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Cyanoresorc[5]arenes: Isolation, Conformation and Crystal Structure

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As a result of our ongoing studies on resorcarenes, we obtained three new resorc[5]arene decamethyl ethers **3a**–**3c** containing cyanomethyl side chains together with the three previously described resorc[4]arenes **2a**–**2c** by treatment of 2-(2,4-dimethoxyphenyl)acrylonitrile (**1**) with $BF_3{\cdot}Et_2O$. From the X-ray crystallographic structure of **3a**, molecular mechanics calculations of the three novel stereoisomers in the gas phase, and the NMR spectroscopic data, the three compounds were attributed architectures of partial 1,3-alternate (**3a**), partial cone (**3b**) and partial 1,2-alternate (**3c**). The relative positions of the substituents were determined by DIF NOE experiments.

Introduction

Calixarenes[1] are macrocyclic compounds containing a number (four to 16 or more) of hydroxylated aromatic rings, arranged in a cyclic array through *meta* connections through methylene groups. Although most attention during the past twenty years has been devoted to the calix[4]arenes, larger members such as calix[5]arenes[1b] and calix[6]arenes[1e] have raised some interest. Konishi et al.[2] reported the synthesis of resorc[5]arenes and resorc[6]arenes by acid-catalysed condensation of 2-propylresorcinol with formaldehyde diethyl acetate, whilst Sherman et al.,[3] utilizing 2-methylresorcinol and diethoxymethane as starting materials, recently synthesized [*n*]cavitands with $n \geq 4$. In both cases the compounds containing five aromatic subunits had highly symmetric cone conformations. Conversely, resorc[5]-arene decamethyl ethers with a foreseeably higher variety of stereoisomers have not yet been reported. Our previous studies[4] had shown that the outcomes of tetramerization reactions of 2,4-dimethoxycinnamic acid derivatives on treatment with $BF_3{\cdot}Et_2O$ were in some way dependent on the chain lengths of the substrates: 2-(2,4-dimethoxyphenyl)-acrylonitrile (**1**), for example, gave the three 1,2-alternate (**2a**), 1,3-alternate (**2b**) and cone (**2c**) stereoisomers,[5] whereas a longer-chain substrate such as 2,4-dimethoxycinnamic acid valinamide, in addition to the classical cone and 1,2-alternate forms, also afforded two more chair-like stereoisomers.[6] Moreover, we also pointed out that the tetramerization of (*E*)-2,4-dimethoxycinnamic acid derivatives proceeds through the monomer-dimer-tetramer sequence.[4] Both monomer and dimer may undergo *E*/*Z* isomerization in the reaction medium, but the influence on the cyclization reaction of geometrical isomerism in the substrate has never been investigated. This paper deals with the results obtained from experiments in which the pure (*E*) and (*Z*) forms, as well as an (*E*/*Z*) mixture of **1**, were subjected to $BF_3{\cdot}Et_2O$ treatment, in a stainless-steel reactor, under constant temperature and pressure conditions. HPLC monitoring of these reactions allowed the isolation and identification of three new cyanoresorc[5]arenes with three different novel architectures (**3a**–**3c**).

Results and Discussion

As reported previously,[5] monomer **1** was obtained as a mixture (*E*/*Z* = 3:2) from the Wittig–Horner reaction between 2,4-dimethoxybenzaldehyde and diethyl (cyanomethyl)phosphonate/K_2CO_3 in absolute ethanol. In order to investigate the influence of the *E*/*Z* stereochemistry of the substrate on the subsequent cyclization (Scheme 1), we purified the crude product by column chromatography on silica gel and obtained **1** as two separate isomers (97–98% purities, checked by HPLC), and subjected the pure (*E*) and (*Z*) forms, as well as the crude (*E*/*Z*) mixture (3:2), to treatment with $BF_3{\cdot}Et_2O$. All the reactions were carried out in a stainless-steel reactor, to keep both the reaction temperature and the substrate/Lewis acid ratio (1:1.5) con-

