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Synthesis and Conformational Properties of Nonsymmetric Pillar[5]arenes and Their Acetonitrile Inclusion Compounds

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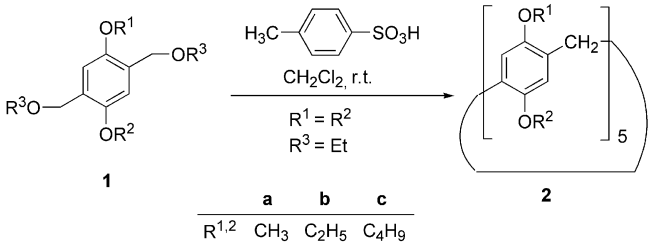
The catalytic cyclocondensation of 1-butoxy-4-methoxy-2,5-bis(methoxymethyl)benzene (**1d**) affords a statistical mixture of the regioisomeric pillar[5]arenes **3a–d** in high yield. The alkoxy groups are arranged stereoselectively in a mode so that they avoid steric interactions. The rotation of the benzene rings is, at room temperature, fast in terms of the NMR timescale and leads to a de facto C_s symmetry for **3a–c** and a C_{5h} symmetry for **3d**. All four structural isomers can encapsulate two CH_3CN guest molecules. The structure determinations are based on four crystal structure analyses (constitutions) and NMR spectroscopic measurements (conformations).

Introduction

Macrocyclic hosts, such as crown ethers,[1] cyclodextrins,[2] cucurbiturils,[3] and calixarenes,[4] play an outstanding role in host–guest chemistry. The recently obtained pillararenes[5,6] represent a novel type of macrocyclic hosts. They are *para*-bridged analogues of calixarenes, which have *meta*-bridges. [1.1.1.1.1]Paracyclophane[7] is the parent compound of pillar[5]arenes.

We published in a short paper a catalytic process that permits the efficient synthesis of pillar[5]arenes and the first access to pillar[6]arenes.[8] Symmetrical 1,4-dialkoxy-2,5-bis(ethoxymethyl)benzenes **1a–c** react smoothly in CH_2Cl_2 at room temperature in the presence of *p*-toluenesulfonic acid to afford pillar[5]arenes **2a–c** (86–95% yield). Scheme 1 shows this novel type of cyclocondensation reaction. The crucial question was then how nonsymmetrical starting compounds **1** ($R^1 \neq R^2$), which have the reacting alkoxymethyl groups in nonequivalent positions of the benzene ring, behave. Can regio- and/or stereoselectivity be observed or not?



Scheme 1. Catalytic cyclocondensation reaction of symmetric starting compounds **1** to pillar[5]arenes **2**.

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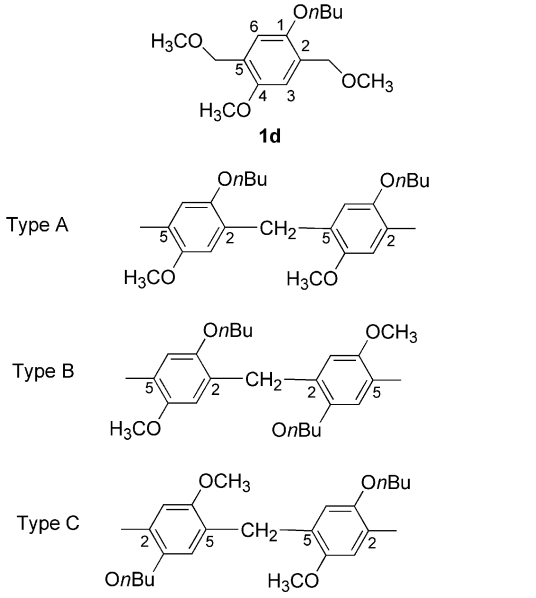
Results and Discussion

Synthesis

We investigated in this context the reactivity of 1-butoxy-4-methoxy-2,5-bis(methoxymethyl)benzene (**1d**). Scheme 2 reveals that **1d** can perform three different types (A–C) of condensation reactions for the formation of the CH_2 bridges between the benzene rings. In principle, four arrangements of three types of links, A, B, and C, can exist in a cyclopentamer: A_5, A_3BC, ABACA, and ABCBC. Obvious restrictions are that for each type B, the ring must contain a type C and vice versa, and two types B as well as two types C can never be direct neighbors or neighbors separated by A_n. Scheme 3 illustrates the four possible regioisomeric cyclopentamers of **1d**. The alkoxy groups are drawn in such a way that no steric interaction between the two alkoxy groups in the *ortho* position of the CH_2 bridges exists. The inner alkoxy groups can be oriented upwards and the outer alkoxy groups downwards or opposite.

