Electronic Supplementary Information

Cyclic and acyclic acetals as safe, nonaqueous formaldehyde equivalents for the synthesis of pillararenes

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1. General Methods

1,2-Dichloroethane (DCE), 1,2-dichlorobenzene (*o*-DCB) and boron trifluoride etherate ($BF_3{\cdot}OEt_2$) were purchased from Beantown Chemicals. Dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), ethyl acetate (EtOAc) and hexanes (Hex) were purchased from VWR. 1,4-Diethoxybenzene (DEB), diethoxymethane (DEM), dimethoxymethane, 1,3-dioxolane, chlorocyclohexane and 1,3,5-trioxane were purchased from Thermo Scientific Chemicals. All commercially available materials were used as received without further purification.

Compounds were characterized by ^1H and ^{13}C nuclear magnetic resonance (NMR), and mass spectrometry. NMR spectra were obtained on a Bruker 300 MHz and 400 MHz spectrometer. Chemical shifts (δ) in ^1H NMR were reported in parts per million (ppm) relative to residual proton signals in $CDCl_3$ (7.26 ppm) at room temperature. Chemical shifts (δ) in ^{13}C NMR were reported in parts per million (ppm) relative to residual proton signals in $CDCl_3$ (77.2 ppm) at room temperature. NMR splitting parameters are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. MALDI-TOF mass spectra were acquired using Bruker Daltonics - Ultraflex II MALDI TOF/TOF.

2. Experimental Methods

2.1. General Method A for Catalyst Screening

To a solution of 1,4-diethoxybenzene (5.00 mmol, 1 equiv) and diethoxymethane (6.25 mmol, 1.25 equiv) in CH_2Cl_2 (100 mL), the appropriate acid catalyst was added all at once at room temperature. After 30 min, the reaction mixture was quenched and washed with 0.1 M NaOH (aq) solution (3 × 200 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was adsorbed onto silica gel and the product was purified by column chromatography to give ethoxypillar[5]arene, EtO-PA[5] (eluent: CH_2Cl_2:Hex - 1:3) and ethoxypillar[6]arene, EtO-PA[6] (eluent: CH_2Cl_2:Hex - 3:1) as white solids.

2.2. Experimental Methods for Solvent Screening

Ethoxypillararene Synthesis with DCE, CH_2Cl_2 and $CHCl_3$:

To a solution of 1,4-diethoxybenzene (5.00 mmol, 1 equiv) and diethoxymethane (6.25 mmol, 1.25 equiv) in chlorinated solvent (100 mL), $BF_3{\cdot}OEt_2$ (12.5 mmol, 2.5 equiv) was added all at once at room temperature. After 30 min, the reaction mixture was quenched and purified by general method A.

Ethoxypillararene Synthesis with o-DCB:

To a solution of 1,4-diethoxybenzene (5.00 mmol, 1 equiv) and diethoxymethane (6.25 mmol, 1.25 equiv) in *o*-DCB (100 mL), $BF_3{\cdot}OEt_2$ (12.5 mmol, 2.5 equiv) was added all at once at room temperature. After 30 min, the reaction mixture was quenched and washed with 0.1 M NaOH (aq) solution (3 × 200 mL). The organic layer was collected and dried over Na_2SO_4. The reaction mixture was loaded onto a silica gel column packed with hexane. The product was

purified by column chromatography to give 49% yield of EtO-PA[5] (eluent: CH_2Cl_2:Hex - 1:3) and 5% yield of EtO-PA[6] (eluent: CH_2Cl_2:Hex - 3:1) as white solids.

Ethoxypillararene Synthesis with Chlorocyclohexane:

To a solution of 1,4-diethoxybenzene (5.00 mmol, 1 equiv) and diethoxymethane (6.25 mmol, 1.25 equiv) in chlorocyclohexane (100 mL), $BF_3{\cdot}OEt_2$ (12.5 mmol, 2.5 equiv) was added all at once at room temperature. After 30 min, the reaction mixture was quenched with Et_3N (25 mmol). The reaction mixture was loaded onto a silica gel column packed with hexane. The product was purified by column chromatography to give 43% yield of EtO-PA[5] (CH_2Cl_2:Hex - 1:3) and 25% yield of EtO-PA[6] (eluent: CH_2Cl_2:Hex - 3:1) as white solids.

2.3. General Method for Acetal Screening

To a solution of 1,4-diethoxybenzene (5.00 mmol, 1 equiv) and acetal (6.25 mmol, 1.25 equiv) in DCE (100 mL), $BF_3{\cdot}OEt_2$ (12.5 mmol, 2.5 equiv) was added all at once at room temperature. The reaction mixture was quenched and purified by general method A.

2.4. Pillararene Synthesis from Other Arenes

Methoxypillar[5]arene Synthesis:

To a solution of 1,4-dimethoxybenzene (5.00 mmol, 1 equiv) and diethoxymethane (6.25 mmol, 1.25 equiv) in DCE (100 mL), $BF_3{\cdot}OEt_2$ (12.5 mmol, 2.5 equiv) was added all at once at room temperature. After 30 min, the reaction mixture was quenched and purified by general method A to give 87% yield of methoxypillar[5]arene, MeO-PA[5] (CH_2Cl_2:Hex - 1:1) as a white solid.

2-Bromoethoxypillar[5]arene Synthesis:

1,4-bis(2-bromoethoxy)benzene was synthesized according to literature procedures.[1] To a solution of 1,4-bis(2-bromoethoxy)benzene (0.50 mmol, 1 equiv) and diethoxymethane (0.625 mmol, 1.25 equiv) in DCE (2.2 mL), $BF_3{\cdot}OEt_2$ (1.25 mmol, 2.5 equiv) was added all at once at 70° C. After 30 min, the reaction mixture was quenched and purified by general method A to give 60% yield of 2-bromoethoxypillar[5]arene, Br-PA[5] (CH_2Cl_2:Hex - 2:1) as a white solid.

