BRIDGED BIS-TRÖGER'S BASE MOLECULAR TWEEZERS AS NEW CAVITAND FAMILY

Martin HAVLÍK[a1], Václav PARCHAŇSKÝ[a2], Petr BOUŘ[b], Vladimír KRÁL[a3] and Bohumil DOLENSKÝ[a4,*]

[a] *Department of Analytical Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail:* [1] *havlikm@vscht.cz,* [2] *vparchansky@gmail.com,* [3] *kralv@vscht.cz,* [4] *dolenskb@vscht.cz*

[b] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic; e-mail: bour@uochb.cas.cz*

Received March 13, 2009
Accepted April 27, 2009
Published online July 16, 2009

Dedicated to Dr. Alfred Bader with heartfelt thanks for his fatherly support of Czech scientists.

New molecular tweezers based on bis-Tröger's base with methoxycarbonyl groups on its pincers was prepared. These groups were converted into hydroxymethyl groups, which were interconnected by a linker to give the bridged molecular tweezers, a cavitand. The cavitand was studied and its ability to bind nitrobenzene was compared with similar bis-Tröger's base molecular tweezers.

Keywords: Bis-Tröger's base; Molecular tweezers; Binding; Cavitand.

One of today chemistry mainstreams deals with intermolecular interactions and their utilization in construction of molecular tools, e.g., molecular reactors and receptors. A significant part of these studies employs container-shaped molecules, the cavitands, i.e., the hollow molecules with an accessible cavity. Those cavities were found to be the stage of many unique and exploitable processes. Because those processes are extremely useful, e.g., in the development of molecular robotics, there is an increasing requirement for new cavitands differing namely in their cavity shape, size, charge, hydrophilicity, etc. Note that the famous cavitands such as calixarenes, cyclodextrins and cucurbiturils have largely cylindrical cavities[1]. In this article, we present the first member of a new cavitand family based on bridged bis-Tröger's base molecular tweezers.

The common Tröger's base[2] (TB) derivatives[3] consist of two arenes, which are fused to the opposite sides of methylene-bridged 1,5-diazocine. Due to

doi:10.1135/cccc2009036

this structure, the TB derivatives are rigid molecules, in which the arenes make an angle of 80–114°. That makes TB derivatives coveted building blocks of molecular engineers to build up, e.g., selective receptors. Recently, there were introduced new TB derivatives[4], the bis-Tröger's bases (bisTB), in which one arene is common to two TB units. Due to that, next two arenes of certain *syn*-bisTB diastereoisomers are parallel at a distance of about 0.7 nm, and mimic pincers of tweezers. These molecules excellently fulfill the requirements to be classified as molecular tweezers (0.64–0.70 nm)[5]. We demonstrate here that the pincers of *syn*-bisTB can be bridged with a proper linker to form a cavitand.

EXPERIMENTAL

The NMR spectra were obtained with a Varian Mercury Plus (300.077 MHz for ^{1}H and 75.460 MHz for ^{13}C) at 23 °C in $CDCl_3$ or DMSO-d_6. The chemical shifts (δ) are presented in ppm (relative to TMS) and the coupling constants (*J*) in Hz. Mass spectra were obtained by atmospheric pressure chemical ionization (APCI) with an LTQ Orbitrap spectrometer. The fluorescence spectra (λ, nm; ε, l cm^{-1} mol^{-1}) were recorded with FluoroMax-2 at 298 K. Silica (32–63 D, 60 Å) was used for separation by column chromatography. Molecule pictures are provided by HyperChem[6]. The distances were measured and calculated with Mercury 1.4.2 (build 2)[7].

