Electronic Supplementary Information

Synthesis of borasiloxane-based macrocycles by multicomponent condensation reactions in solution or in a ball mill

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1. General

All reagents were obtained from commercial sources. The solvents were dried using a solvent purification system from Innovative Technologies, Inc. The compound di-*tert*-butylsilanediol was prepared according to a literature procedure.[1] The condensation reactions in solution were carried out under an atmosphere of dry nitrogen using standard Schlenk techniques. The ^{1}H, ^{13}C and ^{29}Si spectra were recorded on a Bruker Avance DPX-400 or Bruker Avance 200 spectrometer using the residual protonated solvents (^{1}H, ^{13}C) as internal standards or $Si(CH_3)_4$ (^{29}Si) as an external standard. All spectra were recorded at room temperature. Combustion analyses were performed with a Thermo Scientific Flash 2000 Organic Elemental Analyzer. Mass spectra were recorded with a Waters Q-TOF Ultima (ESI), a Varian 1200L triple-quadrupole GC/MS (electron-impact or chemical ionizations, reagent gas: NH_3), or a hybrid linear ion trap Fourier transform ion cyclotron resonance mass spectrometer (LTQ FTICR MS, Thermo Scientific, Bremen, Germany) equipped with a 10 T superconducting magnet (Oxford Instruments Nanoscience, Abingdon, UK). Samples were dissolved at a concentration of 0.1 $mgmL^{-1}$ in toluene and analyzed using the atmospheric pressure photo-ionisation (APPI) ion source at a flow rate of 10 $\mu Lmin^{-1}$. IR spectra were recorded on a Perkin Elmer Spectrum One Golden Gate FT/IR spectrometer.

2. Syntheses

Synthesis of 4,4'-bis(azidomethyl)biphenyl[2]

A solution of 4,4'-bis(bromomethyl)biphenyl (1.0 g, 2.9 mmol) and NaN_3 (612 mg, 930 µmol) in DMF (10 mL) was stirred at room temperature for 24 h, then poured into water (50 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with water, brine, dried over anhyd. $MgSO_4$, evaporated carefully and the pure compound was isolated as a white solid. Yield 700 mg, 90%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 4.40 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.69 (C_{ar}), 134.79 (C_{ar}), 128.86 (CH_{ar}), 127.67 (CH_{ar}), 54.65 (CH_2).

HR-MS (m/z): fragments at m/z 237, 222, 209, 194.

Synthesis of 4,4’-bis(aminomethyl)biphenyl[2]

A solution of 4,4'-bis(azidomethyl)biphenyl (1.06 g, 4.00 mmol) in absolute EtOH (150 mL) was degassed and then hydrogenated in the presence of Pd/C (20%, 80 mg) under 1 atm of H_2 for 6 h at room temperature; the reaction progress was monitored by TLC (SiO_2; eluent: CH_2Cl_2–7M NH_3 in MeOH, 9:1). After filtration and evaporation of the solvent, a white precipitate was isolated which was recrystallized from toluene. Yield 490 mg, 57%.

^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.57$ (d, $J = 8.2$ Hz, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 3.92 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 142.52$ (C_{ar}), 139.66 (C_{ar}), 127.67 (CH_{ar}), 127.34 (CH_{ar}), 46.38 (CH_2).

HR-MS (m/z): 212.1320 $[M]^+$, fragments at m/z 213, 211, 196.

Synthesis of $[(t\text{-}Bu)_2SiO_2B(p\text{-}C_6H_4CHO)]_2$ (1)

Synthesis by ball-milling

Di-*tert*-butylsilanediol (138 mg, 784 µmol) and 4-formylbenzeneboronic acid (117 mg, 784 µmol) were added to 5 ml grinding jar and ball-milled 2 x 45 min at 30 Hz. The resulting white solid was suspended in diethyl ether (5 ml) and the pure product was obtained after centrifugation and filtration. Yield: 0.30 g; 75%.

Synthesis in solution

A solution of di-*tert*-butylsilanediol (138 mg, 784 µmol) and 4-formylbenzeneboronic acid (117 mg, 784 µmol) in benzene or toluene (60 mL) was heated under reflux using a Dean-Stark trap for 12 h. The clear solution was concentrated by evaporation and from the concentrated solution white crystals of **1** appeared. Yield 0.30 g; 65%. Crystals suitable for X-ray diffraction were grown by slow evaporation of a solution of **1** in benzene.

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.14$ (s, 18H), 7.92 (d, $J = 8.1$ Hz, 2H), 8.08 (d, $J = 8$ Hz, 2H), 10.09 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 192.52$ (C=O), 138.30 (C_{ar}), 135.72 (CH_{ar}), 128.96 (CH_{ar}), 27.27 (CH_3), 20.32 ($C(CH_3)_3$).

^{29}Si NMR (79 MHz, $CDCl_3$, TMS) $\delta = -22.30$.

EI (m/z): 581 $[M+H]^+$

Anal. calcd. (%) for $C_{30}H_{46}B_2O_6Si_2$ (580.47): C 62.07, H 7.99, N 0.00; found: C 62.14, H 7.94, N 0.00.

FT-IR υ_{max}/cm^{-1}: 2934(s), 2859(s), 1706(s), 1565 (m), 1472(s), 1386(s), 1294(vs), 1202 (s), 1142(s), 1012(m), 823(vs), 730 (m), 662 (vs), 575(vs).

Synthesis of macrocycle 2

Synthesis by ball-milling

4,4'-Bis(aminomethyl)biphenyl (25 mg, 120 µmol), di-*tert*-butylsilanediol (41 mg, 240 µmol) and 4-formylbenzeneboronic acid (35 mg, 240 µmol) were added to a 5 ml grinding jar and ball-milled 2 x 45 min at 30 Hz. The resulting white solid was suspended in 3 ml of dry diethyl ether, centrifugated, decanted, and a white solid was obtained. Yield: 75 mg; 85%.