3. Pillararene Formation Using Different Forms of Paraformaldehyde

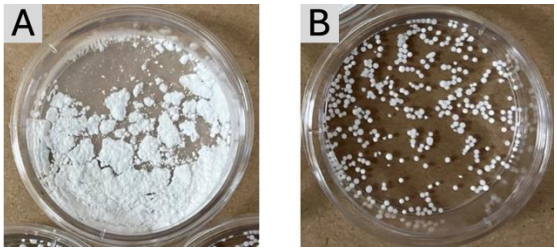

Figure S1. Photo of crystalline paraformaldehyde (A) and paraformaldehyde prills (B) taken inside a fume hood. Samples were placed inside a transparent, closed container.

Table S1. Dependence of pillar[n]arene synthesis in DCE on the form of paraformaldehyde.

Entry	1,4-Dimethoxybenzene (equiv)	Paraformaldehyde (equiv)	$BF_3{\cdot}OEt_2$ (equiv)	Product
1	1.0	3.0 (crystalline)	1.0	63% Methoxypillar[5]arene
2	1.0	3.0 (prill)	1.0	Mostly unreacted 1,4-dimethoxybenzene and insoluble linear oligomers

4. NMR Data

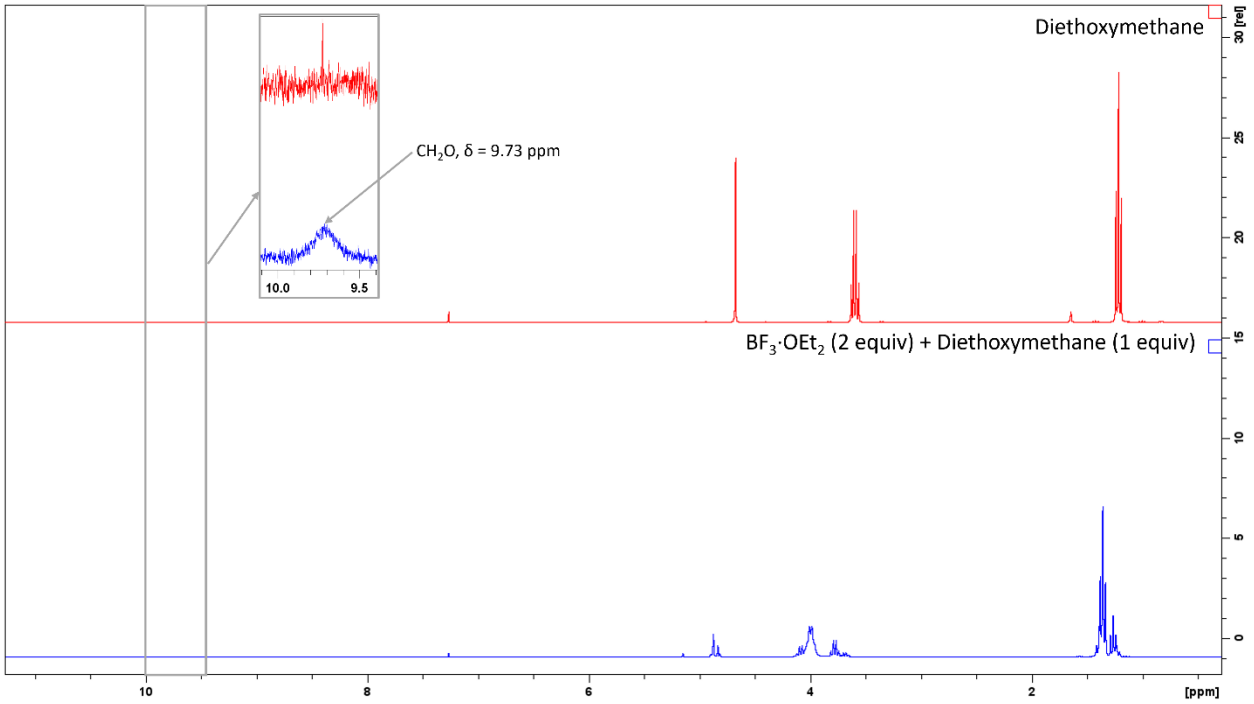

Figure S2. Stacked ^1H NMR spectra of diethoxymethane in $CDCl_3$ and a sample with 2 equiv of $BF_3{\cdot}OEt_2$ added to diethoxymethane in $CDCl_3$.