When we assume that there is no electronic or steric preference for the reaction of **1d** in the 2- or 5-position, which means no regioselectivity of the condensation reaction, then we can expect a product distribution **3a/3b/3c/3d** = 5:5:5:1. This mere statistical ratio was strongly supported by the experimental distribution **3a/3b/3c/3d** = 4.1:4.4:5.0:1.0. The total yield of isolated regioisomers **3a–d** amounted to 79.7%.

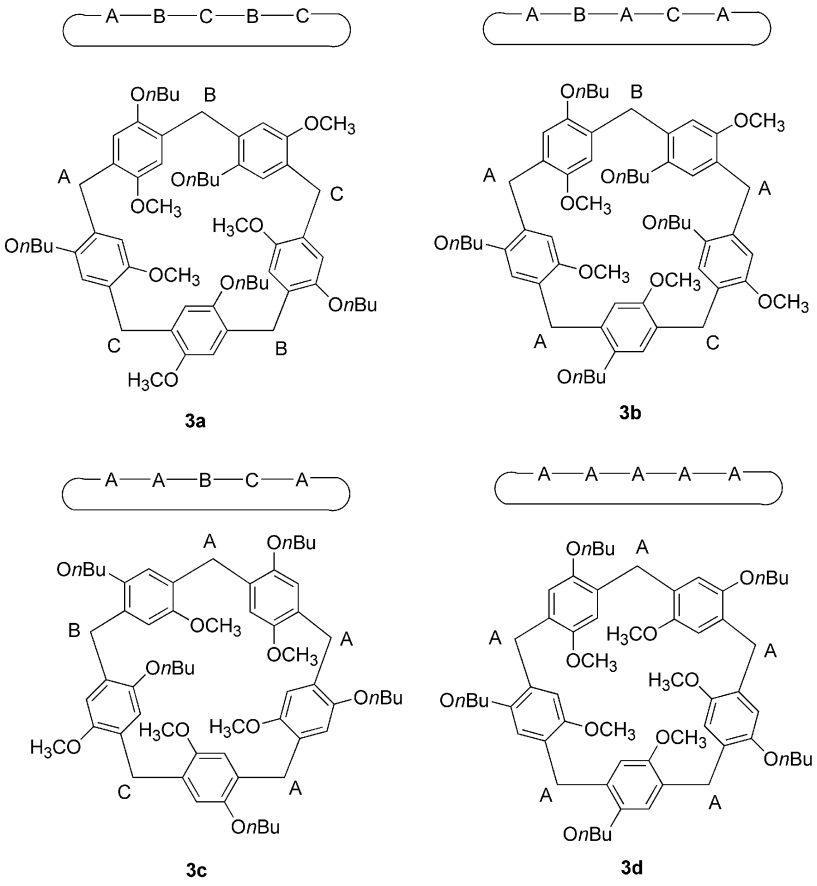


Scheme 2. Formation of different types (A, B, C) of CH_2 bridges in condensation reactions of **1d** (the numbering corresponds to starting compound **1d**).

The regioisomers could be separated by simple column chromatography. The sequence **a**–**d** corresponds to the sequence of the column elusion. The structures were determined on the basis of the four crystal structures. In solution, pillar[5]arenes **3a**–**d** display an average planar conformation on the NMR timescale, because the pillar conformations can exchange rapidly, when the 1,4-phenylene units turn so that the OCH_3 groups can preferentially move through the cavity.

Isomer **3d** gave the simplest NMR spectra. Its number of ^1H and ^{13}C NMR signals corresponds exactly to one repeating unit, which means that **3d** must have a highly symmetrical structure with a C_5 axis. Moreover, the geminal CH_2 bridge protons as well as the geminal OCH_2 protons are chemically equivalent. Figure 1 and Table 1 show part of the aliphatic region of the ^1H NMR spectra of **3a**–**d**. Highly symmetrical isomer **3d** (C_{5h}) displays a singlet for the five OCH_3 groups (δ = 3.659 ppm) and a singlet for the five CH_2 bridges (δ = 3.748 ppm). For the less-symmetrical regioisomers **3a**–**c** (C_s), both singlets are split into five singlets each. These singlets are partially overlapping, but their superposition is less than the superposition of the 10 signals of the aromatic protons or the 5 triplet signals of the OCH_2 groups (see the Experimental Section).