Synthesis in solution

Method A

A solution of 4,4'-bis(aminomethyl)biphenyl (25 mg, 120 μmol), di-*tert*-butylsilanediol (41 mg, 240 μmol) and 4-formylbenzeneboronic acid (35 mg, 240 μmol) in dry benzene (50 ml) was heated under reflux for 12 h using a Dean Stark trap. Subsequently, the solvent was removed under vacuum and the residue was suspended in diethyl ether, filtered and re-dissolved in dry chloroform (1 mL). Upon addition of hexane (100 mL), the product precipitated in the form of a white powder, which was isolated by filtration and dried under vacuum. Yield: 20 mg; 22%

Method B

A solution of 4,4'-bis(aminomethyl)biphenyl (25 mg, 120 μmol) and dialdehyde **1** (68 mg, 120 μmol) in dry benzene (50 ml) was heated under reflux for 12 h using a Dean Stark trap. Subsequently, the solvent was removed under vacuum and the residue was dissolved in dry chloroform (5 mL). Upon addition of hexane (100 mL), the product precipitated in the form of a white powder, which was isolated by filtration and dried under vacuum. Yield: 30mg; 33 %.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.49 – 7.38 (m, 2H), 4.89 (s, 2H), 1.12 (s, 18H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.20 (C=N), 139.91 (C_{ar}), 138.74 (C_{ar}), 138.51 (C_{ar}), 135.87 (C_{ar}), 135.76 (CH_{ar}), 128.50 (CH_{ar}), 127.81 (CH_{ar}), 127.38 (CH_{ar}), 64.99(CH_2), 27.45 ($\mathit{C}H_3$), 20.49($\mathit{C}(CH_3)_3$).

^{29}Si NMR (79 MHz, $CDCl_3$, TMS) $\delta = -23.26$.

ESI-MS (m/z): 568.58 $[M]^{4+}$, 757.75 $[M]^{3+}$, 1136.13 $[M]^{2+}$.

HR-MS (m/z): 2270.24 $[M]^+$.

Anal. calcd. (%) for $C_{132}H_{174}B_6N_6O_{12}Si_6$ (2270.20): C 69.83, H 7.72, N 3.70; found: C 69.53, H 7.62, N 3.59.

FT-IR υ_{max}/cm^{-1}: 2933(s), 2859(s), 1641(m), 1472(m), 1372(s), 1295(vs), 1138 (s), 1004(s), 828(vs), 802 (s), 664 (vs), 577(vs).

Synthesis of macrocycle 3

Synthesis by ball-milling

Di-*tert*-butylsilanediol (62.5 mg, 35.5 μmol), 4-formylbenzeneboronic acid (53 mg, 35.5 μmol) and *trans*-(*1R,2R)*-1,2-diaminocyclohexane (20 mg, 17.5 μmol) were added to 5 ml grinding jar and ball-milled 2 x 45 min at 30 Hz. The resulting pale yellow solid was dissolved in minimum amount of dichloromethane and hexane was added until a white product formed, which was filtered. Yield: 150 mg; 65%.

Synthesis in solution

A solution of *trans*-(*1R,2R)*-1,2-diaminocyclohexane (8 mg, 75 µmol) and dialdehyde **1** (43.5 mg, 75 µmol) in dry dichloromethane (1.7 mL) was stirred at room temperature for 2 h under inert atmosphere. The solution was concentrated and the pure compound can be isolated as a white solid by precipitation with hexane. Yield: 23 mg, 50%.

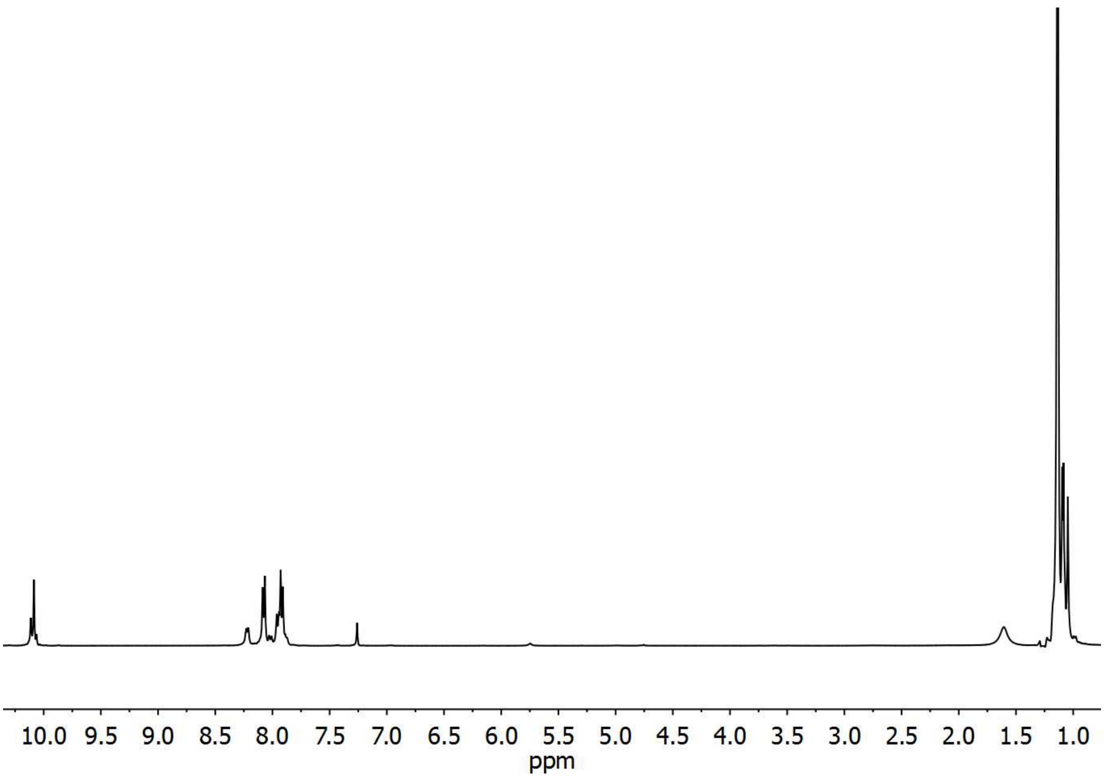
^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.31$ (s, 2H), 7.86 (d, $J = 7.7$ Hz, 4H), 7.64 (d, $J = 7.8$ Hz, 4H), 3.50 – 3.46 (m, 2H), 1.78 (br, 6H), 1.51 (br, 2H), 1.04 (s, 36H).

^{13}C NMR (100 MHz, CD_2Cl_2) $\delta = 160.60$ (C=N), 139.25 (C_{ar}), 135.91 (CH_{ar}), 127.51 (CH_{ar}), 75.07 (CH=N), 33.40 (CH_2), 27.43 (CH_3), 24.95 (CH_2), 20.53 ($C(CH_3)_3$).

^{29}Si NMR (79 MHz, $CDCl_3$, TMS) $\delta = -22.33$.

ESI-MS (m/z): 1976.2 $[M]^+$.