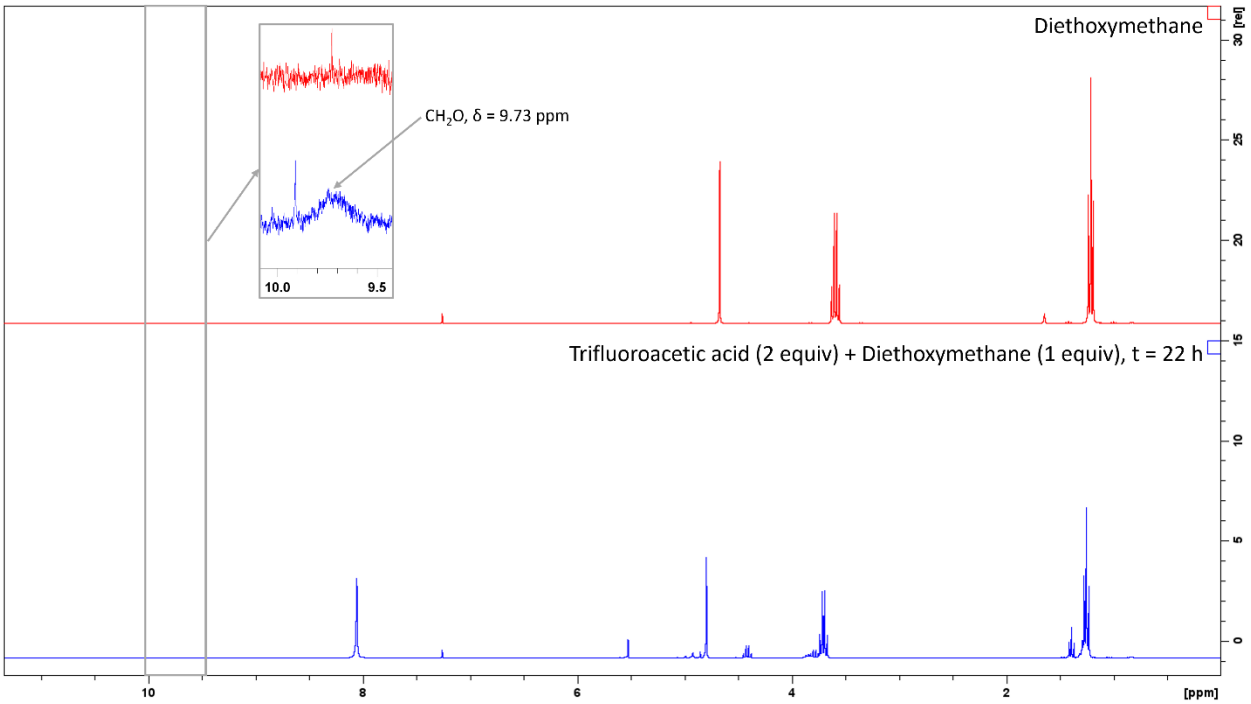

Figure S3. Stacked ^{1}H NMR spectra of diethoxymethane in $CDCl_3$ and a sample with 2 equiv of trifluoroacetic acid added to diethoxymethane in $CDCl_3$ measured 22 h after addition.

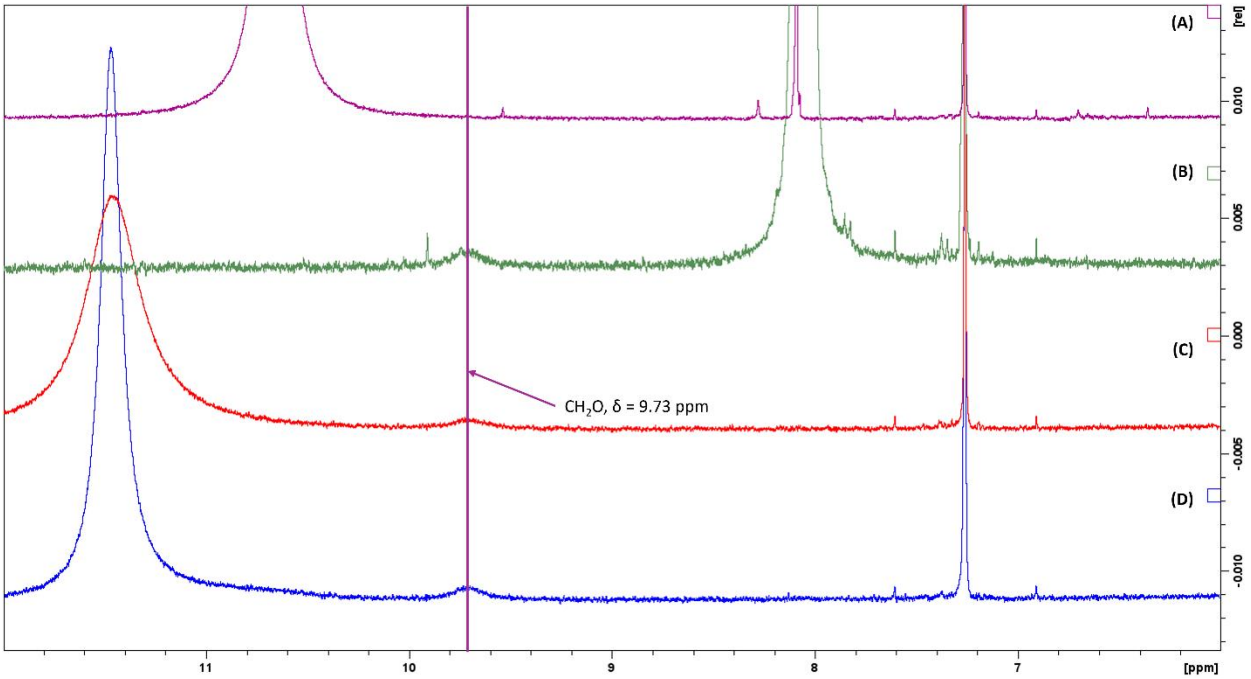

Figure S4. Stacked ^{1}H NMR spectra of (A) a sample with 2 equiv of $BF_3{\cdot}OEt_2$ added to 1,3-dioxolane in $CDCl_3$ measured 23 h after addition, (B) a sample with 2 equiv of trifluoroacetic acid added to diethoxymethane in $CDCl_3$ measured 22 h after addition, (C) a sample with 2 equiv of $BF_3{\cdot}OEt_2$ added to dimethoxymethane in $CDCl_3$ and (D) a sample with 2 equiv of $BF_3{\cdot}OEt_2$ added to diethoxymethane in $CDCl_3$.