The region $3.6 < \delta(^1H) < 3.8$ ppm can be used to distinguish the four regioisomers.[9] An analogous splitting is observed in the ^{13}C NMR spectra. An exact structure correlation is only possible on the basis of the four crystal structure analyses shown below.



Scheme 3. Possible regioisomers **3a**–**d**, which can be obtained by the fivefold cyclocondensation reaction of **1d**.

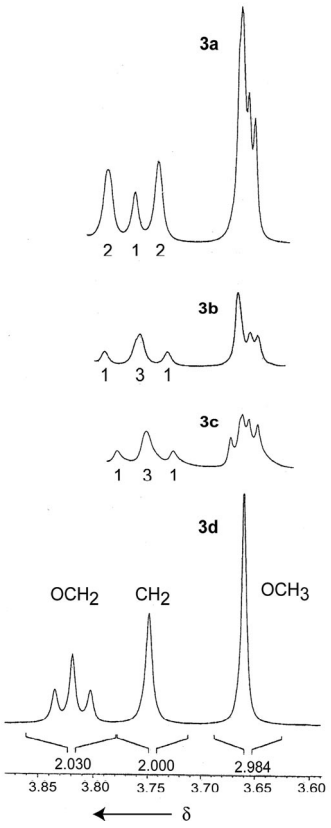


Figure 1. ^{1}H NMR subspectra of **3a**–**d** in $CDCl_3$.

Table 1. Singlet signals of the CH_2 bridges and OCH_3 groups in the ^{1}H NMR spectra of isomers **3a**–**d** (δ values in $CDCl_3$ relative to TMS as internal standard).

Compound	**3a**	**3b**	**3c**	**3d**
CH_2	3.730	3.721	3.736	3.748
	3.730	3.746	3.762	
	3.751	3.746	3.762	
	3.777	3.746	3.762	
	3.777	3.778	3.789	
OCH_3	3.640	3.639	3.681	3.659
	3.646	3.646	3.670	
	3.652	3.656	3.670	
	3.652	3.656	3.664	
	3.652	3.656	3.656	

Enantiotopic CH_2 protons require a symmetry plane through their carbon atoms. Therefore, we have to postulate pillararene structures with a rotation of the benzene rings, which is fast in terms of the NMR timescale. Structure **3d** (Scheme 3) has all OCH_3 groups on one side and all OC_4H_9 chains on the other side of the macrocyclic ring. This conformer corresponds to the crystal structure. If this structure will be "frozen" in solution, it would have a C_5 axis as well, but all four proton pairs of different CH_2 groups would be diastereotopic and yet isochronous, which is unlikely. The preference for the conformer with C_5 symmetry can be explained by the fact that this is the only conformer of **3d** in which no steric interaction exists between the alkoxy groups of neighboring benzene rings. ROESY measurements reveal the absence of such interactions. The NMR spectra of **3a**–**c** were interpreted in the same way.

X-ray Studies

Due to the alkoxy groups, the pillar[5]arenes have high electron density in the pillar area. Therefore, cations or electron-deficient compounds represent suitable guest molecules. We crystallized compounds **3a**–**d** in CH_3CN and obtained crystals, which were suitable for X-ray studies. Figures 2, 3, 4, and 5 show ORTEP plots of the obtained structures, which confirm exactly the regio- and stereochemistry that was supposed in Scheme 3. The arrangement of the alkoxy groups could lead to 4 and 16 diastereomeric pairs of enantiomers for **3d** and **3a**–**c**, respectively, out of which just one was realized in each regioisomer. All compounds contain two guest molecules of CH_3CN.