Anal. calcd. (%) for $C_{108}H_{168}B_6N_6O_{12}Si_6$ (1975.90): C 65.61, H 8.57, N 4.25; found: C 65.09, H 8.63, N 4.16.



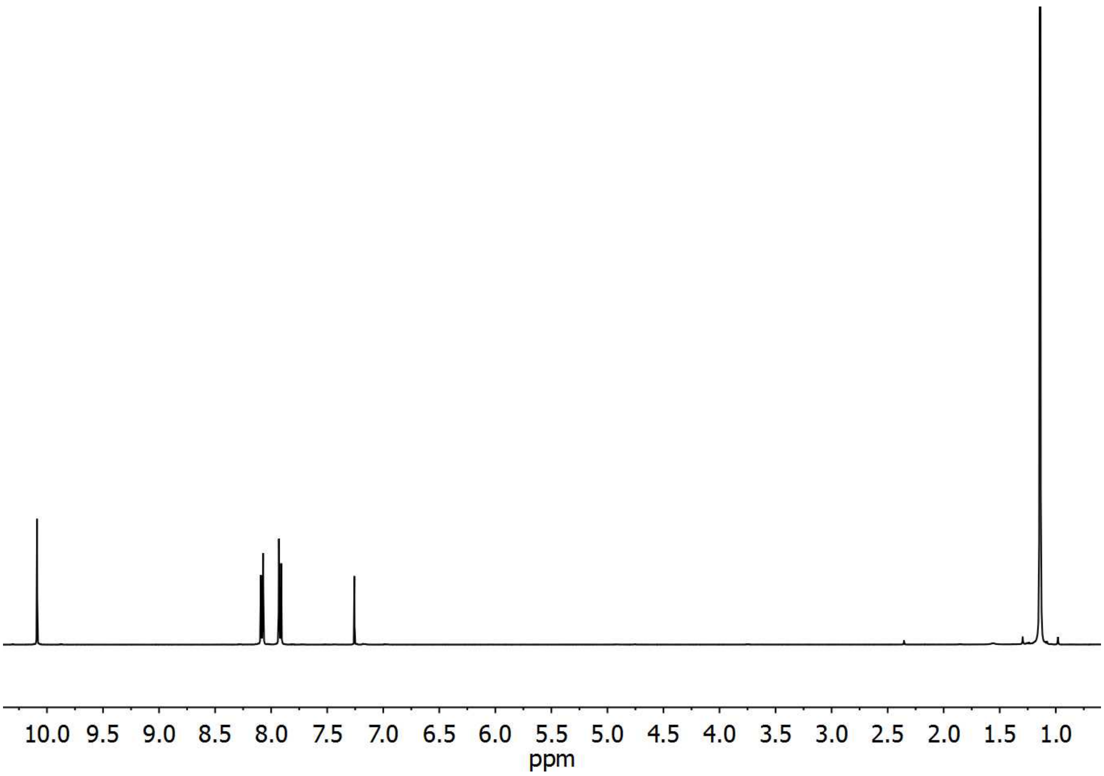


Figure S1: Borasiloxane **1**: ^{1}H NMR ($CDCl_3$) spectra of the material obtained after ball-milling di-*tert*-butylsilanediol and 4-formylbenzeneboronic acid for 90 min at 30 Hz (top), and after washing with diethyl ether (bottom).

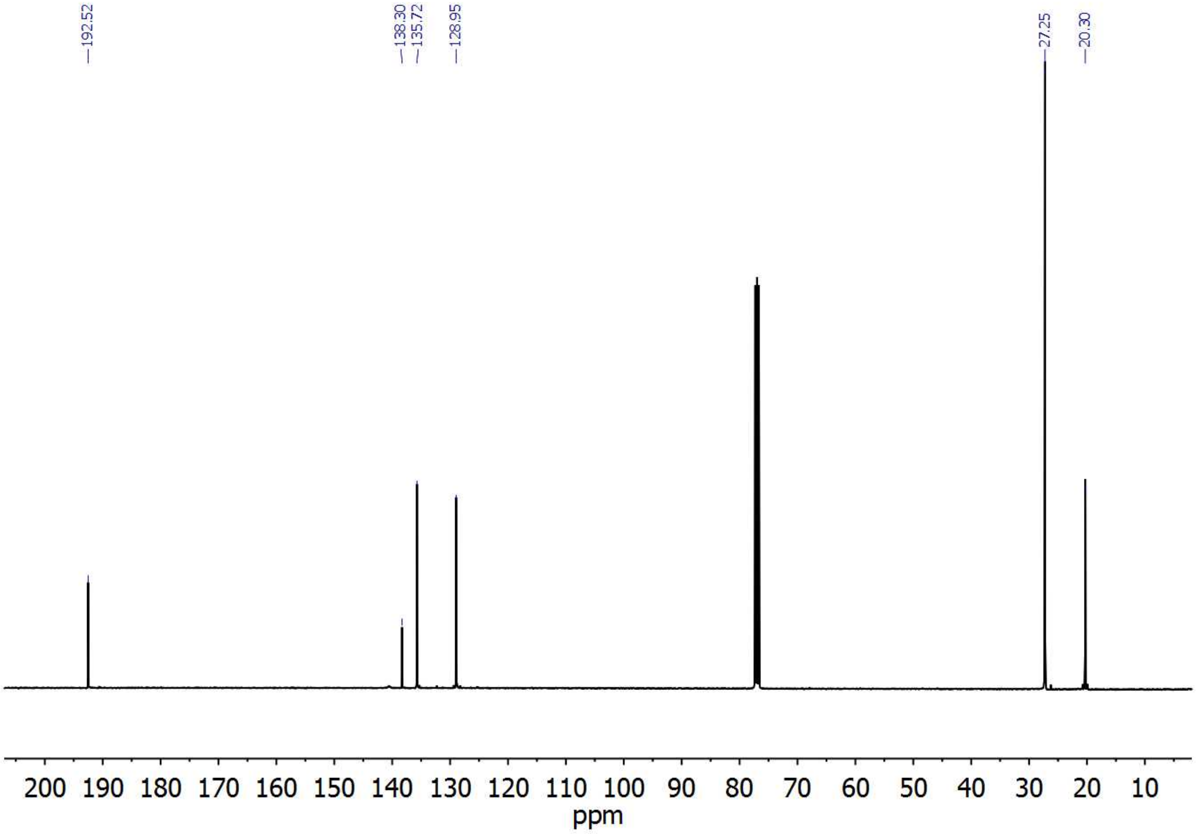


Figure S2: ^{13}C NMR ($CDCl_3$) spectrum of aldehyde **1**.