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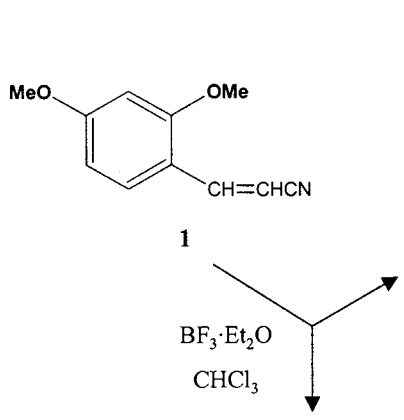
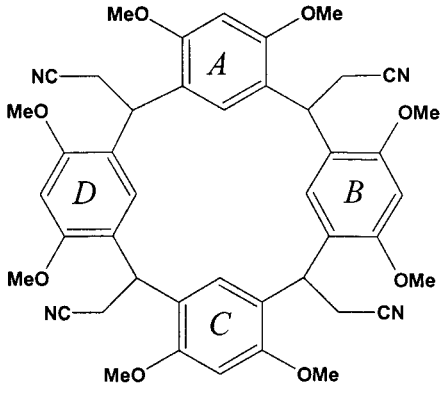
stant. An extensive study relating to the influence of Lewis acid, temperature and reaction time had already provided information on the relative ratios of the different stereoisomers and their interconversions for a series of *C*-alkylcalixresorc[4]arenes.[4]

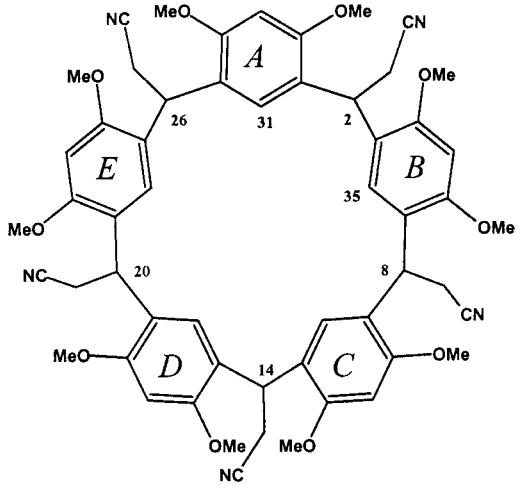
For the HPLC monitoring of the cyclization reaction we chose to use a HPLC π-acid brush-type stereoselective stationary phase,[7] which had already shown high affinity for amido-resorc[4]arenes.[6a] Although the expected macrocycles were not chiral, the above phase proved to be useful for establishing H-bond (or dipole–dipole) and π–π stacking interactions with them, thus providing the large diastereoselectivity usually needed for rapid determination of stereoisomer ratios in crude reaction mixtures. During the development of our HPLC method, we also investigated the potential for an easy interface to mass spectrometry, through the use of a reversed-phase C_{18} column and polar solvents as eluents. In particular, we applied an Ultra-Performance LC (UPLC) system to the direct analysis of a crude calixarene reaction mixture for the first time, resulting in an improvement of the efficiency of the LC process and producing a very flat van Deemter plot, which allows for fast analysis without compromising the efficiency of the separation process. The system would be of general applicability for reaction monitoring in very short times (10 min, Figure 1).

Periodic HPLC analysis of the reaction mixture containing the pure (*E*) isomer of monomer **1** revealed the formation of the previously described[5] cyanoresorc[4]arenes with 1,2-alternate (**2a**), 1,3-alternate (**2b**) and cone (**2c**) conformations, together with three further unknown components. Repeated semipreparative HPLC experiments allowed the isolation of the new components of the reaction mixture – namely **3a**, **3b** and **3c** – in almost pure states (95–99%,





	conformation
2a	1,2-alternate
2b	1,3-alternate
2c	cone



	conformation
3a	partial 1,3-alternate
3b	partial cone
3c	partial 1,2-alternate

Scheme 1. Cyclization of 2-(2,4-dimethoxyphenyl)acrylonitrile (**1**).