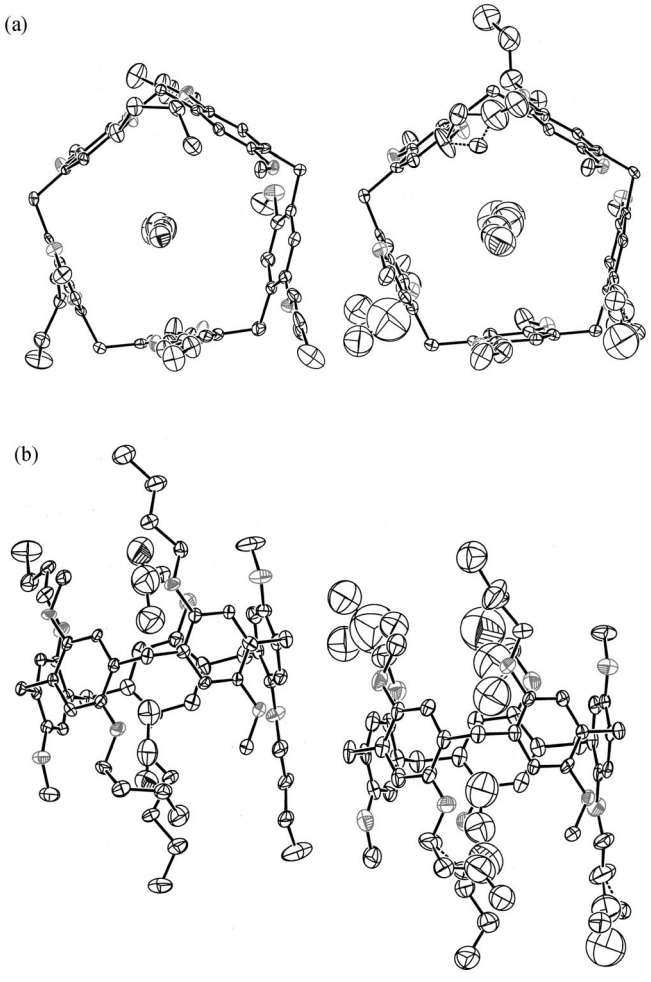


Figure 2. Crystal structure of pillar[5]arene **3a**·2CH_3CN, which contains two slightly different molecules: (a) view from above and (b) view from the side.

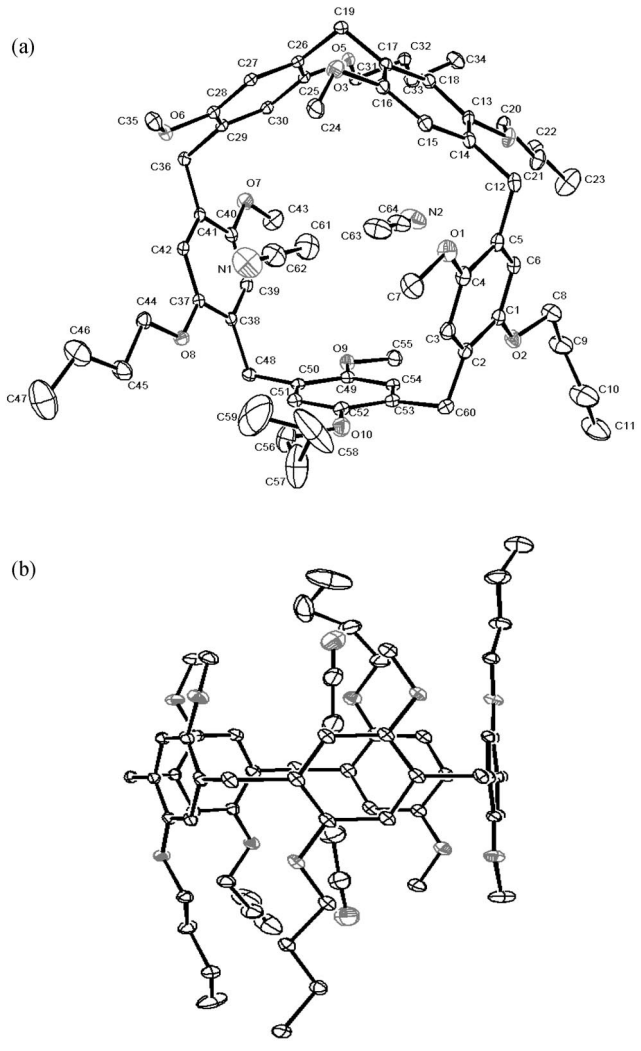


Figure 3. Crystal structure of pillar[5]arene **3b**·2CH_3CN: (a) view from above and (b) view from the side.