Preparation of Tetramine **4b**

Dibromide **2**[8] (1.9 g, 3.8 mmol) was treated with methyl 6-amino-2-naphthoate (5 g, 24.9 mmol) and K_2CO_3 (0.6 g, 4.3 mmol) in DMF (200 ml) at 80 °C for 5 h. The reaction mixture was evaporated to dryness in vacuo. The residue was separated by column chromatography ($CHCl_3$/Et_2O 10:1) to give 1.5 g (54%) of tetramine **4b**. ^{1}H NMR (DMSO-d_6): 8.73 s, 2 H; 8.23 d, 2 H, *J* = 1.3; 7.61 d, 2 × 2 H, *J* = 8.8; 7.43 s, 1 H; 7.35 s, 1 H; 7.28 d, 2 H, *J* = 8.8; 6.92 dd, 2 H, *J* = 8.8, *J* = 2.1; 6.81 t, 2 H, *J* = 4.7; 6.49 d, 2 H, *J* = 2.1; 4.24 d, 4 H, *J* = 4.7; 3.85 s, 6 H; 1.45 s, 18 H. ^{13}C APT NMR (DMSO-d_6): 166.58 (C), 153.70 (C), 148.64 (C), 137.44 (C), 134.85 (C), 130.37 (CH), 129.96 (CH), 129.27 (C), 126.50 (CH), 125.26 (CH), 125.04 (C), 124.98 (CH), 121.53 (CH), 121.45 (C), 118.72 (CH), 102.21 (CH), 78.98 (C), 51.72 (CH_3), 42.62 (CH_2), 28.11 (CH_3). HRMS (APCI): for $C_{42}H_{47}N_4O_8$ [M + H^+] calculated 735.3394, found 735.3381.

Preparations of bisTBs **1a** and **1b**

a) Preparation of **1a** diastereoisomers were described previously[8]. *anti*-**1a**: UV ($CHCl_3$), λ_{max} (log ε): 243 (4.66), 283 (4.12), 295 (3.97), 329 (3.23). *syn*-**1a**: UV ($CHCl_3$), λ_{max} (log ε): 242 (4.66), 283 (4.05), 295 (3.92), 329 (3.23).

b) Tetramine **4b** (1.0 g, 1.4 mmol) was dissolved in TFA (50 mL) and paraformaldehyde (0.5 g, 10.8 mmol of "CH_2O") was added, and the reaction mixture was stirred at room temperature for 1 h. The solution was alkalinized at 0 °C with 25% aqueous NH_3 and extracted with CH_2Cl_2. The organics were extracted with water, dried over Na_2SO_4 and evaporated to

dryness in vacuo. The residue was separated by column chromatography ($CHCl_3$/methanol 20:1) to give crude isomer *anti*-**1b** followed by *syn*-**1b**. Isomer *anti*-**1b** was purified by column chromatography (toluene/acetone 9:1 to 7:3) to obtain 340 mg (43%). Isomer *syn*-**1b** was purified by column chromatography (toluene/acetone 1:1) to obtain 267 mg (34%).

anti-**1b**: ^{1}H NMR ($CDCl_3$): 8.48 d, 2 H, *J* = 1.7; 8.04 dd, 2 H, *J* = 8.8, *J* = 1.7; 7.76 d, 2 H, *J* = 8.8; 7.67 d, 2 H, *J* = 8.8; 7.29 d, 2 H, *J* = 8.8; 7.10 s, 1 H; 6.50 s, 1 H; 4.98 d, 2 H, *J* = 16.7; 4.66 d, 2 H, *J* = 16.7; 4.58 d, 2 H, *J* = 16.7; 4.34 d, 2 H, *J* = 12.5; 4.26 d, 2 H, *J* = 12.5; 4.25 d, 2 H, *J* = 16.7; 3.96 s, 6 H. ^{13}C APT NMR ($CDCl_3$): 167.15 (C), 147.37 (2 × C), 133.70 (C), 131.40 (CH), 129.85 (C), 129.17 (CH), 126.22 (C), 126.07 (CH), 125.22 (CH), 125.17 (CH), 123.87 (C), 121.46 (CH), 121.41 (C), 121.06 (CH), 66.48 (CH_2), 57.09 (CH_2), 57.04 (CH_2), 52.18 (CH_3). UV ($CHCl_3$), λ_{max} (log ε): 250 (4.87), 313 (4.30). HRMS (APCI): for $C_{36}H_{31}N_4O_4$ [M + H$^+$] calculated 583.2345, found 583.2332.