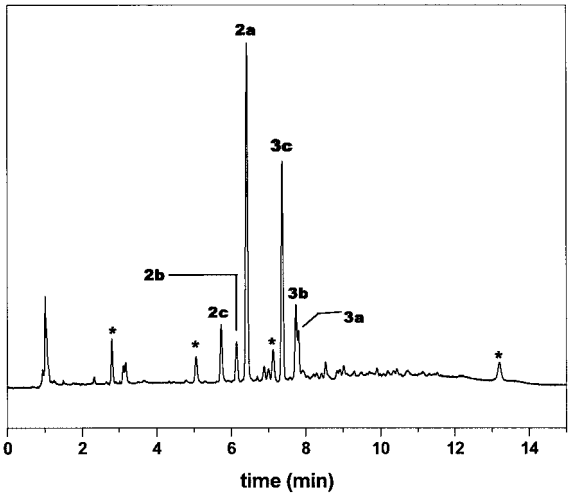


Figure 1. Ultra-Performance LC (UPLC) profile of a crude reaction mixture. Asterisks denote unknown impurities.

checked by HPLC). The NMR spectroscopic data (Table 1) for proton and protonated carbon revealed a general 2:2:1 distribution (3:2 or 4:1 in cases of superimposition), suggesting that the new compounds were cyanoresorc[5]arenes, as confirmed by the molecular peaks at *m/z* 968.4 ([M + Na]$^+$) found in their ESI mass spectra. Single-crystal X-ray diffraction analysis showed that compound **3a** (99% purity, checked by HPLC) crystallizes with one guest toluene molecule in the intramolecular voids of the crystal lattice. A water molecule – statistically distributed over two different positions – in a 1:2 stoichiometric ratio with the macrocycle, and not interacting with it, was also found in the crystal lattice. The molecular architecture of **3a** (Figure 2) appeared quite complex. In the solid state the macrocycle did not possess intrinsic symmetry elements usable as a reference system for calculating the orientations of the five aromatic rings. This problem was overcome by adopting the conformational parameters Φ and χ, previously proposed for the description of calixarene conformations.[8,9] The reciprocal orientation of two adjacent benzene rings is defined by the two torsion angles Φ and χ (with their signs), as shown in Figure 3, where Φ is the torsion angle $C_3A–C_2A–Cb–C_6B$ and χ is the torsion angle $C_2A–Cb–C_6B–C_5B$.

The conformations of the five-membered macrorings (or any *n*-membered macrocycle) can thus be unequivocally described by the five pairs of torsion angles Φ and χ, which in sequence convey the reciprocal orientations of adjacent

Table 1. ^{13}C and ^1H NMR chemical shifts (δ, ppm) for compounds **3a**, **3b** and **3c**.[a]