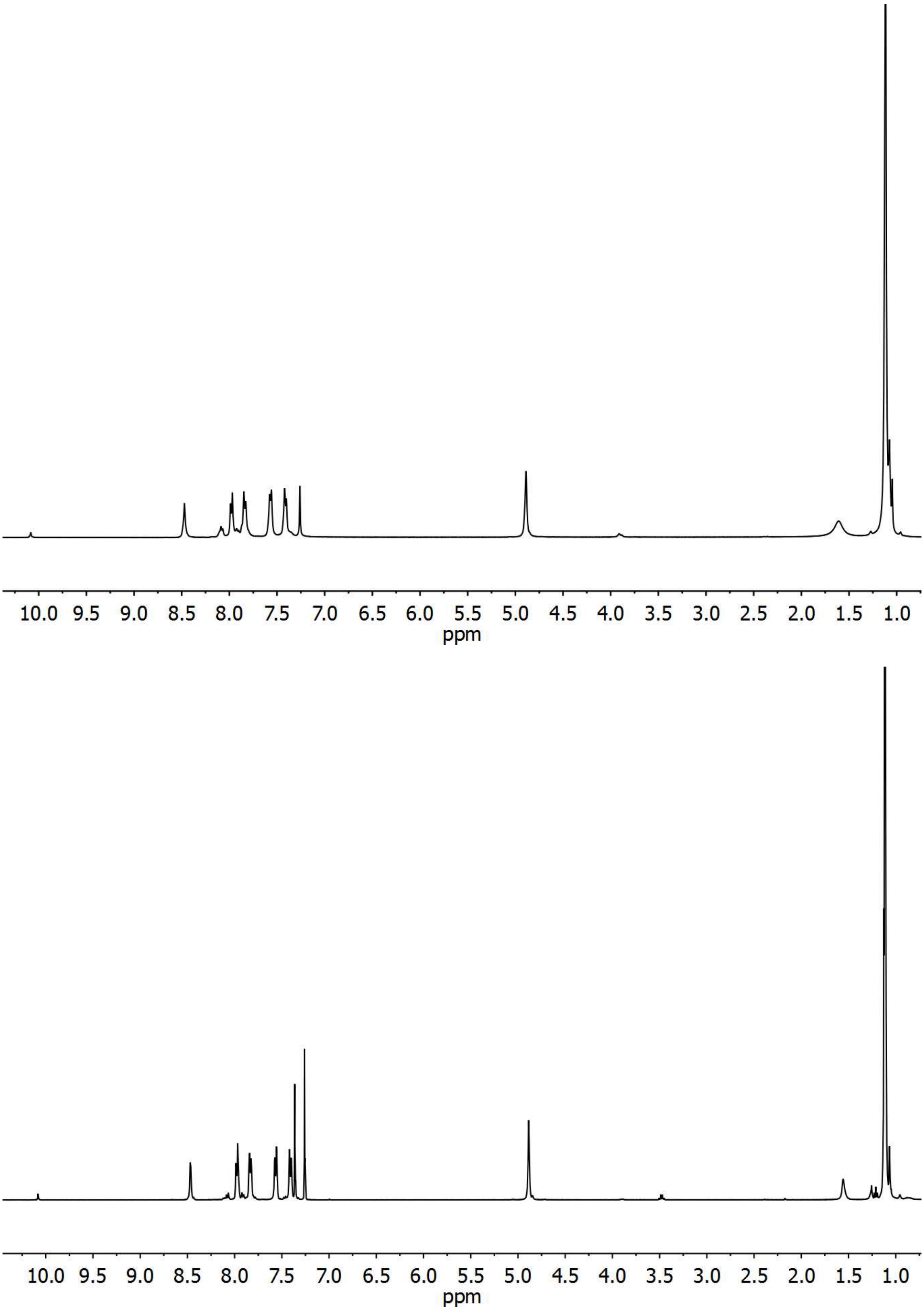


Figure S3: Macrocycle **2**: ^{1}H NMR ($CDCl_3$) spectrum of the material obtained after ball-milling 4,4’-bis(aminomethyl)biphenyl, di-*tert*-butylsilanediol and 4-formylbenzeneboronic acid for 90 min at 30 Hz (top), and the spectrum of the material obtained after heating a solution of 4,4’-bis(aminomethyl)biphenyl and dialdehyde **1** in benzene under reflux for 12 h (bottom).