syn-**1b**: ^{1}H NMR ($CDCl_3$): 8.35 d, 2 H, *J* = 1.7; 7.93 dd, 2 H, *J* = 8.8, *J* = 1.7; 7.64 d, 2 H, *J* = 8.8; 7.60 d, 2 H, *J* = 8.8; 7.22 d, 2 H, *J* = 8.8; 7.03 s, 1 H; 6.49 s, 1 H; 4.97 d, 2 H, *J* = 16.7; 4.66 d, 2 H, *J* = 16.7; 4.42 d, 2 H, *J* = 16.7; 4.37 d, 2 H, *J* = 13.5; 4.32 d, 2 H, *J* = 13.5; 4.20 d, 2 H, *J* = 16.7; 3.88 s, 6 H. ^{13}C APT NMR ($CDCl_3$): 167.03 (C), 147.61 (C), 147.51 (C), 133.56 (C), 131.26 (CH), 129.67 (C), 128.96 (CH), 126.05 (C), 126.00 (CH), 125.16 (CH), 124.99 (CH), 123.97 (C), 121.46 (CH), 121.45 (C), 121.40 (CH), 66.53 (CH_2), 56.97 (CH_2), 56.79 (CH_2), 52.07 (CH_3). UV ($CHCl_3$), λ_{max} (log ε): 250 (4.83), 314 (4.20). HRMS (APCI): for $C_{36}H_{31}N_4O_4$ [M + H$^+$] calculated 583.2345, found 583.2335.

Preparation of bisTB **1c**

BisTB *syn*-**1b** (100 mg, 172 μmol) was dissolved in THF (25 ml) and LAH (38 mg, 1000 μmol, 0.5 ml of 2 M solution in THF) was added at room temperature, and then stirred for 3 h. The solution was carefully quenched with water and evaporated to dryness in vacuo. The residue was separated by column chromatography (CH_2Cl_2/methanol 93:7) to obtain 75 mg (83%) of bisTB **1c**. ^{1}H NMR (DMSO-d_6): 7.53 m, 6 H; 7.33 dd, 2 H, *J* = 8.8, *J* = 1.4; 7.14 d, 2 H, *J* = 8.8; 6.95 s, 1 H; 6.54 s, 1 H; 5.18 t, 2 H, *J* = 5.5; 4.82 d, 2 H, *J* = 17.0; 4.59 d, 2 H, *J* = 16.7; 4.51 d, 4 H, *J* = 5.5; 4.38 d, 2 H, *J* = 17.0; 4.23 d, 2 H, *J* =12.5; 4.19 d, 2 H, *J* = 12.5; 4.10 d, 2 H, *J* = 16.7. ^{13}C APT NMR (DMSO-d_6): 147.36 (C), 144.68 (C), 138.46 (C), 129.94 (C), 129.69 (C), 127.09 (CH), 125.40 (CH), 125.00 (CH), 124.65 (CH), 124.48 (CH), 123.56 (C), 121.11 (C), 120.96 (CH), 120.72 (CH), 65.90 (CH_2), 62.67 (CH_2), 56.35 (CH_2), 56.22 (CH_2). HRMS (APCI): for $C_{34}H_{31}N_4O_2$ [M + H$^+$] calculated 527.2447, found 527.2438.