Ethoxypillar[5]arene (EtO-PA[5])

^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm) 1.36 (t, 30H, *J* = 7.0 Hz), 3.77 (s, 10H), 3.88 (q, 20H, *J* = 7.0 Hz), 6.81 (s, 10H). ^{13}C NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm) 149.8, 128.5, 114.6, 63.6, 29.6, 15.4. MALDI-TOF calculated for $C_{55}H_{70}NaO_{10}^{+}$ $[M+Na]^{+}$ 913.486, found 913.571. These spectral data match with the reported data.[2]

Ethoxypillar[6]arene (EtO-PA[6])

^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm) 1.29 (t, 36H, *J* = 7.0 Hz), 3.88 (m, 36H), 6.70 (s, 12H). ^{13}C NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm) 150.6, 128.0, 115.4, 64.1, 31.1, 15.3. MALDI-TOF calculated for $C_{66}H_{84}NaO_{12}^{+}$ $[M+Na]^{+}$ 1091.585, found 1091.684. These spectral data match with the reported data.[3]

Methoxypillar[5]arene (MeO-PA[5])

^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm) 3.70 (s, 30H), 3.79 (s, 10H), 6.83 (s, 10H). ^{13}C NMR (300 MHz, $CDCl_3$, 298 K) δ (ppm) 150.8, 128.3, 113.9, 55.8, 29.6. MALDI-TOF calculated for $C_{45}H_{50}NaO_{10}^{+}$ $[M+Na]^{+}$ 773.330, found 773.277. These spectral data match with the reported data.[4]

2-Bromoethoxypillar[5]arene (Br-PA[5])

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) 3.63 (t, 20H, *J* = 5.66 Hz), 3.85 (s, 10H), 4.23 (t, 20H, *J* = 5.66 Hz), 6.92 (s, 10H). ^{13}C NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) 149.8, 129.2, 116.3, 69.1, 30.8, 29.6. MALDI-TOF calculated for $C_{55}H_{60}Br_{10}NaO_{10}^{+}$ $[M+Na]^{+}$ 1702.582, found 1702.540. These spectral data match with the reported data.[5]

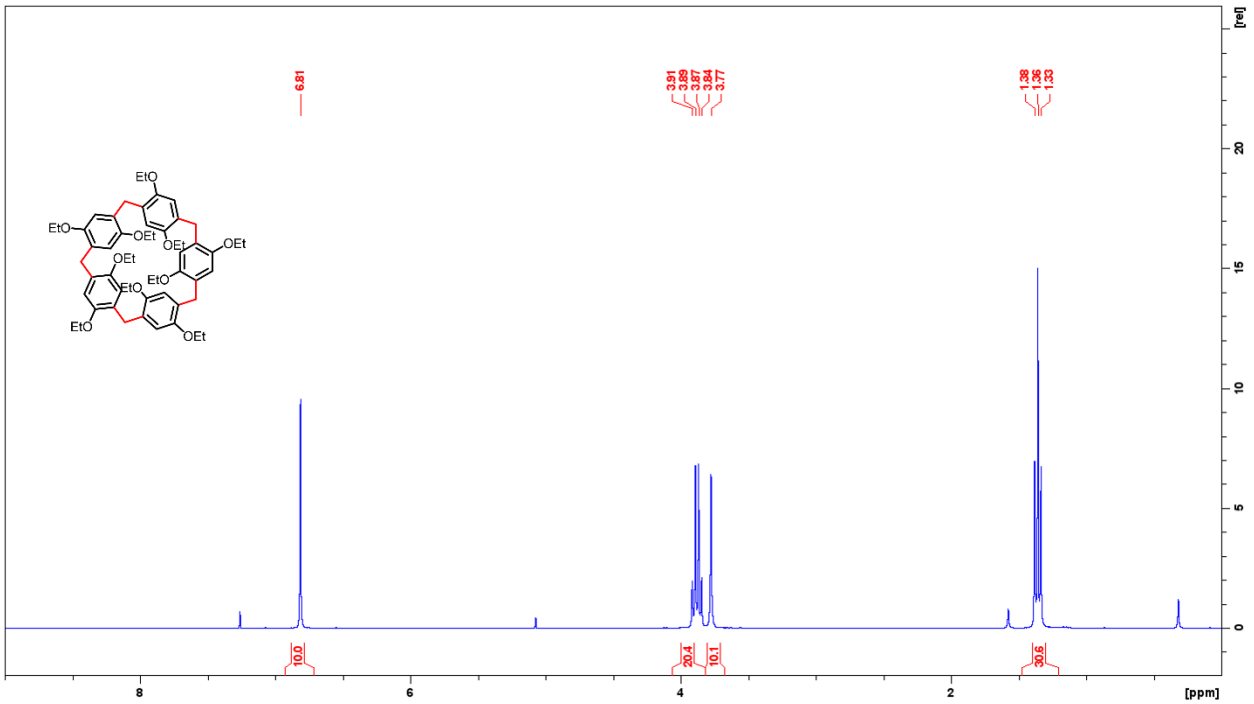

Figure S5. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, 298 K) of EtO-PA[5].