	Compound **3a**		Compound **3b**		Compound **3c**	
	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H
C=O	156.73 (×2)		157.28		157.32	
			156.84		(×2)	
	156.49 (×2)		156.61			
			156.28		156.45 (×2)	
	156.26		156.10			
CH_i	126.97 (×3)	6.82 br. s (2 H)	127.35 (×2)	6.85 s (2 H)	127.68 (×2)	6.67 br. s (2 H)
		6.38 s	126.51	7.48 br s	127.42 (×2)	6.16 s (2 H)
	126.81 (×2)	6.51 br. s (2 H)	125.80 (×2)	6.19 br s (2 H)	126.57	6.98 s
C–C	122.72		122.38		121.94 (×2)	
	122.01		121.59			
	121.56		121.46		121.41 (×2)	
	121.43		121.11			
	121.30		120.73		120.63	
CN	119.41		(×2)		(×2)	
	119.34 (×2)		(×2)		(×2)	
	119.19 (×2)		118.77		118.97	
CH_e	96.23 (×2)	6.43 s (2 H)	96.59	6.25 s	96.42	6.50 s
	95.71 (×3)	6.44 s (2 H)	95.99 (×2)	6.51 s (2 H)	96.04 (×2)	6.46 s (2 H)
		6.47 s	95.74 (×2)	6.39 s (2 H)	95.16 (×2)	6.41 s (2 H)
OMe	56.32	3.88 s	56.09	3.95 s	56.10	3.89 s
	55.98	3.83 s	55.95	3.81 s	55.98	3.85 s
	55.83	3.79 s	55.85	3.79 s	55.77	3.80 s
	55.79	3.78 s	55.79	3.35 s	55.70	3.78 s
	55.64	3.77 s	55.60	3.73 s	55.13	3.44 s
CH	33.43 (×2)	4.94 dd (2 H) (9, 7)	33.75 (×2)	4.91 dd (2 H) (8, 6)	33.06 (×2)	4.70 dd (2 H) (10, 6)
		5.00 dd (2 H) (8.5, 6.5)		4.75 t (8)		4.81 t (7.5)
	31.44 (×3)	4.65 t (7)	33.28	5.03 t (2 H) (7)	31.81	5.07 t (2 H) (7)
			31.00 (×2)		31.75 (×2)	
CH_2	22.96 (×2)	2.74 dd (16, 6.5)	22.49 (×2)	3.04 dd (16.5, 6)	22.62 (×2)	2.85 dd (16, 7)
		2.60 dd (16, 8.5)		2.97 dd (16.5, 8)		2.79 dd (16, 7)
	22.67 (×2)	2.68 dd (16.5, 7)	22.16 (×2)	2.73 dd (16, 7)	21.31 (×3)	2.80 dd (16, 6)
		2.48 dd (16.5, 9)		2.67 dd (16, 7)		2.57 dd (16, 10)
	22.37	2.99 d (7)	21.18	2.23 d (8)		2.46 d (7.5)

[a] The relative intensities of the carbon signals were confirmed by the integration of the corresponding HETCOR-related protons. Coupling constants (Hz) are given in parentheses.