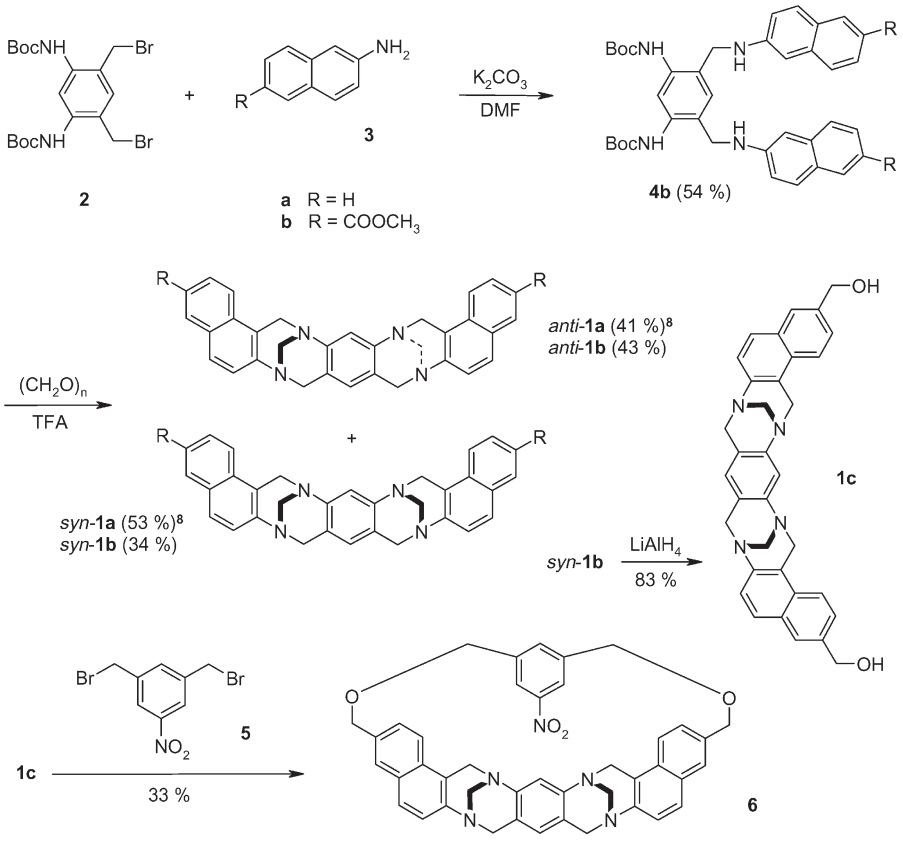
Preparation of the Cavitand **6**

BisTB **1c** (50 mg, 95 μmol) and dibromide **5** [9] (29 mg, 95 μmol) was dissolved in DMF (12 ml) and NaH (20 mg, 833 μmol) was added at room temperature, and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was evaporated to dryness in vacuo. The residue was purified by preparative TLC ($CHCl_3$/methanol 93:7) to give 21 mg (33%) of cavitand **6**. ^{1}H NMR ($CDCl_3$): 8.13 s, 2 H; 7.58 m, 6 H; 7.40 dd, 2 H, *J* = 8.7, *J* = 1.7; 7.19 d, 2 H, *J* = 8.7; 7.16 s, 1 H; 7.00 s, 1 H; 6.43 s, 1 H; 4.97 d, 2 H, *J* = 16.7; 4.81 d, 2 H, *J* = 11.4; 4.63 d, 2 H, *J* = 16.6; 4.54 d, 2 H, *J* = 11.4; 4.38 m, 10 H; 4.15 d, 2 H, *J* = 16.6. ^{13}C APT NMR ($CDCl_3$): 148.28 (C), 147.66 (C), 145.47 (C), 140.33 (C), 133.56 (C), 132.03 (CH), 130.94 (C), 130.27 (C), 128.55 (CH), 127.71 (CH), 127.45 (CH), 124.94 (CH), 124.66 (CH), 124.04 (C), 122.08 (CH), 121.51 (C), 121.12 (2 × CH), 73.41 (CH_2), 69.92 (CH_2), 66.70

(CH_2), 57.15 (CH_2), 57.06 (CH_2). Fluorescence ($CHCl_3$, λ_{exc} = 354), λ_{max}: 467. HRMS (APCI): for $C_{42}H_{36}N_5O_4$ [M + H^+] calculated 674.2767, found 674.2763.

