step-by-step preparation is time-consuming (involving nine reaction steps) and expensive compared with one-pot preparation. The comparison of preparative yields from commercially available 2,3-dimethylaniline (6% **1b**, 4% **1c**), from the intermediate dibromide **9** (26% **1b**, 18% **1c**), and from commercially available 1,4-benzenediamine (one-pot preparation: 8% **1a**, 13% **1b**, 6% **1c**) shows that, in spite of the poor yields, one-pot preparation is efficient and suitable for upscaling.

The prepared compounds *syn*-**1a**−**c** represent rigid molecular tweezers; e.g., *syn*-**1b** has large pincers close to parallel (32°) and at an appropriate distance (0.67−0.80 nm) from each other.[20] In addition, a tweezer effect was observed when colorless chloroform solutions ($4.3 \times 10^{-3}$ M) of **1b** diastereoisomers were doped with equimolar amounts of tetracyanoethylene, the *syn*-**1b** solution turning darker purple than *anti*-**1b**. The formations of charge-transfere complexes[21] were followed by UV−vis absorption spectra (Figure 1).

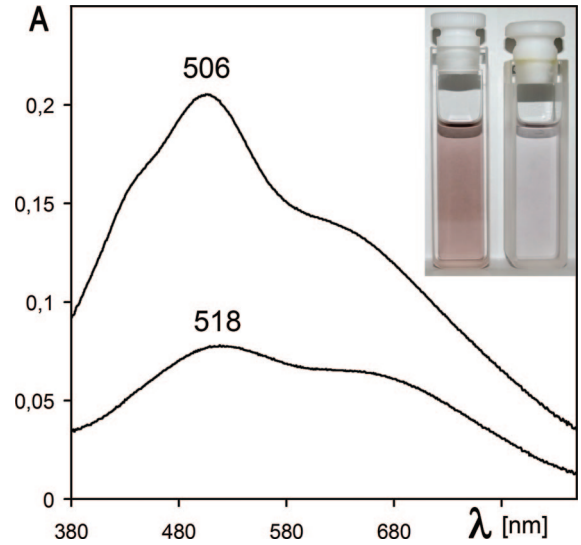



**Figure 1.** Charge-transfer bands of tetracyanoethylene complexes with *syn*-**1b** (upper spectrum, left cuvette) and *anti*-**1b** (lower spectrum, right cuvette).

Further detailed studies of the binding abilities of bisTBs are already underway.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all presented compounds and complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Measurements were made on the molecular model of *syn*-**1b**, wherein the geometry was optimized by MM2. The angle is formed by planes of naphthalene moieties, and the distances were measured between the centroids of the naphthalene rings (see the abstract picture).

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