Calix-Tris-Tröger’s Bases – A New Cavitand Family

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Context

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**EXPERIMENTAL PART**

All $^1$H and $^{13}$C NMR experiments were recorded at 300.08 and 75.46 MHz, respectively. Chemical shifts $\delta$ (ppm) are referenced to the internal standard Me$_4$Si for both $^1$H and $^{13}$C NMR spectra; the coupling constants $J$ are given in Hertz (Hz). The correlation techniques g-HSQC, g-COSY, 1D NOESY (mixing time 600 ms) were recorded under common conditions. The g-HMBC spectra were recorded with parameters of $^{1}J_{CH}$ coupling 180 Hz (parameter $j_{1hx}$ at Varian Mercury NMR machine) and $^{2}J_{CH}$ coupling 8 Hz (parameter $j_{2hx}$ at Varian Mercury NMR machine). The chemical shifts and coupling constants for $H^*_a$, $H^*_b$, $H^*_a$, $H^*_b$ and $H^*_b$ in calix-$1b$ and calix-$1c$ were determined by simulation as six-spins system by MestRe-C 4.4.6 (Mestrelab Research, Spain). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-640697 (calix-$1e$) and CCDC-640698 (throne-$1c$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). The preparations of compounds $2b$, $3b$, $4b$, throne-$1b$, $2a$, $3a$ and $4a$, and unsuccessful attempt of throne-$1a$ preparation were described previously.$[^6a]$

Preparation of nitroamide $2c$

5-methoxy-2-nitrobenzoic acid (12.9 g, 65.5 mmol) was refluxed with SOCl$_2$ (40 mL) in toluene (50 mL) for 5 h. The volatile part of reaction mixture was evaporated and residue codestillated with toluene (2×20 mL). Residual brown oil was added to solution of 1,3,5-triaminobenzene (2.02 g, 16.4 mmol) in pyridine (20 mL) and DMF (40 mL). Reaction mixture was stirred 12 h at room temperature and 1 h at 50 °C. After cooling, 1 L of water was added. The formed precipitate of $2c$ (6.10 g, 63% yield) was filtered off, washed with methanol (100 mL) and dichlormethane (150 mL). Additional part of $2c$ (0.75 g, 8% yield) was obtained from the organic part of the filtrate. $^1$H NMR (DMSO-d$_6$): 3.92 (9H, s, OCH$_3$), 7.20 (6H, m), 7.87 (3H, s), 8.15 (3H, d, 8.5), 10.69 (3H, s, NH). $^{13}$C APT NMR (DMSO-d$_6$): 56.57 (OCH$_3$), 106.69 (CH), 114.22 (CH), 115.33 (CH), 126.92 (CH), 135.67, 138.68, 139.41, 163.51, 164.16. Elemental analysis for C$_{30}$H$_{24}$N$_6$O$_{12}$ calcd: 54.55 %C, 3.66 %H, 12.72 %N; found: 54.22 %C, 3.93 %H, 12.82 %N.

Preparation of aminoamide $3c$

A flask was charged with 1.00 g (1.5 mmol) of $2c$, 100 mg of Pd/C (10%), 50 mL of methanol, and 10 mL of DMF. The mixture was stirred over night under H$_2$ atmosphere. The catalyst was filtrated off through cellite and the filtrate was concentrated in vacuo to obtained 0.86 g of $3e$ (100% yield). $^1$H NMR (DMSO-d$_6$): 3.72 (9H, s), 5.80-6.20 (6H, br s), 6.72 (3H, d, 8.8), 6.89 (3H, dd, 8.8, 2.8), 7.20 (3H, d, 2.8), 7.81 (3H, s), 10.08 (3H, br s). $^{13}$C APT NMR (DMSO-d$_6$): 55.61
Preparation of hexaamine 4c