RESULTS AND DISCUSSION

The required bisTB **1b** was prepared based on the protocol we have published recently for preparation of bisTB **1a** (Scheme 1)[8]. Thus, dibromide **2** was treated with an excess of naphthylamine **3b** to produce tetramine **4b** in 54% preparative yield. The following treatment with paraformaldehyde in TFA led to the formation of both diastereoisomers of bisTB **1b** in preparative yields 43 and 34% of *anti*-**1b** and *syn*-**1b**, respectively. Both ester func-



SCHEME 1
Preparation of cavitand **6**

tions of the *syn*-**1b** were reduced by $LiAlH_4$ to corresponding dihydroxy-bisTB **1c** (83% yield). The treatment of **1c** with dibromide **5** gave cavitand **6** in a preparative yield of 33%.

Since we were not successful in obtaining a single crystal for X-ray diffraction analysis, the Fig. 1 shows the covalent structure and molecular model of cavitand **6**, wherein the geometry was optimized by RM1 method[10]. The cavity volume of cavitand **6** could be estimated as cuboid, which is defined by the width 0.78 nm, length 0.85 nm and depth 0.36 nm, wherein the width and length are decreased by about van der Waals radius of carbon (0.17 nm). That gives the cavity volume about 0.149 nm^3 (90 ml mol^{-1}, 0.13 ml g^{-1}), which is similar to cucurbituril[6] (0.164 nm^3)[11] or α-cyclodextrin (0.174 nm^3)[12].

The ability of cavitand **6** to bind nitrobenzene in chloroform was tested by the titration experiment followed by quenching of fluorescence. Since both α-cyclodextrin and cucurbituril[6] show insufficient solubility in chloroform, we have compared the binding ability of cavitand **6** and non-bridged bisTB molecular tweezers *syn*-**1a**. As nitrobenzene is added, the fluorescence intensities of both compounds fall down, partly due to the expected interactions and partly due to the nitrobenzene absorption at both excitation and emission wavelengths. Because of that, the binding constants were determined with LETAGROP[13] after correction[14] for the

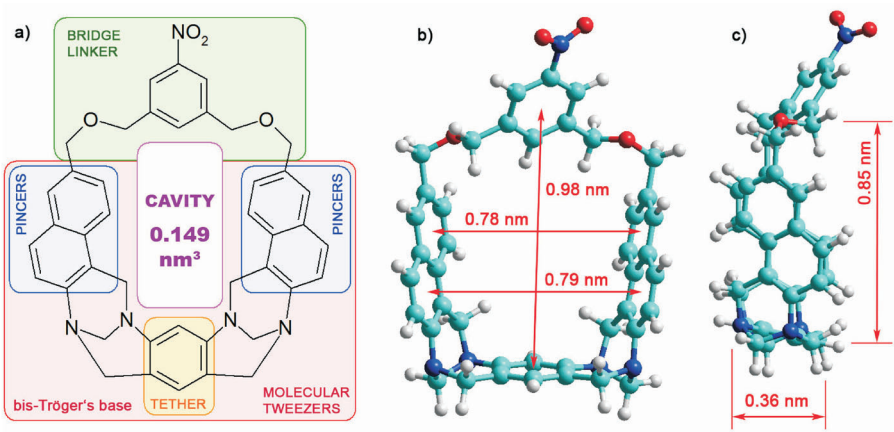


FIG. 1
Structural compartments of cavitand **6** (a); the lowest energy structure of cavitand **6** (optimized by RM1) (b, c); the view into cavitand **6** with the distances of the centroids of opposite aromatic rings (b); the side view with estimation of the cavity length and depth (c)

nitrobenzene absorptions (Fig. 2). In the case of *syn*-**1a** the formation of the expected (*syn*-**1a**)·($PhNO_2$) complex was confirmed and the binding constant 1 200 ± 400 l mol^{-1} (ΔG = 17.0 ± 1.0 kJ mol^{-1}) was determined. Unfortunately, in the case of cavitand **6**, no binding of nitrobenzene was observed. Since it is important for the design of new cavitands, we have tried to point out the origin of the binding failure.