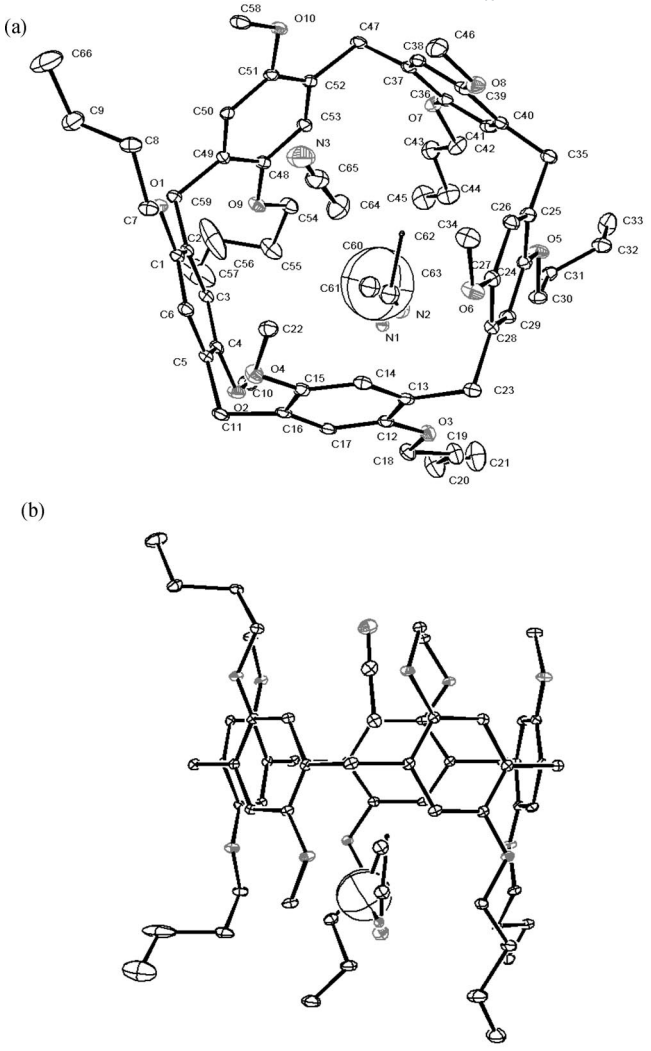


Figure 4. Crystal structure of pillar[5]arene **3c**·2CH_3CN: (a) view from above and (b) view from the side. C60-63–N1-2 is one disorder CH_3CN.

Related to the pillar structure, the electropositive methyl carbon atoms are in the inner region of the cavity and the electronegative nitrogen atoms point outside.

Figure 6 illustrates the elementary cell of **3c**·2CH_3CN. It confirms the distinct assignment of the pair of acetonitrile guests to each host molecule in the stack.

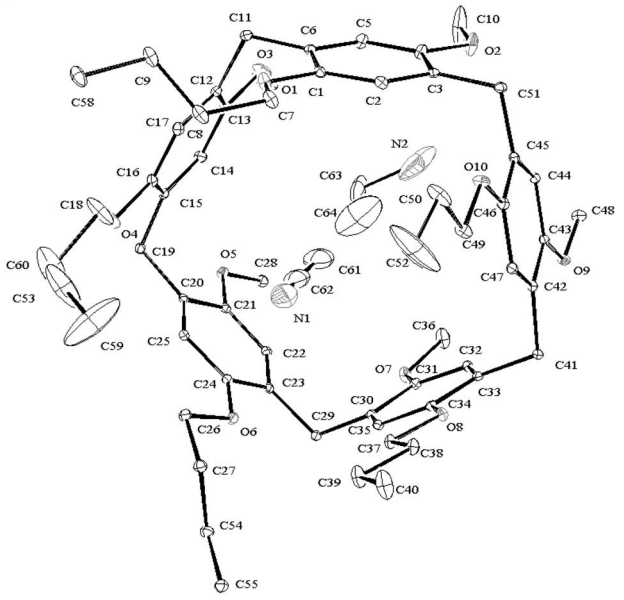
The molecular structures of **3a**–**d** are more or less regular pentagons, which can be characterized by their equal side lengths ℓ, their angles α, which are close to 108 °C, and their diameters d_1 and d_2, which determine the cavity. Table 2 depicts these values for **3b**–**d** (regioisomer **3a** has similar parameters but it exists in the crystal in two slightly different molecules). The planes of the benzene rings are almost perpendicular (β ca. 85°) to the plane of the macrocycle, which is defined by the carbon atoms of the CH_2 bridges. The diameters d_1 and d_2 are in the range of 800 and 900 pm, respectively, which resembles the diameter of narrow nanotubes.

Conclusions

Nonsymmetric hydroquinone derivative **1d** in the cyclocondensation reaction with *p*-toluenesulfonic acid as the catalyst gave a mixture of regioisomeric pillar[5]arenes (79.7%). Separation by column chromatography afforded four possible isomers **3a**–**d** in a ratio that corresponds almost to the mere statistic ratio of 1:5:5:5. Structure determination (constitution and conformation) was based on crystal-structure analyses and spectroscopic methods (^{1}H NMR, ^{13}C NMR, ROESY, MS: MALDI-TOF).

On the basis of the here-discussed methoxy–butoxy systems and their NMR spectroscopic studies, it is evident that the reaction of 1-ethoxy-4-methoxyhydroquinone with paraformaldehyde in the presence of BF_3·$O(C_2H_5)_2$[10] should be reinvestigated to distinguish between structural isomers and stereoisomers.