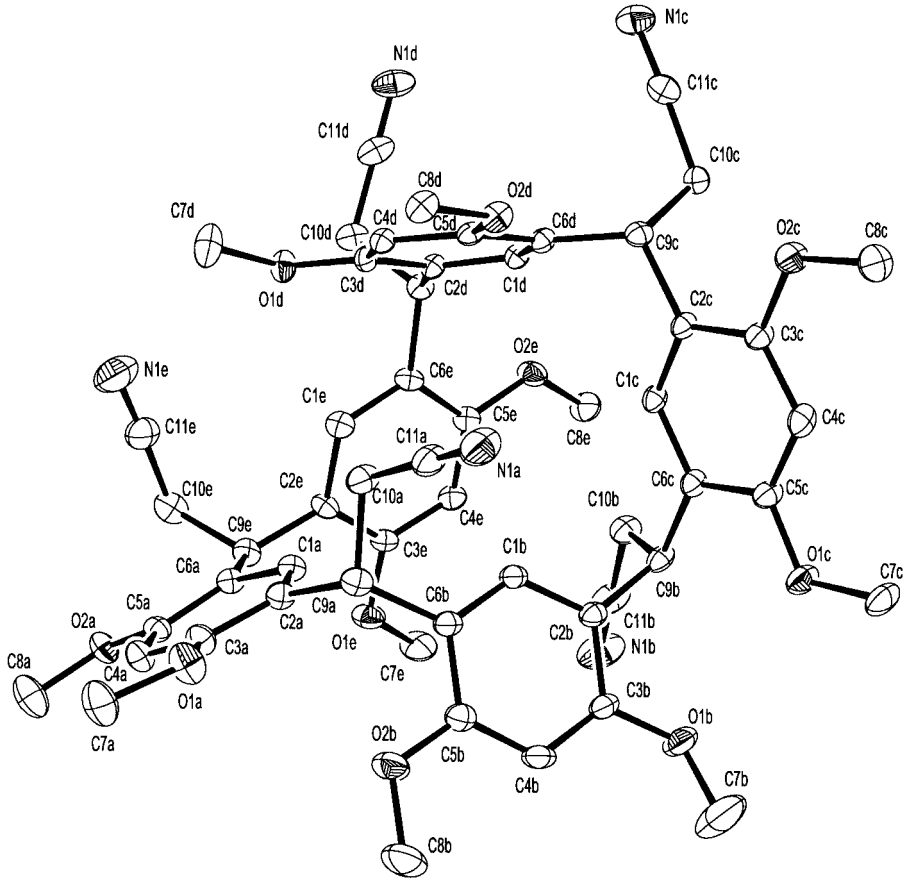


Figure 2. Perspective view of compound **3a** (partial 1,3-alternate stereoisomer) with the atom numbering scheme. Hydrogen atoms have been omitted for clarity.

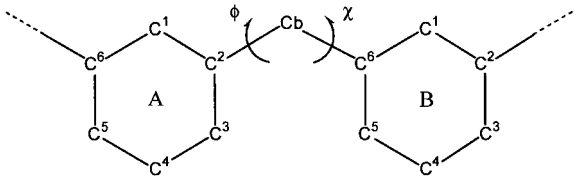


Figure 3. Torsion angles between two adjacent benzene rings.

benzene rings, namely A–B, B–C, C–D, D–E and E–A. The sequence of torsion angles should proceed counterclockwise along the macroring containing the maximum number of C_1 carbons.[9] Apart from the values of the conformational parameters, their signs immediately indicate the shape of the macrocycle. Tetrameric cone conformations, for instance, are always characterized by the sequence (+–,+–,+–,+–), while the sequences (+–,++,–+,––) and (++,––,++,––) belong to tetrameric 1,2-alternate and to 1,3-alternate conformations, respectively. Accordingly, the molecular conformation of compound **3a**, as defined by its X-ray structure, can be expressed by a symbolic representation (*s.r.*) by use of the Schönflies symbol for the symmetry followed by the sequence of signs of Φ and χ pairs: C_1 (++,––,+–,++,––).

Other possible conformations of the pentameric macrocycles in the gas phase were suggested by molecular mechanics (MM) studies with the MMFF force field implemented in SPARTAN '04.[10a] Similar results were obtained with the AMBER* force field[10b] as implemented in the program MacroModel.[10c] As a result, three optimized geometries (Figure 4) were obtained; the conformational parameters and the symbolic representations of the three stereoisomers are summarized in Table 2. Looking at the architecture of Figure 4 A and the corresponding *s.r.*: C_1 (+–,–+,+–,+–,+–), we may observe that the four ABDE rings form a cone structure, as suggested by a relative sequence of signs coincident with the tetrameric sequence in the cone conformation. More precisely, ABDE assume a flattened cone arrangement, which, notably, is in close agreement with the values of torsion angles with the analogous structure of a dimethoxy derivative of *p-tert*-butylcalix[4]arene:[9] AB +74.0, –124.0; BC +102.0, –63.0. CD +64.0, –107.8; DA +116.0, –58.1. The fifth ring is inserted diagonally in this structure, to form a new architecture that we may define as partial cone. Such a structure can be schematically represented as in Figure 5, in which the aromatic rings are seen from the side of the majority of the methoxy groups and are drawn according to the approximate nearest

angle they form with the plane defined by the methine groups: solid line = 90°, bold line = 0°, dotted line = –90°. To agree with the NMR findings, this structure in solution can be represented as the result of an equilibrium between two equivalent forms, similarly to what has been reported for the cone tetramer.[11] The oscillations of aromatic rings B/D and E/A on opposite sides of the symmetry plane, as well as that of ring C perpendicular to the symmetry plane, do not produce any change in the symmetry of the total architecture.