Inspection of the fluorescence spectra (Fig. 3) shows that molecular tweezers *syn*-**1a** has a high-frequency band at 387 nm and a less intensive low-frequency band at 756 nm. In contrast, cavitand **6** has the high-frequency band at 467 nm (red shift 80 nm, significantly less intensive than high-frequency band of *syn*-**1a**) and no low-frequency band (below 900 nm). Since the covalent structure of *syn*-**1a** is a subset of the cavitand **6** structure, so different spectra are not expected. Next, when nitrobenzene is added to *syn*-**1a** the intensities of both its bands are reduced and red-shifted by 10–20 nm. In other words, the spectrum of **6** is more similar to the spectrum of the (*syn*-**1a**)·($PhNO_2$) complex than pure *syn*-**1a**. Obviously, this is a consequence of the cavitand **6** bridge, which is a certain equivalent of nitrobenzene. The nitrobenzene bridge could be either bound by the cavity of another cavitand molecule to form an intermolecular complex $(\mathbf{6})_n$ wherein $n > 1$, or immersed into the cavity of the same molecule to form an intramolecular complex $(\mathbf{6})_1$. As the fluorescence intensity of both

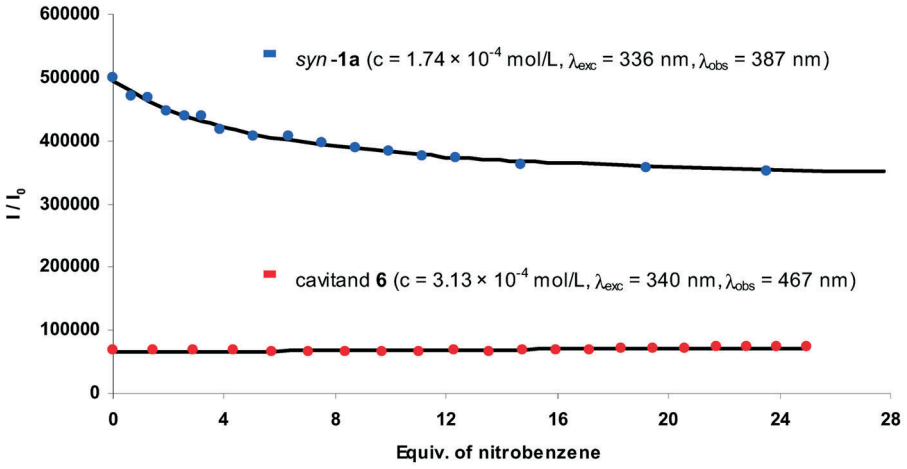


FIG. 2
The titration experiments of *syn*-**1a** and **6** with nitrobenzene

intermolecular and intramolecular complex could be similar to that of the desirable nitrobenzene complex $(\mathbf{6})_m \cdot (PhNO_2)_n$, the potential binding could not be detectable when is followed by the fluorescence quenching. In other words, our negative observation can be interpreted in two ways: (i) no complexation of nitrobenzene occurred because a self-complex is much stronger than the expected one and (ii) the complexation cannot be observed by fluorescence quenching.

It is well known that an intramolecular process is usually preferred over similar but intermolecular one. Since the intramolecular complex of $(\mathbf{6})_1$ is a conformer, we have performed conformational search by molecular modeling[15] using the dispersion-corrected DFT method (DFT-D)[16]. The functional BPW91 on 6-31G basis was used. In contrary to the computation by semi-empirical RM1 method, the DFT-D computation has revealed two conformers (Fig. 4). The nitrobenzene bridge of filled-**6** conformer is immersed in the cavity (intramolecular complex), while in the case of empty-**6** conformer is outside the cavity. The geometries of these conformers were optimized and their energies were calculated on the DFT-D/BPW91/6-31G** level. The energy difference ca. 18 kJ mol^{-1} (4.2 kcal mol^{-1}) corresponds to the ratio of empty-**6** to filled-**6** ca. 0.0008 (at 298 K), which makes the binding less probable.