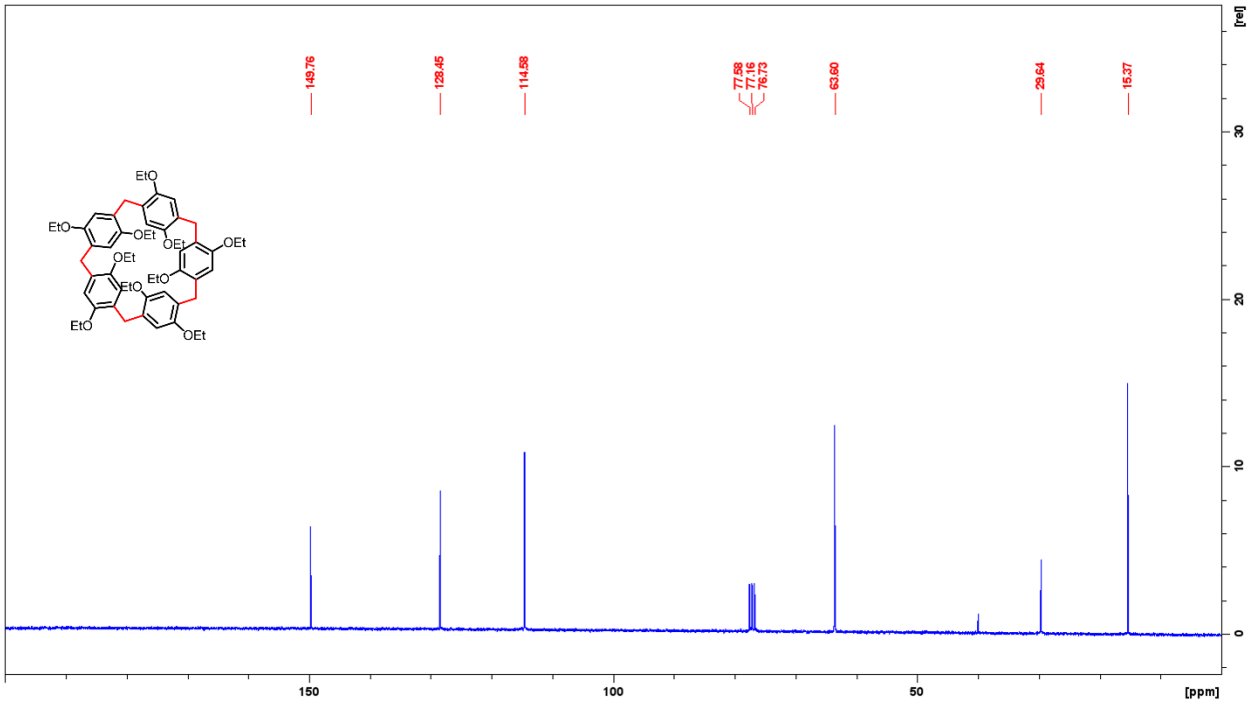

Figure S6. ^{13}C NMR spectrum (300 MHz, $CDCl_3$, 298 K) of EtO-PA[5].

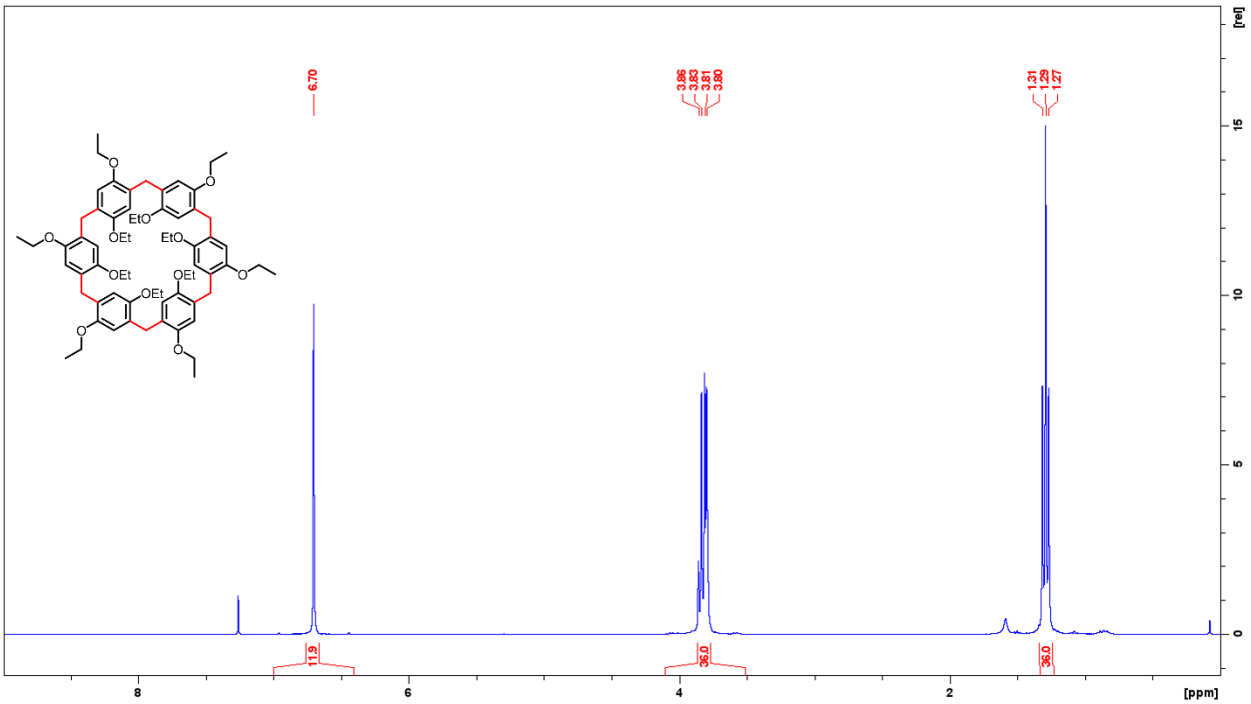

Figure S7. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, 298 K) of EtO-PA[6].