Indeed, DIF NOE experiments (see Table 3) on compound **3b** suggested a similar arrangement for the aromatic rings and revealed the positions of the substituents, which are shown in the sketch of Figure 5 with a solid line when they are pointing up (towards the observer) and with a dotted line when they are pointing down, with respect to the methine proton. The C-14 substituent (CH_2 at δ = 2.23 ppm) of compound **3b** is on the same side as the H_i protons (δ = 6.19 ppm) of the equivalent A/E aromatic rings, which are in turn on the same side as the B/D aromatic rings targeted by H_i at δ = 6.85 ppm. Selective irradiations also revealed the proximity of (B/D)-H_i to the C-2/C-26 methines, as well as that of (C)-H_i to the C-2/C-26 methylenes. In conclusion, compound **3b** was assigned a partial cone conformation with the *rtttc*[11] substitution pattern (Figure 5). All the substituents can be considered pseudoaxial, although axial-equatorial terminology seems inadequate for such oscillating architectures. The high-field values for H_i (δ = 6.19 ppm) and the C-14 methylene require that the A/E rings be partially flattened to push the relative protons under the influence of B/D rings.

If we ignore the D ring (and its signs) in the structure of Figure 4 (B), we clearly obtain a 1,2-alternate (tetrameric) conformation and its relative sequence of signs. The extra D ring, inserted as a flattened ring, produces an architecture that can be represented as in the relative sketch (Figure 6). By analogy, irradiation of the 2H signal in compound **3c**, at δ = 2.85 ppm, revealed the proximity of the two relative methylene groups in relation to the H_i protons (1 H at δ = 6.98 and 2 H at δ = 6.67 ppm) of the D and the C/E rings, respectively. In effect, three adjacent aromatic rings (C, D, E) with the same orientation are thus identified.

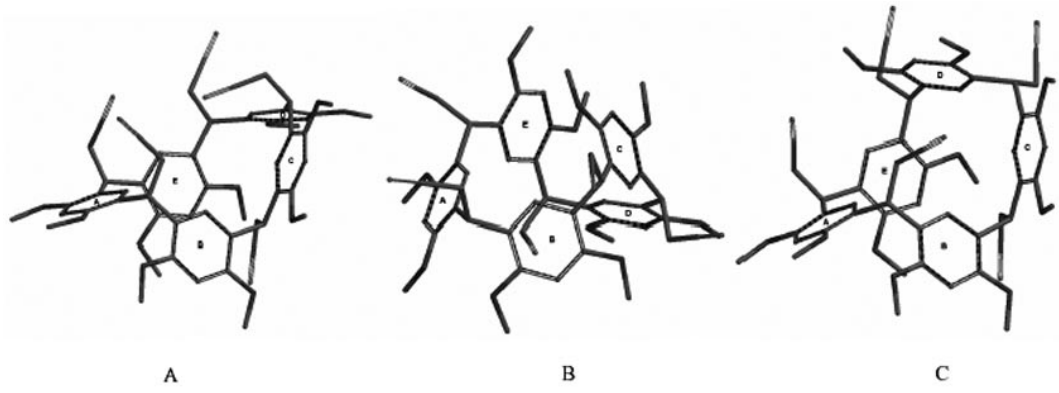


Figure 4. Optimized geometries in the gas phase. A) Partial cone stereoisomer **3b**. B) Partial 1,2-alternate stereoisomer **3c**. C) Partial 1,3-alternate stereoisomer **3a**.

Table 2. Conformational parameters (Φ and χ) and symbolic representations (*s.r.*) for compounds **3a**, **3b** and **3c**.