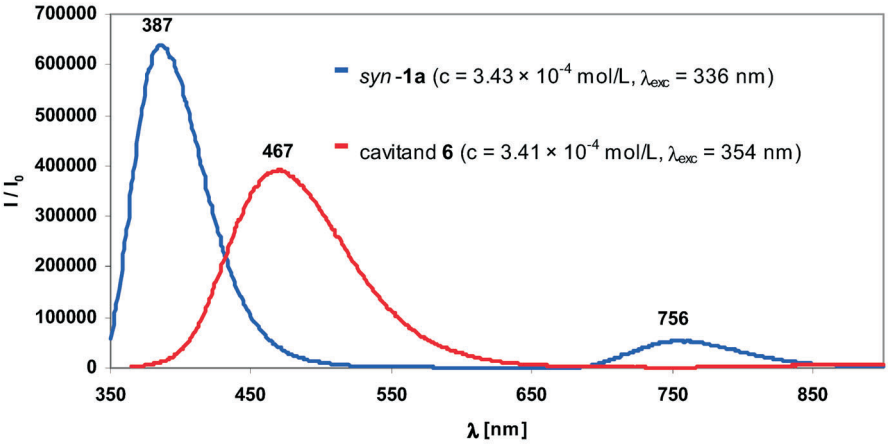


FIG. 3
Fluorescence spectra of *syn*-**1a** and cavitand **6**

Those arguments suggest the conclusion that there is no binding of nitrobenzene to cavitand **6**. However, it should be kept in mind that ortho protons of the nitrobenzene bridge of filled-**6** conformer are not equivalent, but only one signal is observed in the experimental NMR spectrum of cavitand **6**. It could mean the bridge of cavitand **6** is not permanently bound in the cavity.

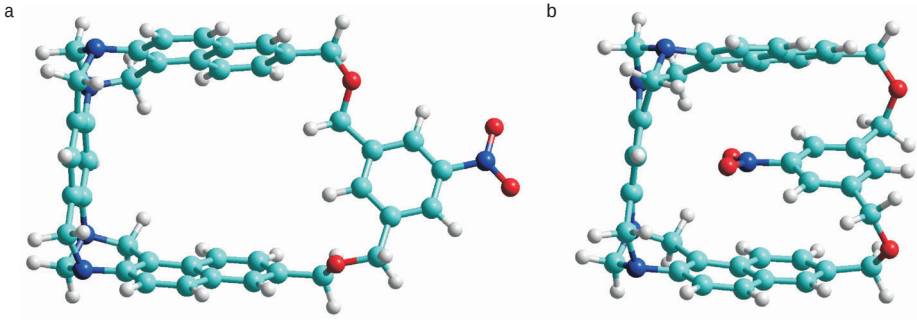


FIG. 4
The conformers empty-**6** (a) and filled-**6** (b)

CONCLUSION

We have shown the pincers of the molecular tweezers base on bisTBs can be interconnected forming molecule with cavity, a cavitand. Based on our previous results[8,17] we believe this cavitand type can be modified in many ways. The molecular tweezers can be prepared with a variety of pincers and tethers to increase or decrease their length, width, depth, shape and many physico-chemical properties of the cavity. In addition, both bridges and molecular tweezers can bear other functional groups to adjust the binding constant and selectivity, or a probe to report a binding. A detailed research of these cavitands is in progress and the results will be published soon.

This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic (MSM 6046137307 and LC06077), and the Czech Science Foundation (203/08/1445 and 203/06/0786).

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