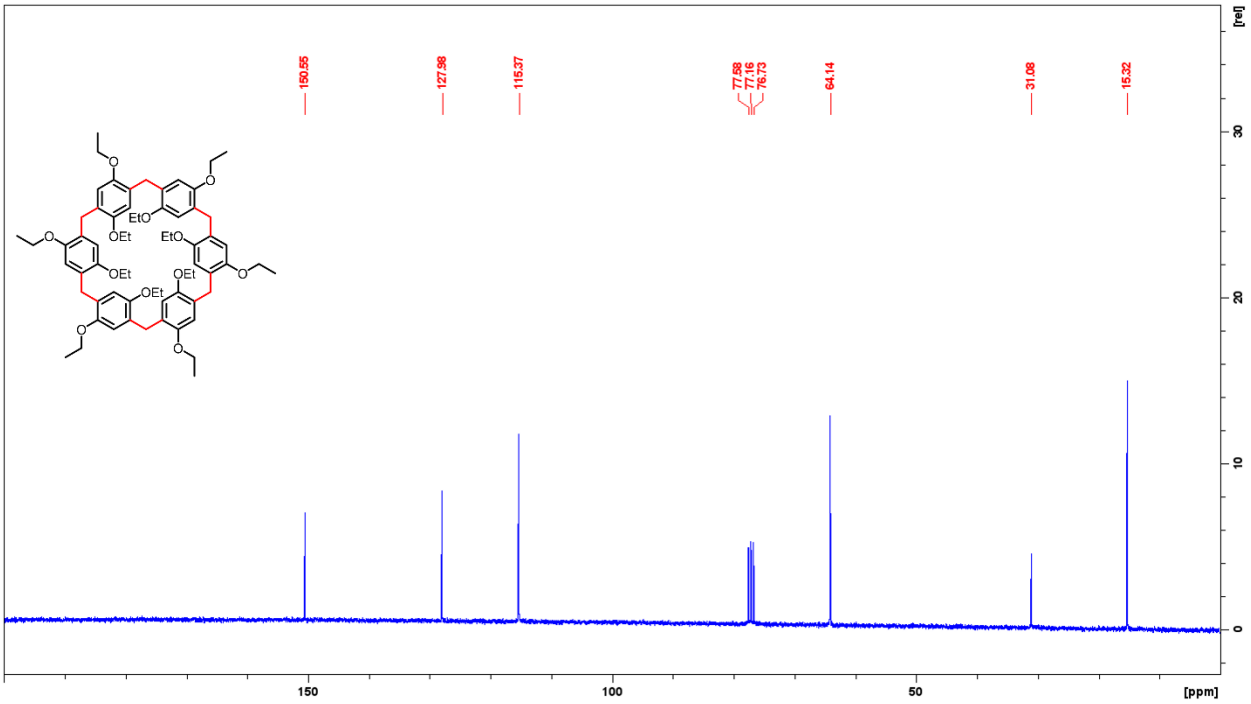

Figure S8. ^{13}C NMR spectrum (300 MHz, $CDCl_3$, 298 K) of EtO-PA[6].

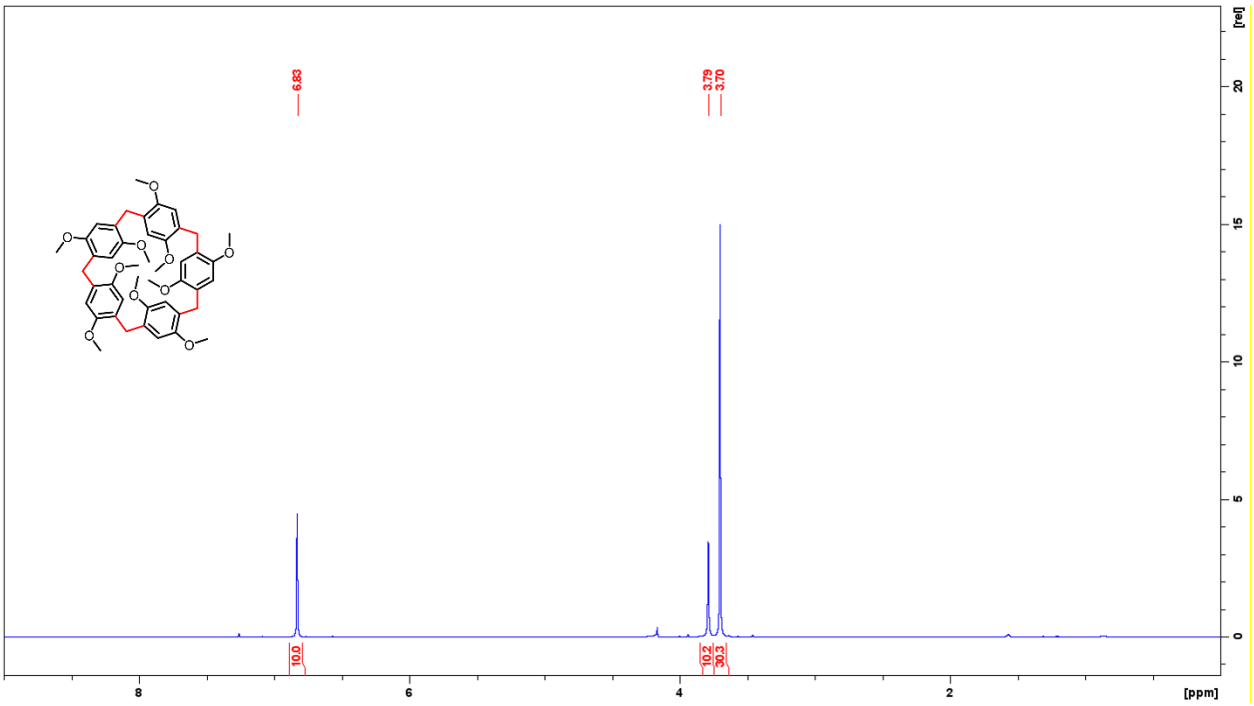

Figure S9. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, 298 K) of MeO-PA[5].