(a)



(b)

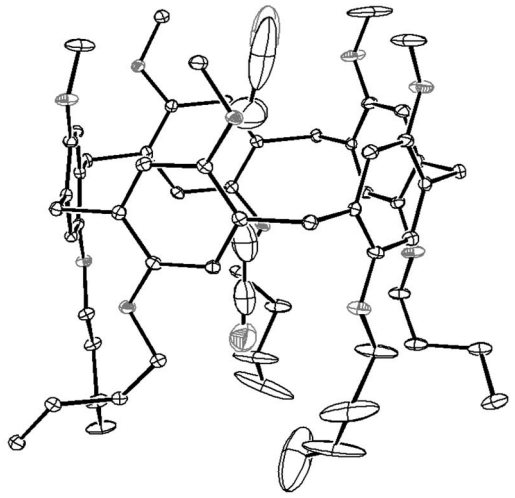


Figure 5. Crystal structure of pillar[5]arene **3d**·2CH_3CN: (a) view from above and (b) view from the side.

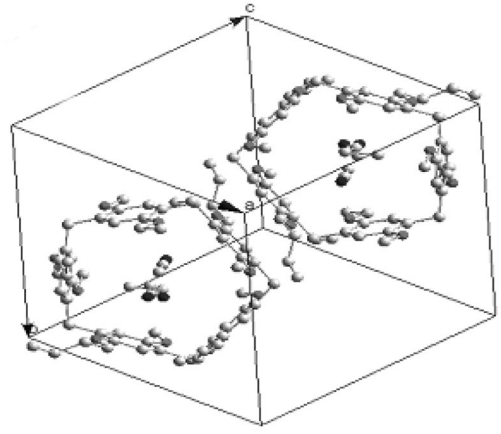
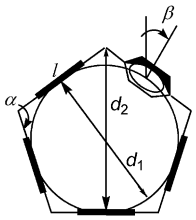


Figure 6. Arrangement of **3c** in the elementary cell.

Table 2. Selected data of the crystal structures.



	3b	3c	3d
Average side length l [pm]	583.7 ± 0.7	584.8 ± 2.1	584.7 ± 1.3
Average angle α [°]	111.5 ± 0.1	110.8 ± 1.4	111.0 ± 1.2
Diameter $d_1 = \frac{l}{\tan 36^\circ} \sim 1.38\ l$ [pm]	806	807	807
Diameter $d_2 = \frac{l}{2}\left(\frac{1+\cos 36^\circ}{\sin 36^\circ}\right) \sim 1.54\ l$ [pm]	899	901	900

Crystallization of the obtained nonsymmetric pillar[5]-arenes in acetonitrile yielded host–guest complexes with two CH_3CN molecules in the cavities (four crystal structure analyses). The arrangement of the alkoxy chains in the crystals corresponds to the least steric interaction of these chains. Thus, 1 of 4 possible diastereomers is realized for **3d** and 1 of 16 diastereomers for **3a**–**c** each.

At room temperature in solution, the benzene rings show fast rotation in terms of the NMR timescale. Therefore, **3a**–**d** exhibit an average planar conformation.

Experimental Section

General: ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker DRX 400 spectrometer by using $CDCl_3$ as the solvent and TMS as an internal standard. Mass spectra (GC–MS) were recorded with an Agilent GC–MS-t5975 mass spectrometer. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass measurements were performed with an Autoflex III smartbeam spectrometer. TLC was performed by using commercial Merck silica gel plates (GF254), and visualization was effected at 254 nm.

1-Butoxy-4-methoxy-2,5-bis(methoxymethyl)benzene (1d): A mixture of 1-butoxy-4-methoxy-2,5-bis(chloromethyl)benzene[11,12] (3.1 g, 11.2 mmol) and $NaOCH_3$ (5.13 g, 95.0 mmol) was heated at reflux in CH_3OH (60 mL) for 3–4 h. The mixture was concentrated, treated with H_2O (60 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and recrystallized from C_2H_5OH. Colorless solid, yield 2.4 g (80%), m.p. 41–42 °C (ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.4 Hz, 3 H, CH_3), 1.47 (m, 2 H, CH_2), 1.72 (m, 2 H, CH_2), 3.40 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.80 (s, 3 H, 4-OCH_3), 3.94 (t, ^3J = 6.4 Hz, 2 H, OCH_2), 4.46 (s, 2 H, Ar-CH_2), 4.48 (s, 2 H, Ar-CH_2), 6.89 (s, 1 H, Ar-H), 6.91 (s, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.3 (CH_2), 31.5 (CH_2), 56.1 (Ar-OCH_3), 58.3, 58.4 (OCH_3), 68.6 (OCH_2), 69.2, 69.3 (Ar-CH_2O), 111.1, 112.7 (C-3, C-6), 126.1, 126.7 (C-2, C-5), 150.4, 150.9 (C-1, C-4) ppm. GC–MS: *m*/*z* (%) = 268 (72) $[M]^{+\cdot}$, 180 (100), 150 (90), 121 (25).