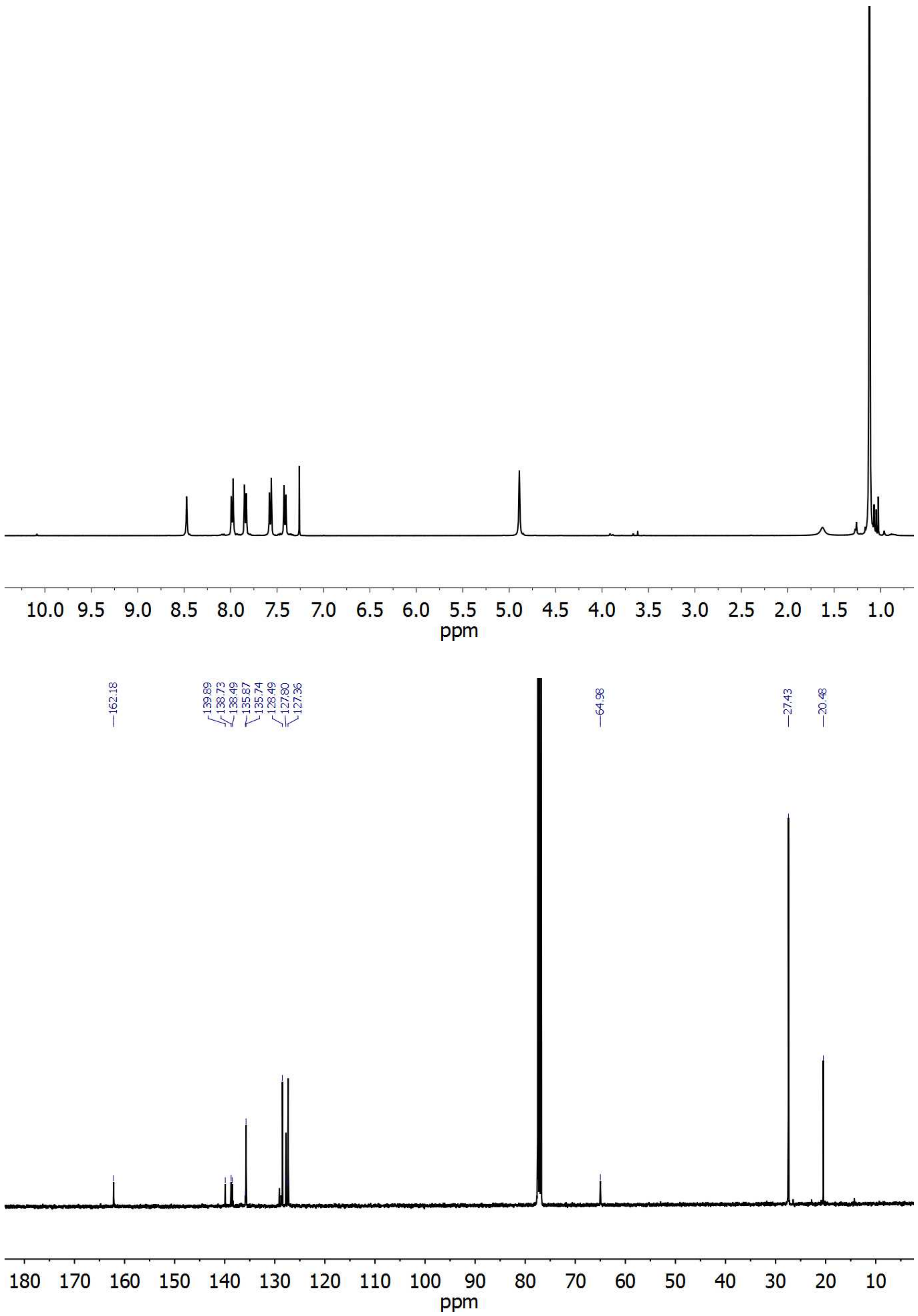
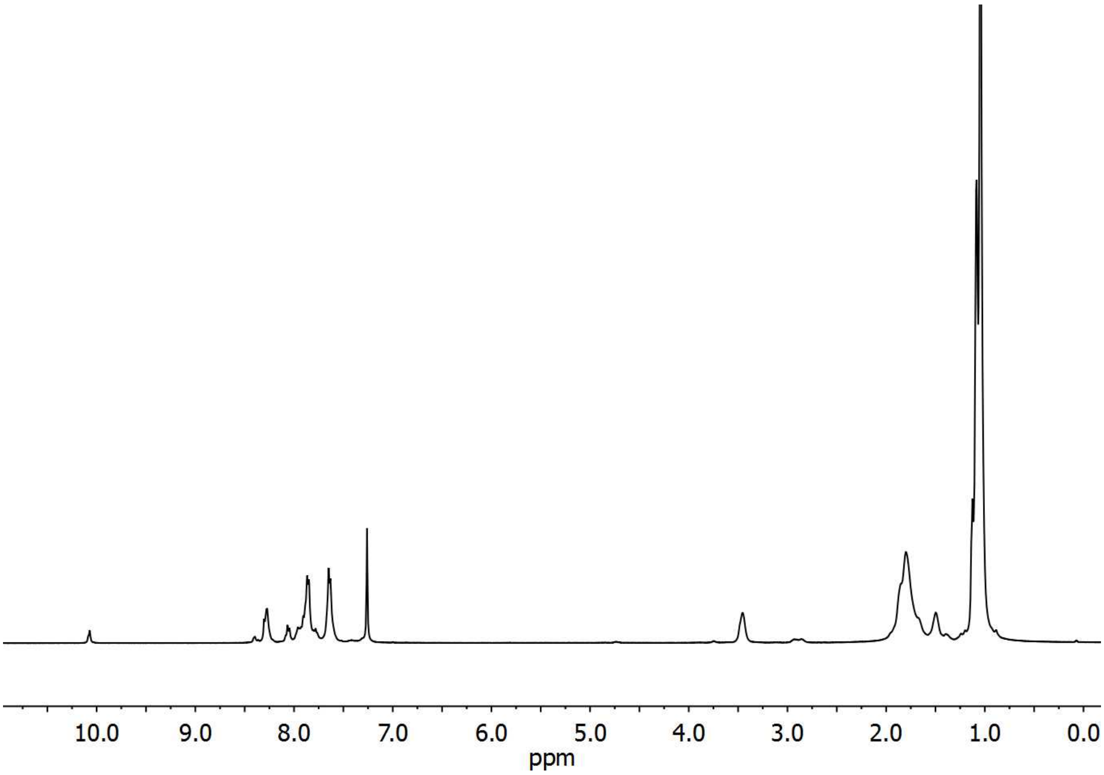


Figure S4: ^1H and ^{13}C NMR ($CDCl_3$) spectra of macrocycle **2** after purification by recrystallization.