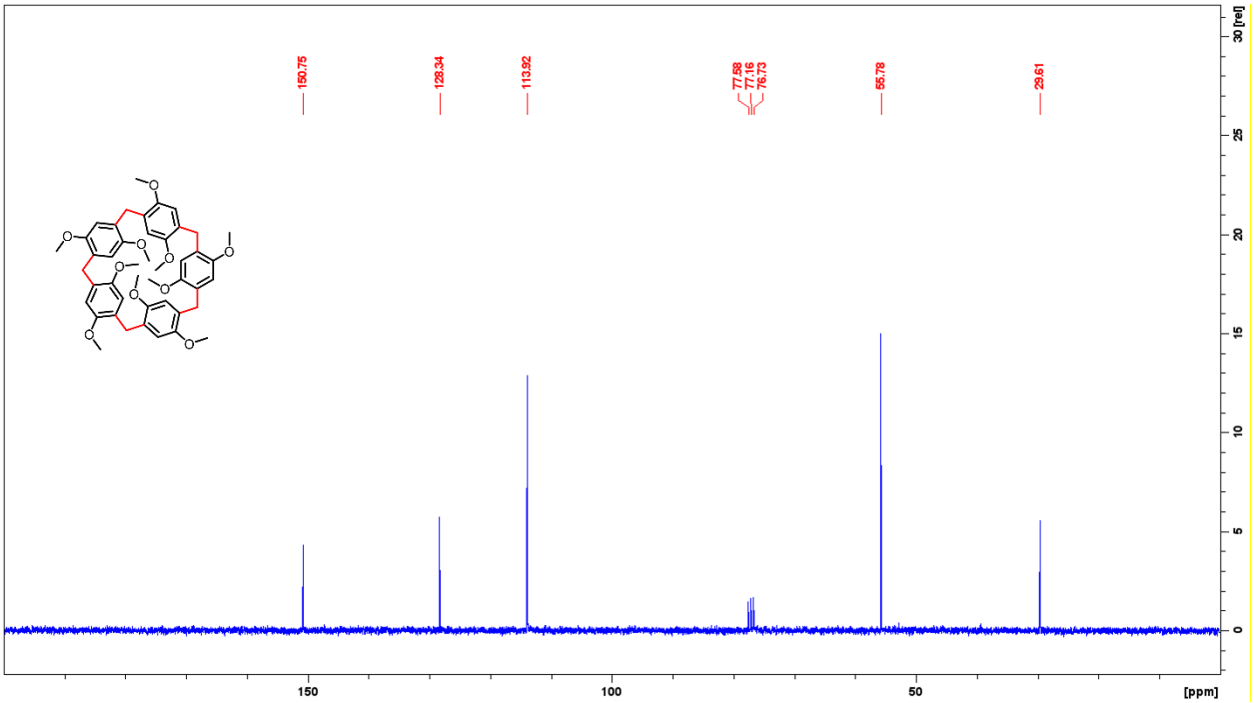

Figure S10. ^{13}C NMR spectrum (300 MHz, $CDCl_3$, 298 K) of MeO-PA[5].

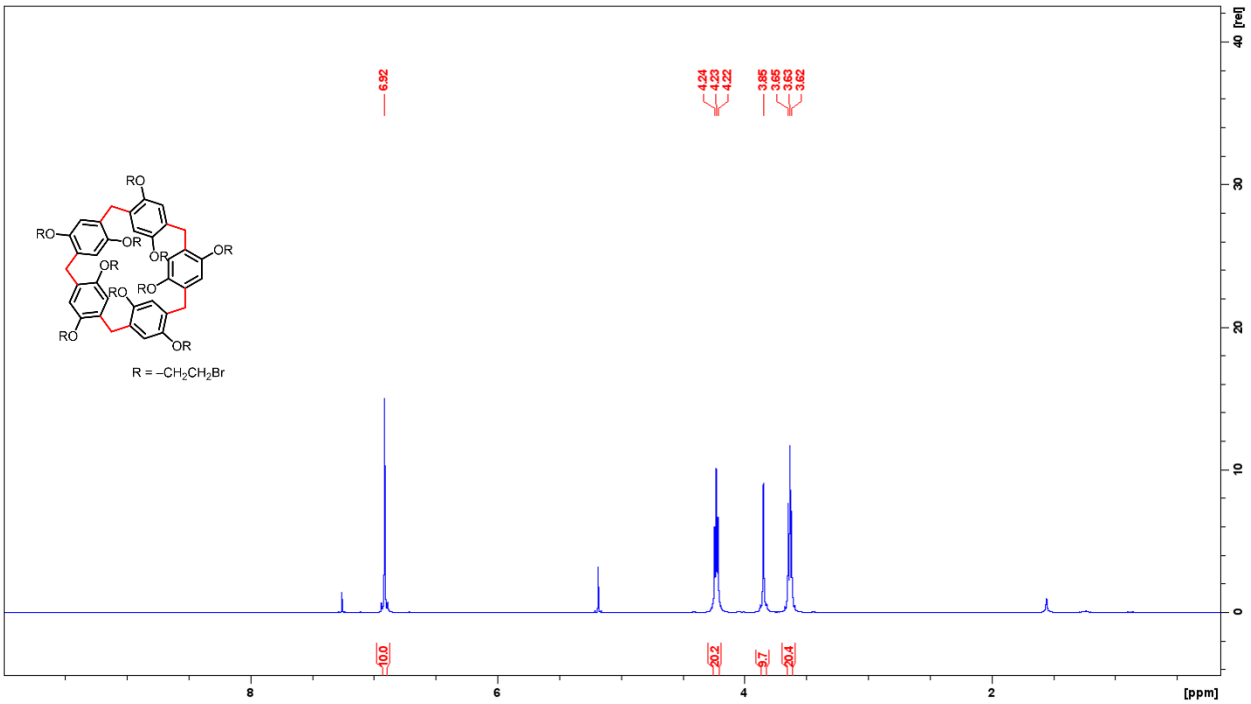

Figure S11. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of Br-PA[5].