Rings	X-ray structure[a]		Compound **3a**		Compound **3b**		Compound **3c**	
	Φ [°]	χ [°]	Φ [°]	χ [°]	Φ [°]	χ [°]	Φ [°]	χ [°]
A–B	120.7 (7)	79.8 (8)	105.7	75.0	117.4	–78.1	102.5	–92.1
B–C	–123.3 (7)	–87.1 (7)	–129.4	–68.3	–132.1	69.1	93.1	110.2
C–D	153.9 (7)	–95.5 (7)	115.2	–79.0	161.7	–93.5	–61.2	157.4
D–E	81.6 (7)	118.0 (6)	91.9	98.1	106.3	–52.7	–131.9	58.9
E–A	–115.2 (7)	–177.6 (6)	–77.1	–165.2	71.0	–155.6	–171.4	–68.2
s.r.	C_1 ++,––,+–,++,––		C_1 ++,––,+–,++,––		C_1 +–,–+,+–,+–,+–		C_1 +–,++,–+,–+,––	

[a] Estimated standard deviations (SD) reported in parentheses were obtained from geometrical calculations on the X-ray crystal structure.

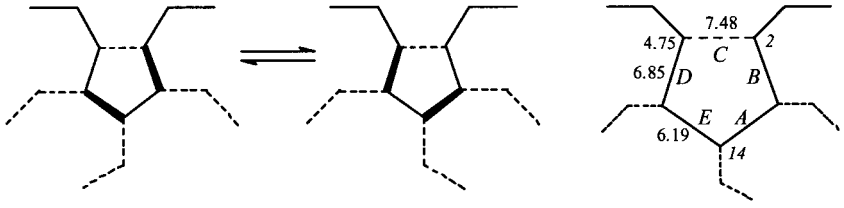


Figure 5. Sketch and proton resonances of compound **3b** in solution.

Table 3. DIF NOE measurements for compounds **3b** and **3c**.

	Compound **3b** Irradiated proton		Compound **3c** Irradiated proton	
CH	4.75	2.23 (CH_2, 8%), 6.19 (H_i, 3.5%)	4.70×2	6.67 (H_i, 6%), *ca* 2.80 (CH_2, 3%),
	5.03×2	ca. 2.70 (CH_2×2, 4%)	5.07×2	3.85 (OMe, 3.5%), 2.85 (CH_2, 4%)
CH_2	2.23	6.19 (H_i, 14%), 4.75 (CH, 11%)	2.46	6.16 (H_i, 11%), 4.81 (CH_2, 12%)
	2.73	6.85 (H_i, 5.5%), 6.19 (H_i, 5.5%), 5.03 (CH, 12%)	2.85	6.98 (H_i, 4.5%), 6.67 (H_i, 2.5%), 5.07 (CH, 8.5%)
	ca. 3.0	7.48 (H_i, 7.5%), 4.91 (CH, 13%)		
H_i	6.19	6.85 (H_i, 5%), 2.23 (CH_2, 8.5%)		
	6.85×2	6.19 (H_i, 6%), 4.91 (CH, 2%)		
	7.48×2	ca. 3.0 (CH_2, 12%)		
OMe	3.95	6.51 (H_e, 6.5%)	3.80	6.50 (H_e, 7%)
	3.81	6.51 (H_e, 4%)	3.78	6.46 (H_e, 7%)
	3.79	6.39 (H_e, 4%)	3.44	6.41 (H_e, 6%)
	3.73	6.39 (H_e, 6%)		
	3.35	6.25 (H_e, 5%)		