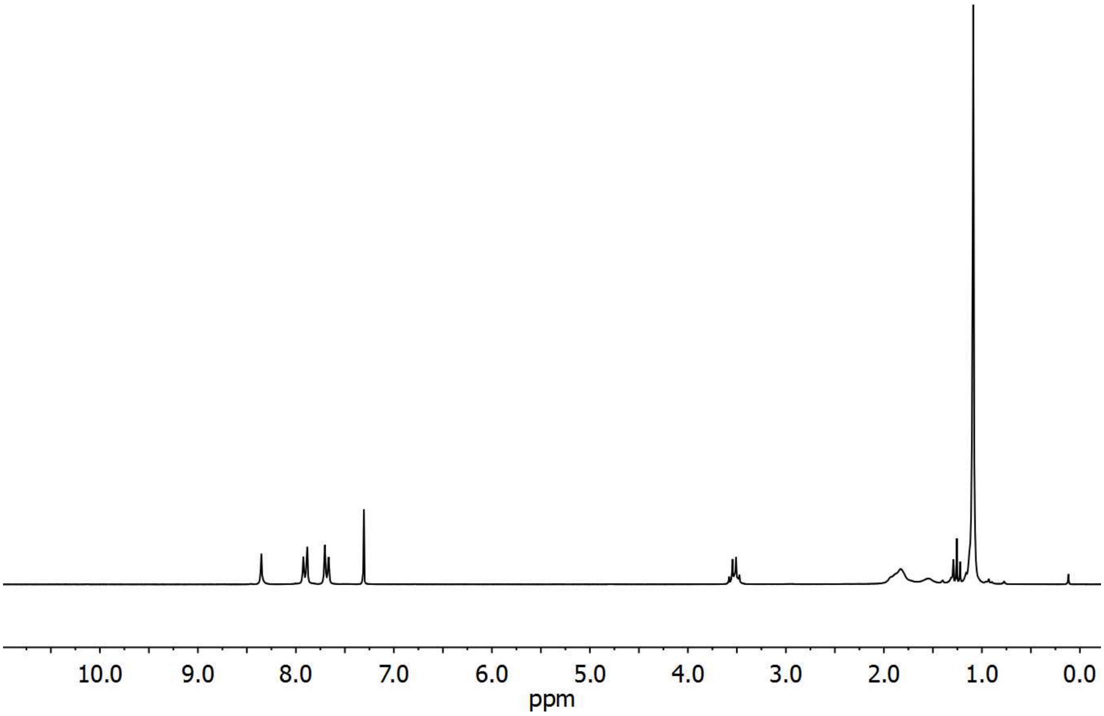


Figure S5: Macrocycle **3**: ^{1}H NMR ($CDCl_3$) spectrum of the material obtained after ball-milling di-*tert*-butylsilanediol, 4-formylbenzeneboronic acid and *trans*-(*1R,2R)*-1,2-diaminocyclohexane for 90 min at 30 Hz (top), and of macrocycle **3** after purification by recrystallization (bottom).

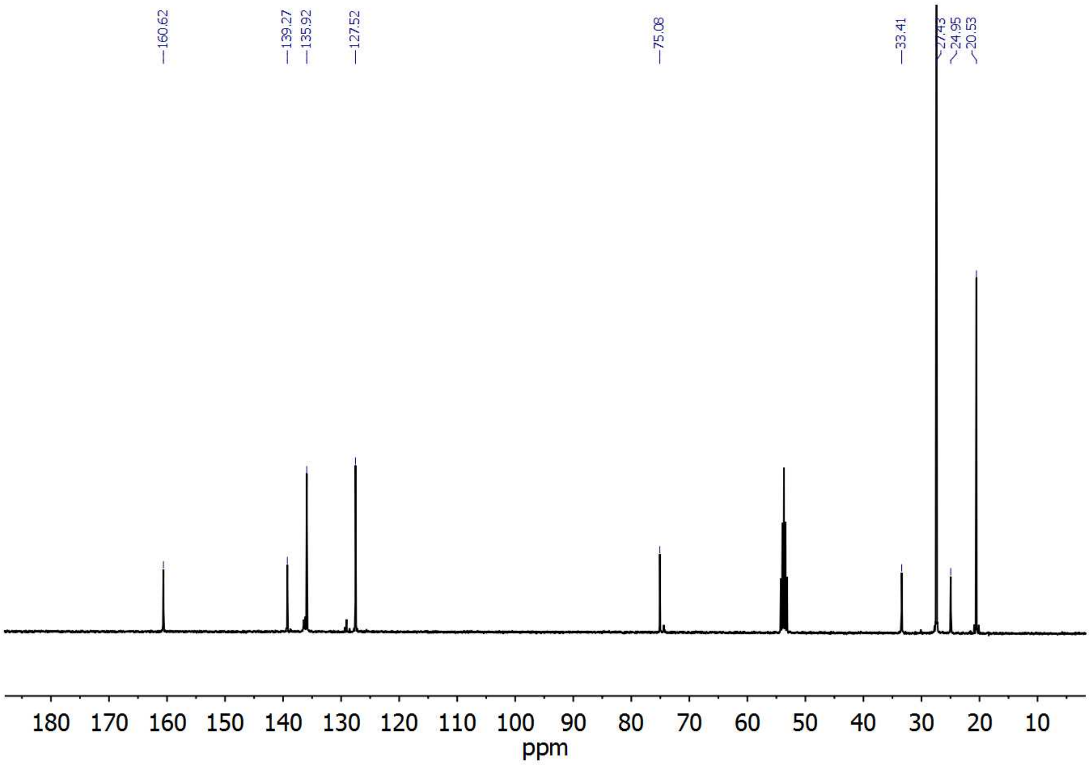


Figure S6: ^{13}C NMR ($CDCl_3$) spectra of macrocycle **3**.