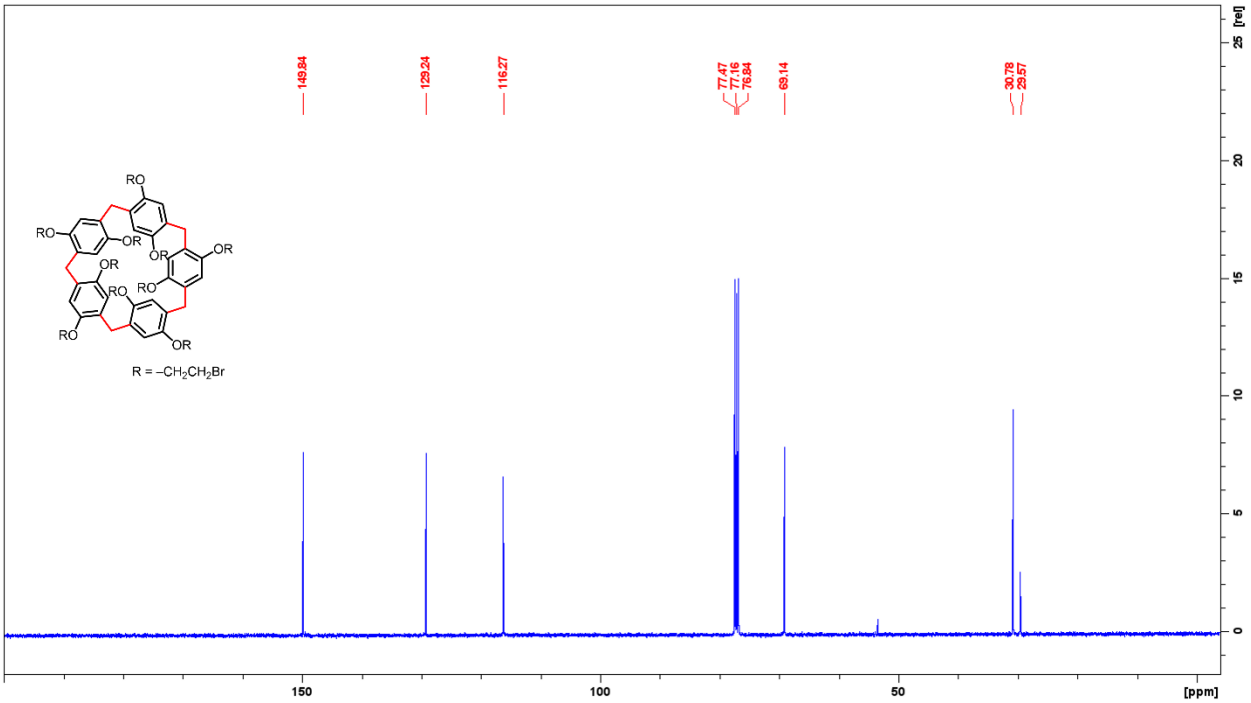

Figure S12. ^{13}C NMR spectrum (400 MHz, $CDCl_3$, 298 K) of Br-PA[5].

5. Pillararene Synthesis in $CHCl_3$ with Different Stabilizers

Table S2. Effect of stabilizer on the synthesis of ethoxypillar[n]arene in chloroform.

Entry	Equiv			Solvent	Yield
	DEB	DEM	$BF_3{\cdot}OEt_2$		
1	1.00	1.25	2.50	$CHCl_3$ (0.05 M), 1% ethanol stabilizer	68% DEB recovered, 14% mixture of EtO-PA[5] and EtO-PA[6]
2	1.00	1.25	2.50	$CHCl_3$ (0.05 M), amylene stabilizer	48% EtO-PA[5] and 6% EtO-PA[6]
3	1.00	1.25	2.50	$CHCl_3$ (0.05 M), amylene stabilizer and 1% of ethanol	94% DEB recovered

6. References

1. X. Tan, Y. Wu, S. Yu, T. Zhang, H. Tian, S. He, A. Zhao, Y. Chen and Q. Gou, *Talanta*, 2019, **195**, 472-479.
2. M. Da Pian, C. A. Schalley, F. Fabris and A. Scarso, *Org. Chem. Front.*, 2019, **6**, 1044-1051.
3. Chelsea R. Wilson, Evan F. W. Chen, Austia O. Puckett and F. Hof, *Org. Synth.*, 2022, ***99***, 125-138.
4. T. Boinski and A. Szumna, *Tetrahedron*, 2012, **68**, 9419-9422.
5. P. U. A. I. Fernando, Y. Shepelytskyi, P. T. Cesana, A. Wade, V. Grynko, A. M. Mendieta, L. E. Seveney, J. D. Brown, F. T. Hane, M. S. Albert and B. DeBoef, *ACS Omega*, 2020, **5**, 27783-27788.