3.5 M toluene solution of LAH (18 mL, 63 mmol) was slowly added to 3c (1.30 g, 2.3 mmol) in dioxane (40 mL). Then the reaction mixture was refluxed for 14 h. The flask was placed into ice bath and 6 mL of water, followed by 7 mL of aqueous solution of NaOH (15%) and 10 mL of water were cautiously added. The mixture was filtered and the filtrate was evaporated in vacuo to obtain 1.12 g of 4c (93% yield). 1H NMR (DMSO-d6): 3.57 (9H, s), 3.91 (6H, d, 5.5), 4.45 (6H, br s), 5.30 (6H, m), 6.54 (6H, m), 6.69 (3H, t, 1.6). 13C APT NMR (DMSO-d6): 44.12 (CH 2), 55.23 (OCH 3), 87.64 (CH), 112.22 (CH), 114.38 (CH), 115.51 (CH), 125.32, 139.80, 150.20, 150.89. LRMS (FAB+): for C30H37N6O3 (MH+) calcd: 529.29; found: 529.29.

Preparation of throne-1c

Hexaamine 4c (1.21 g, 2.3 mmol) and 1.00 g of paraformaldehyde were added to trifluoroacetic acid (145 mL). The reaction mixture was stirred 1 h at 50 °C, then diluted with ice water (1 L), and conc. aq. ammonia was added to pH 14. The mixture was extracted with CH2Cl2 (3 × 150 mL). The organic parts were combined, washed with brine, dried over Na2SO4, and evaporated in vacuo to dryness. By repeating column chromatography on silica (CH2Cl2/EtOAc/ethanol 250:250:12) 80 mg of by-product 5 (6% yield) 320 mg of crude Tris-TB throne-1c were obtained. The crystallization of crude throne-1c from CH2Cl2/acetone gave 240 mg (18% yield) of pure throne-1c.

By-product 5: 1H NMR (CDCl3): 2.80 (3H, s, NCH3), 3.71 (3H, s, OCH3), 3.73 (3H, s, OCH3), 3.75 (3H, s, OCH3), 3.91 (1H, d, 16.7), 3.95 (1H, d, 10.8), 4.01 (1H, d, 15.8), 4.02 (1H, d, 13.3), 4.04 (1H, d, 10.6), 4.13 (1H, d, 12.7), 4.18 (1H, d, 15.6), 4.19 (1H, d, 12.2), 4.28 (3H, m), 4.46 (1H, d, 16.9), 4.47 (1H, d, 17.1), 4.52 (1H, d, 17.9), 4.56 (1H, d, 17.2), 4.59 (1H, d, 16.6), 6.41 (1H, d, 2.9), 6.46 (1H, d, 2.8), 6.50 (1H, t, 1.7), 6.67 (1H, s), 6.78 (4H, m), 7.07 (1H, d, 8.8), 7.11 (1H, d, 8.8). 13C APT NMR (CDCl3): 38.93 (NCH3), 53.60 (CH2), 55.25 (CH2), 55.29 (OCH3), 55.35 (OCH3), 55.55 (CH2), 55.64 (OCH3), 55.84 (CH2), 59.08 (CH2), 66.76 (CH2), 67.00 (CH2), 71.05 (CH2), 110.54 (CH), 110.68 (CH), 111.73 (CH), 113.17 (CH), 113.20 (CH), 113.82 (CH), 113.97 (CH), 115.76 (CH), 117.98, 118.77, 123.75, 126.20 (CH), 126.27 (CH), 128.60, 128.75, 140.33, 140.77, 140.92, 145.82, 147.53, 148.00, 152.54, 155.86, 155.96. HRMS (FAB+): for C36H39N6O3 (MH+) calcd: 603.3084; found: 603.3056. Based on these characteristics and 2D NMR spectra (g-COSY, g-HSQC, g-HMBC) the following structure was deduced.
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**Throne-1c**: $^1$H NMR (CDCl$_3$): 3.60 (1H, d, 16.8), 3.65 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.82 (1H, d, 16.5), 3.88 (1H, d, 16.7), 4.08 (1H, d, 12.8), 4.10 (1H, d, 12.2), 4.16 (1H, d, ~13), 4.18 (1H, d, ~13), 4.19 (2H, s), 4.29 (1H, d, 17.4), 4.36 (1H, d, 17.0), 4.41-4.52 (5H, m), 4.53 (1H, d, 17.4), 4.56 (1H, d, 17.0), 6.25 (1H, d, 2.9), 6.41 (1H, d, 2.9), 6.45 (1H, d, 2.9), 6.69 (1H, dd, 8.8, 2.9), 6.76 (1H, dd, 8.8, 2.9), 6.78 (3H, dd, 8.8, 2.9), 7.08 (1H, d, 8.8), 7.12 (1H, d, 8.8), 7.15 (3H, d, 8.8). $^{13}$C APT NMR (CDCl$_3$): 54.67 (2 × CH$_2$), 55.08 (2 × CH$_2$), 55.31 (OCH$_3$), 55.36 (OCH$_3$), 55.38 (OCH$_3$), 55.57 (CH$_2$), 56.19 (CH$_2$), 66.69 (CH$_2$), 66.74 (CH$_2$), 66.97 (CH$_2$), 110.53 (CH), 110.66 (2 × CH), 113.80 (CH), 114.08 (CH), 114.46 (CH), 117.94, 118.25, 119.02, 125.84 (CH), 126.28 (CH), 126.38 (CH), 128.38, 128.50, 128.54, 140.82, 140.94, 141.17, 143.94, 144.26 (2 × C), 155.92, 155.99, 156.09. HRMS (FAB$^+$): for C$_{36}$H$_{37}$N$_6$O$_3$ (MH$^+$) calcd: 601.2927; found: 601.2939.