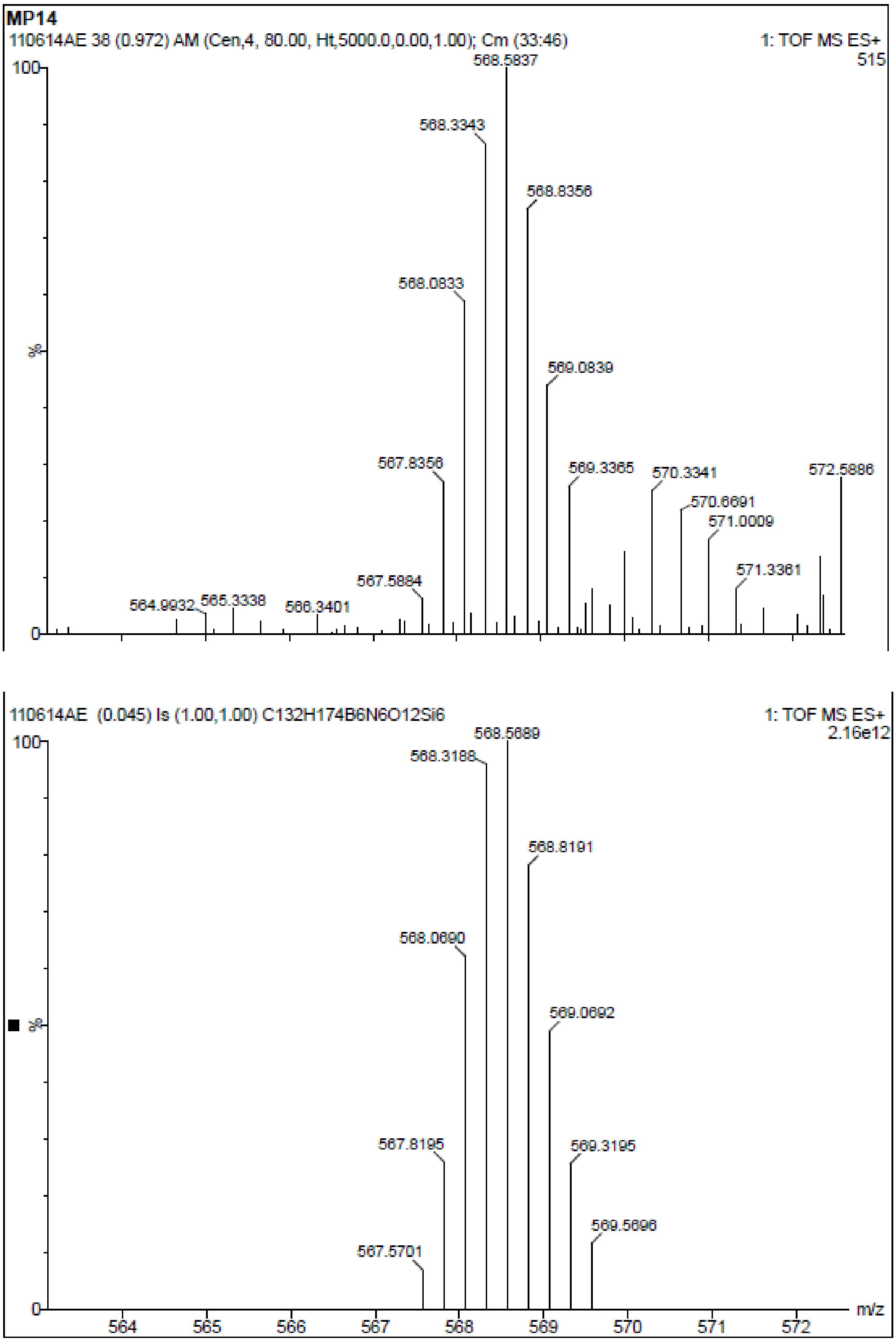


Figure S7: Part of the ESI+ mass-spectrum of macrocycle **2** (top) and calculated isotopic distribution of the 4+ charged species (bottom).

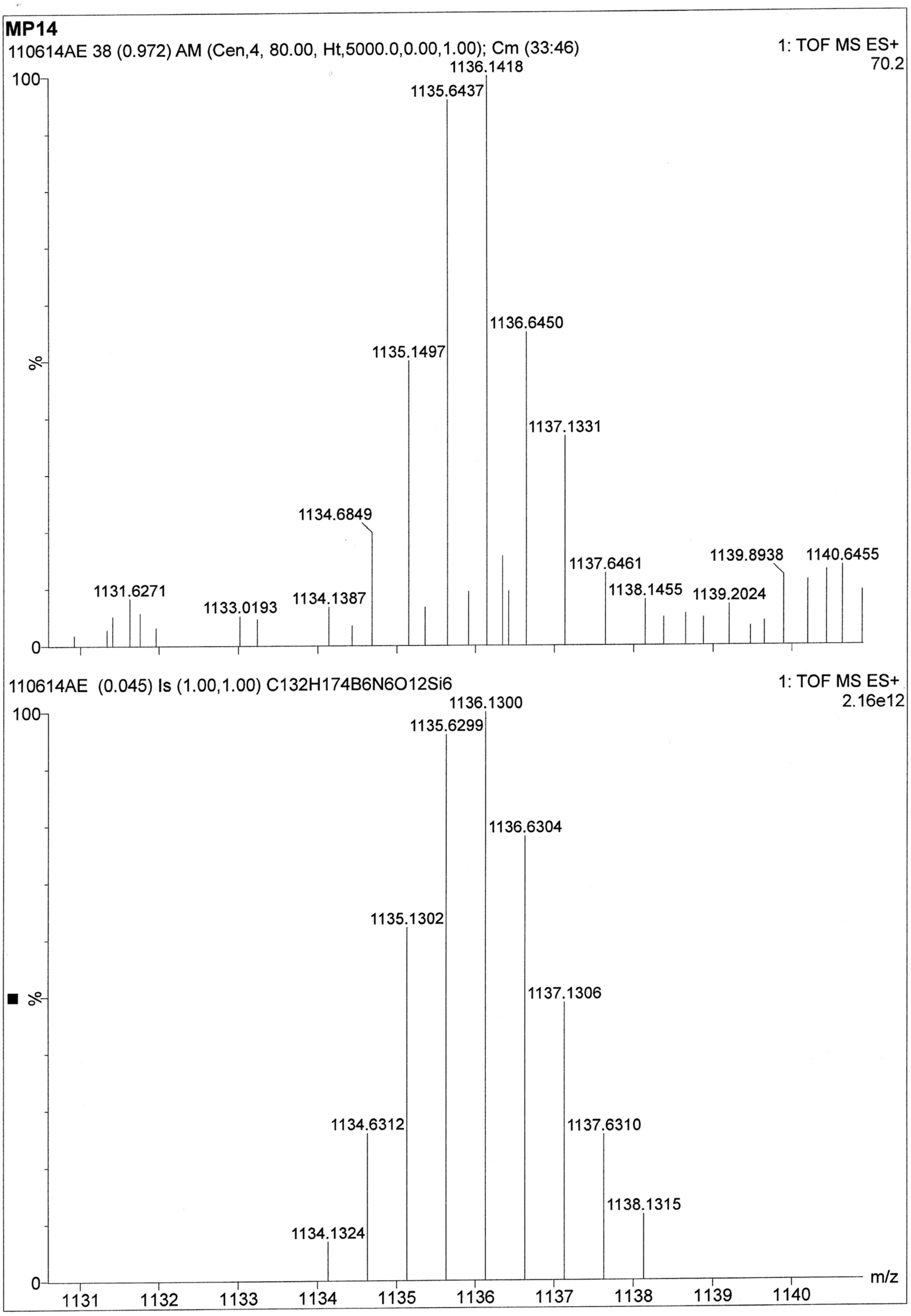


Figure S8: Part of the ESI+ mass-spectrum of macrocycle **2** (top) and calculated isotopic distribution of 2+ charged species (bottom).