General Procedure for the Preparation of Pillar[5]arenes 3a–d: A mixture of **1d** (3.22 g, 12.0 mmol) and *p*-toluenesulfonic acid hy-

Table 3. Details of the X-ray crystal structure analyses of pillar[5]arenes **3a**–**d** with encapsulated acetonitrile.

	3a	**3b**	**3c**	**3d**
Empirical formula	$C_{60}H_{80}O_{10}{\cdot}2CH_3CN$	$C_{60}H_{80}O_{10}{\cdot}2CH_3CN$	$C_{60}H_{80}O_{10}{\cdot}2CH_3CN$	$C_{60}H_{80}O_{10}{\cdot}2CH_3CN$
Formula weight	1043.35	1043.35	1043.35	1043.35
Crystal system	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a [Å]	14.600(4)	11.9884(14)	12.371(3)	12.498(3)
b [Å]	21.059(6)	12.2548(14)	15.814(4)	14.169(3)
c [Å]	21.442(6)	21.975(2)	16.184(4)	18.250(4)
α [°]	71.102(4)	82.887(2)	80.729(4)	78.225(3)
β [°]	80.949(5)	76.674(2)	80.629(4)	78.502(3)
γ [°]	77.290(4)	77.049(2)	83.087(4)	75.391(3)
V [Å^3]	6058(5)	3052.7(6)	3068.5(12)	3024.0(12)
Z	4	2	2	2
D_{calcd} [g cm^{-3}]	1.144	1.135	1.129	1.144
μ [mm^{-1}]	0.08	0.076	0.075	0.076
F(000)	2256	1128	1128	1124
θ Range [°]	1.20–25.00	1.71–25.20	2.58–25.03	2.65–25.03
Reflections collected	44932	22175	7293	21020
R(int)	0.1288	0.0209	0.0070	0.0250
R_1,$wR[I>2\sigma(I)]$	0.1084, 0.2674	0.0758, 0.2127	0.0765, 0.2136	0.0868, 0.2286
R_1, wR(all data)	0.276, 0.3648	0.1113, 0.2584	0.0894, 0.2351	0.1089, 0.2537

drate (288 mg, 1.5 mmol) was stirred in CH_2Cl_2 (360 mL) at room temperature for 6–8 h. Water (100 mL) was added, and the water layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and portionwise (up to five portions) separated by column chromatography [3 × 60 cm SiO_2, petroleum ether (b.p. 60–90 °C)/ethyl acetate 400:1] to afford **3a**, **3b**, **3c**, and **3d** in a total yield of 79.7% and a ratio 4.1:4.4:5.0:1.0. When too large portions of the reaction mixture were given on the column, mixed fractions – in particular between **3a** and **3b** were obtained and the chromatography had to be repeated.

Pillar[5]arene 3a: Colorless crystals, yield 516 mg (22.4%), m.p. 142–144 °C (ethyl acetate/ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–0.96 (m, 15 H, CH_3); 1.47–1.54 (m, 10 H, CH_2), 1.72–1.75 (m, 10 H, CH_2), 3.640 (s), 3.646 (s), 3.652 (s) (15 H, OCH_3); 3.730 (s), 3.751 (s), 3.777 (s) (10 H, CH_2-bridge); 3.80–3.85 (m, 10 H, OCH_2); 6.762 (s), 6.766 (s), 6.774 (s), 6.784 (s), 6.794 (s) (10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.5 (CH_2), 29.4, 29.6 (CH_2-bridge), 31.9 (CH_2), 55.6, 55.7 (OCH_3), 68.0, 68.1 (OCH_2), 114.0, 114.1, 114.8, 115.0, 115.1 (Ar-H), 128.1, 128.2, 128.3 (Ar-C_q), 150.1, 150.6 (Ar-C_qO) ppm. HRMS (MALDI-TOF): calcd. for $C_{60}H_{80}O_{10}$ $[M]^+$ 960.5844; found 960.6058.