**Preparation of calix-1c by diastereoisomeration**

*Throne-1c* (54 mg) was dissolved in 5 mL of TFA and warmed at 110 °C for 15 h. The obtained mixture of *throne-1c* and *calix-1c* in ratio 97:3 was separated by preparative TLC (Uniplate Silica Gel GF, 20 cm × 20 cm × 0.1 cm, with PA zone, CH$_2$Cl$_2$/CH$_3$OH 97:3). The diastereoisomer *throne-1c* was subject of next diastereoisomerization. The collected portions of *calix-1c* from five isomerizations gave 6 mg (11% yield). The single crystal for X-ray analysis was obtained by crystallization from mixture CH$_2$Cl$_2$/CH$_3$OH. The $^1$H and $^{13}$C chemical shifts in NMR spectra were assigned based on g-COSY, g-HSQC, g-HMBC and 1D NOEDIF spectra analogously to assignment on bisTB derivatives.$^{[6c]}$

*Calix-1c*: $^1$H NMR (CDCl$_3$): 3.64 (9H, s, H12), 3.65 (3H, d, 16.8, H7$a$), 4.18 (3H, d, 17.7, H9$b$), 4.18 (3H, d, 12.3, H8$^a$ or H8$^b$), 4.20 (3H, d, 12.3, H8$^a$ or H8$^b$), 4.48 (3H, d, 16.8, H7$b$), 4.66 (3H, d, 17.7, H9$b$), 6.28 (3H, d, 2.9, H6), 6.71 (3H, dd, 8.8, 2.9, H2), 7.11 (3H, d, 8.8, H3). $^{13}$C NMR (CDCl$_3$): 54.91 C7, 55.35 C12, 56.09 C9, 66.39 C8, 110.67 C6, 114.49 C2, 120.40 C10, 125.98 C3, 128.23 C5, 141.26 C4, 144.31 C11, 156.16 C1. HRMS (FAB$^+$): for C$_{36}$H$_{37}$N$_6$O$_3$ (MH$^+$) calcd: 601.2927; found: 601.2908.
One-pot preparation of throne-1b

A vial was charged with 86 mg (0.70 mmol) of 1,3,5-triaminobenzene, 249 mg (2.32 mmol) of \( p \)-toluidine and 199 mg (equiv. of 6.63 mmol of CH\(_2\)O) of paraformaldehyde, and 4 mL of TFA was added. The vial was closed with a cup, and the mixture was vigorously stirred for 24 h in 60 °C oil bath. The mixture was cool down and diluted with 200 mL of water, and alkalized by adding of 5 mL of conc. aqueous ammonium. The mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 20 mL). The organic parts were dried over MgSO\(_4\) and evaporated in vacuo to dryness. Repeating separation on preparative TLC (CH\(_2\)Cl\(_2\)/CH\(_3\)OH 100:3) gave 8 mg (2% yield) of throne-1b. The NMR characteristics confirm the identity with the compound isolated previously.\(^{[6c]}\)