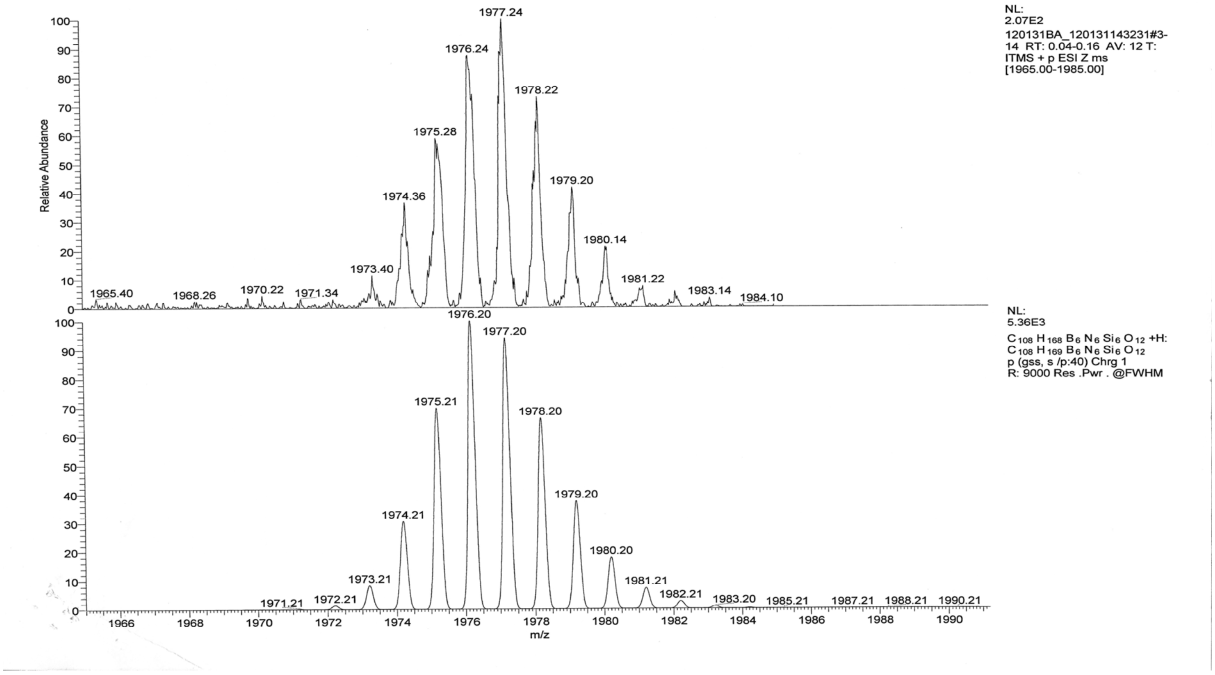


Figure S9: Part of the ESI+ mass-spectrum of macrocycle **3** (top) and calculated isotopic distribution of 1+ charged species (bottom).

3. Computational Modeling

Computational models were obtained by conformational search with molecular mechanics (MMFF force field) and subsequent minimization of the lowest energy conformer by using a Restricted Hartree Fock (RHF) method with a 3-21G* basis set implemented in the software Spartan '10 (v. 1.1.0, demo version).[3] Five minimized conformers were analyzed for each molecule. The computational method was validated by using the crystal structure of **1** as benchmark, comparing the calculated geometrical properties with the experimental data obtained from X-ray diffractometry. The differences between calculated and experimental values were around ±1%.

4. Crystallographic Analyses

The diffraction data of compound **1** were measured at low temperature [100(2) K] using Mo K_α radiation on a Bruker APEX II CCD diffractometer equipped with a kappa geometry goniometer. The datasets were reduced by EvalCCD[4] and then corrected for absorption.[5] A summary of the crystallographic data, the data collection parameters, and the refinement parameters are given in Table S1. The solution and refinement were performed by SHELX.[6] The crystal structure was refined using full-matrix least-squares based on F^2 with all non hydrogen atoms anisotropically defined. Hydrogen atoms were placed in calculated positions by means of the "riding" model.

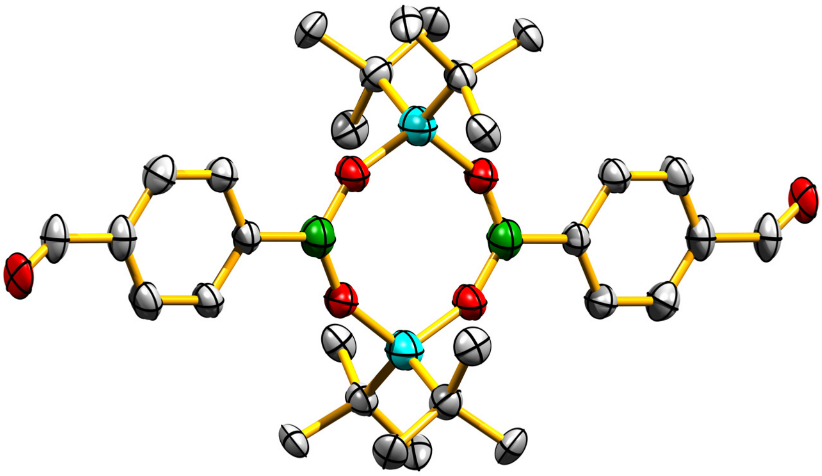


Figure S7. Molecular structure of borasiloxane **1** in the crystal. Hydrogen atoms are omitted for clarity.

Table S1. Crystallographic data for **1**.

	1	
Empirical formula	$C_{30}H_{46}B_2O_6Si_2$	
Formula weight	580.47	
Temperature /K	100(2)	
Wavelength / Å	0.71073	
Crystal system	triclinic	
Space group	*P*-1	
Unit cell dimensions	a = 8.4713(9) Å	α= 109.911(7)°
	b = 10.5851(7) Å	β= 94.902(8)°
	c = 10.6720(11) Å	γ= 109.903(7)°
Volume / $Å^3$	823.76(13)	
Z	1	
Calculated density/ g cm^{-3}	1.170	
Absorption coefficient / mm^{-1}	0.146	
F(000)	312	
Crystal size / mm	0.26 x 0.20 x 0.09	
Measured θ range / ^{o}	3.23 to 27.50	
Index ranges	$-11 \leq h \leq 11, -13 \leq k \leq 13, -13 \leq l \leq 13$	
Reflections collected / unique	10453 / 3753	
R_{int}	0.0353	
Data / restraints / parameters	3753 / 330 / 230	
Goodness-of-fit on F^2	1.096	
Final *R* indices [I>2sigma(I)]	R_1 = 0.0485, wR_2 = 0.1089	
R indices (all data)	R_1 = 0.0682, wR_2 = 0.1194	

10. References

[1] P. D. George, L. H. Sommer and F. C. Whitmore, *J. Am. Chem. Soc.*, 1953, **75**, 1585.

[2] J. C. Rosa, D. Galanakis, A. Piergentili, K. Bhandari, C. R. Ganellin, P. M. Dunn and D. H. Jenkinson, *J. Med. Chem.*, 2000, **43**, 420.

[2] *SPARTAN '10*, Wavefunction, Inc., Irvine (CA), USA, 2011.

[3] A. J. M. Duisenberg, L. M. J. Kroon-Batenburg and A. M. M. Schreurs, *J. Appl. Crystallogr.*, 2003, **36**, 220.

[4] R. H. Blessing, *Acta Crystallogr., Sect. A*, 1995, **51**, 33.

[5] *SHELX*, G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112.