Pillar[5]arene 3b: Colorless crystals, yield 558 mg (24.2%), m.p. 113–114 °C (ethyl acetate/ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92–0.95 (m, 15 H, CH_3); 1.47–1.52 (m, 10 H, CH_2); 1.72–1.75 (m, 10 H, CH_2); 3.639 (s), 3.646 (s), 3.656 (s) (15 H, OCH_3); 3.721 (s), 3.746 (s), 3.778 (s) (10 H, CH_2-bridge); 3.79–3.83 (m, 10 H, OCH_2); 6.755 (s), 6.761 (s), 6.754 (s), 6.778 (s), 6.790 (s), 6.800 (s), 6.809 (s) (10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.5, 19.5 (CH_2), 29.4, 29.6 (CH_2-bridge), 31.9, 31.9 (CH_2), 55.6, 55.7, 55.7, 55.8 (OCH_3), 68.1 (OCH_2), 113.9, 114.0, 114.1, 114.9, 115.0, 115.1 (Ar-H), 127.9, 128.0, 128.1, 128.1, 128.2, 128.3, 128.3 (Ar-C_q), 150.1, 150.5 (Ar-C_qO) ppm. HRMS (MALDI-TOF): calcd. for $C_{60}H_{80}O_{10}$ $[M]^+$ 960.5844; found 960.5995.

Pillar[5]arene 3c: Colorless crystals, yield 636 mg (27.6%), m.p. 131–132 °C (ethyl acetate/ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–0.98 (m, 15 H, CH_3); 1.45–1.55 (m, 10 H, CH_2); 1.74–1.77 (m, 10 H, CH_2); 3.656 (s), 3.664 (s), 3.670 (s), 3.681 (s) (15 H, OCH_3); 3.736 (s), 3.762 (s), 3.789 (s) (10 H, CH_2-bridge); 3.81–3.86 (m, 10 H, OCH_2); 6.766 (s), 6.780 (s), 6.787 (s), 6.795 (s), 6.818 (s), 6.824 (s), 6.830 (s) (10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.5 (CH_2), 29.3, 29.4, 29.5 (CH_2-bridge), 32.0 (CH_2), 55.5, 55.6 (OCH_3), 68.0, 68.1 (OCH_2), 113.9, 114.7, 114.9 (Ar-H), 127.9, 128.1, 128.1, 128.2, 128.3 (Ar-C_q), 150.0, 150.5 (Ar-C_qO) ppm. HRMS (MALDI-TOF): calcd. for $C_{60}H_{80}O_{10}$ $[M]^+$ 960.5844; found 960.6167.

Pillar[5]arene 3d: Colorless crystals, yield 126 mg (5.5%), m.p. 161–162 °C (ethyl acetate/ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.4 Hz, 15 H), 1.51 (m, 10 H, CH_2), 1.75 (m, 10 H, CH_2), 3.66 (s, 15 H, OCH_3), 3.75 (s, 10 H, CH_2-bridge), 3.82 (t, ^3J = 6.4 Hz, 10 H, OCH_2), 6.76 (s, 5 H, Ar-H), 6.82 (s, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.5 (CH_2), 29.5 (CH_2-bridge), 32.0 (CH_2), 55.7 (OCH_3), 67.9 (OCH_2), 114.1, 114.7 (Ar-H), 128.1, 128.1 (Ar-C_q), 150.0, 150.5 (Ar-C_qO) ppm. MS (MALDI-TOF): m/z = 960.7 $[M]^+$, 983.7 $[M + Na]^+$, 999.8 $[M + K]^+$.

Crystal Structure Analyses of 3a–d: Suitable crystals of compounds **3a**, **3b**, **3c**, and **3d** were mounted on glass fibers. Measurements were made with a Smart 1000 CCD diffractometer with graphite-monochromated Mo-K_α radiation. Data were collected at 110 K by using scans to a maximum θ value of 25.00, 25.20, 25.03, 25.03. The data were refined by full-matrix least-squares techniques on F^2 with SHELXL-97, and the structures were solved by direct methods SHELXS-97.[13] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included at geometrically idealized positions. Crystallographic data for **3a**, **3b**, **3c**, and **3d** are summarized in Table 3.

CCDC-795257 (for **3a**) 77751 (for **3b**), -77752 (for **3c**), and -77753 (for **3d**) contain the supplementary data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[9] Concerning the proton signals of the CH_2 bridges, it is plausible that the central singlet in the patterns of **3a**–**c** belongs to the bridge type A and the outer singlets to the bridge types B and C (Figure 1). An exact proof for this assumption is difficult in the ROESY spectra, as the corresponding cross-peaks are very close to the diagonal peaks.

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