*Throne*-1b: \( ^1\)H NMR (CDCl\(_3\)): 2.18 (3H, s, CH\(_3\)), 2.24 (6H, m, 2CH\(_3\)), 3.60 (1H, d, 16.5), 3.73 (1H, d, 16.8), 3.86 (1H, d, 16.5), 4.00-4.65 (15H, m), 6.54 (1H, s), 6.70 (1H, s), 6.74 (1H, s), 6.86-7.14 (6H, m). \(^{13}\)C APT NMR (CDCl\(_3\)): 20.88 (CH\(_3\)), 21.90 (CH\(_3\)), 20.96 (CH\(_3\)), 54.39 (CH\(_2\)), 54.42 (CH\(_2\)), 55.11 (CH\(_2\)), 55.17 (CH\(_2\)), 55.24 (CH\(_2\)), 56.25 (CH\(_2\)), 66.59 (2CH\(_2\)), 66.85 (CH\(_2\)), 117.70 (C), 118.13 (C), 118.82 (C), 124.42 (CH), 124.99 (CH), 125.07 (CH), 126.87 (CH), 126.92 (CH), 127.19 (C), 127.35 (2C), 127.38 (CH), 127.90 (CH), 127.98 (CH), 128.04 (CH), 133.36 (C), 133.38 (C), 133.48 (C), 143.74 (C), 144.03 (C), 144.07 (C), 144.99 (C), 145.09 (C), 145.34 (C). HRMS (FAB\(^+\)): for C\(_{36}\)H\(_{37}\)N\(_6\) (MH\(^+\)) calcd: 553.3080; found: 553.3056.

Preparation of calix-1b by diastereoisomeration

*Throne*-1b (17 mg) was dissolved in 2 mL of TFA and warmed at 110 °C for 17 h. The obtained mixture of throne-1b and calix-1b in ratio 97:3 was separated by preparative TLC (Uniplate Silica Gel GF, 20 cm \( \times \) 20 cm \( \times \) 0.1 cm, with PA zone, CH\(_2\)Cl\(_2\)/CH\(_3\)OH 92:2) to give about 1 mg of calix-1b. The \( ^1\)H and \(^{13}\)C chemical shifts in NMR spectra were assigned based on gCOSY, gHSQC, gHMBC and 1D NOEDIF spectra analogously to assignment on bisTB derivatives.\(^{[6c]}\)

*Calix*-1b: \( ^1\)H NMR (CDCl\(_3\)): 2.16 (9H, s, H12), 3.59 (3H, d, 16.8, H\(_7^a\)), 4.16 (3H, d, 12.4, H\(_8^a\) or H\(_8^b\)), 4.20 (3H, d, 12.4, H\(_8^a\) or H\(_8^b\)), 4.21 (3H, d, 16.6, H\(_9^b\)), 4.45 (3H, d, 16.7, H\(_7^b\)), 4.65 (3H, d, 17.6, H\(_9^b\)), 6.56 (3H, d, 1.4, H6), 6.94 (3H, dd, 8.1, 1.9, H2), 7.06 (3H, d, 8.1, H3). \(^{13}\)C NMR (CDCl\(_3\)): 20.76 C12, 54.63 C7, 56.12 C9, 66.29 C8, 120.32 C10, 124.71 C3, 127.20 C5, 127.42 C6, 128.06 C2, 133.55 C1, 144.25 C11, 145.77 C4.
Approximation of cavity volume calculation

The volume of the \textit{calix-1c} was calculated from X-ray data as the volume of truncated cone with following definition. The nitrogen atoms of central benzene define almost equilateral triangle with side 0.49 nm and the circumscribed circle $d_1 = 0.65$ nm. The oxygen atoms define almost equilateral triangle with side 0.85 nm and the circumscribed circle $d_2 = 0.98$ nm. The distance of the triangle centroids is $h = 0.55$ nm. The dimensions must be decreased by van der Waals diameter; let’s use a correction by 0.16 nm. The volume of the free space for guest is 0.078 nm$^3$. 

\begin{center}
\includegraphics[width=\textwidth]{diagram.png}
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