The single CH_2 (2 H at δ = 2.46 ppm) was found to be in close proximity to the H_i protons (2 H at δ = 6.16 ppm) of the remaining two equivalent A/B aromatic rings. Moreover, the two aromatic ring pairs A/B and C/E were connected to each other through two equivalent methine groups (2 H at δ = 4.70 ppm), which were found to be in close proximity only with the H_i protons (2 H at δ = 6.67 ppm) of the latter. On this basis, the two pairs A/B and C/E are thus in an *anti* orientation as in the 1,2-alternate conformation of the tetramer, affording a final arrangement as in Figure 6. Taking as reference only the aromatic D ring, C-2 and C-26 substituents are under the plane (α or pseudoaxial) of the methine groups, while the other substituents are β or pseudoequatorial (*rtttc* substitution). Notably, the C-14 substituent is in the same arrangement as in the 1,2-alternate tetramer, and analogously shifted to high field (δ = 2.46 ppm). The minor NOE effect of the C-2 methylene on the H_i protons of the C/E rings, in relation to that on the H_i proton of ring A, suggested for compound **3c** an equilibrium between two forms, in which the D and C/E rings are alternatively flattened. We can name compound **3c** as the partial 1,2-alternate stereoisomer, after the relative positions (1,2) of the aromatic ring pair (A/B).

As shown in Table 2, compound **3a** has the same symbolic representation both in the gas phase (Figure 4, C) and in the solid state (Figure 2). In Figure 4 (C), the extra C ring fits in a tetrameric 1,3-alternate structure, formed by the ABDE rings, as confirmed by the relative sequences of signs. Figure 7 presents a sketch of compound **3a**, indicating the *rtttc* distribution of the substituents. The symmetry plane required by the distribution of the NMR signals can be obtained in solution through an equilibrium between the C and the D rings. The equilibrium very probably also involves the B and E rings, which, however, oscillate between two approximately identical positions, and the uninfluential A ring. The relative position (1,3) of the pair of rings B/E can again be used as a criterion for the assignment of a partial 1,3-alternate architecture to compound **3a**.

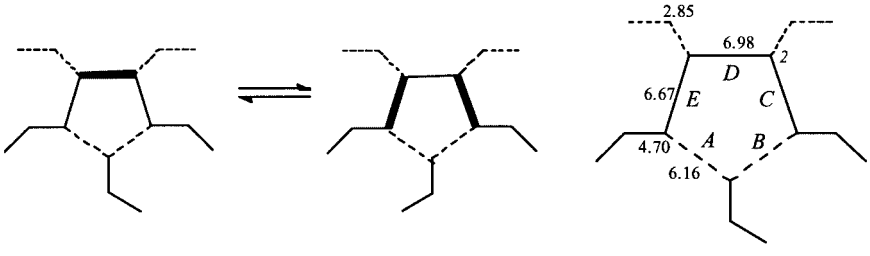


Figure 6. Sketch and proton resonances of compound **3c** in solution.

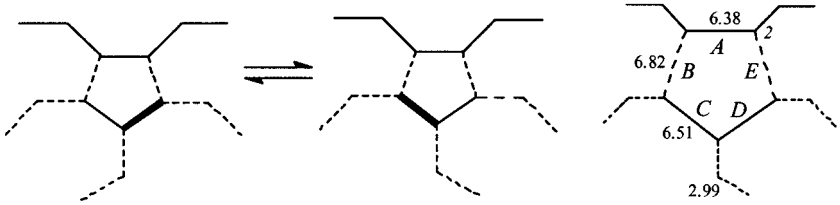


Figure 7. Sketch and proton resonances of compound **3a** in solution.

Notably, if we limit the orientations of the aromatic rings to up (solid line) and down (dotted line), the three simplified arrangements of Figure 5–Figure 7 are the only statistically possible structures, except for a cone conformation with all five rings oriented in the same direction. The coincident substitution patterns (*rtttc*) are substantiated by the DIF NOE experiments, but may suggest that the three compounds **3a**, **3b** and **3c** are conformational isomers and should be interconvertible into one another by appropriate rotations of the aromatic rings. However, no interconversion was observed when tetrachloroethylene solutions of **3a**, **3b** or **3c** were heated in an oven at 90 °C for 4 h, without the addition of the Lewis acid. Examination of CPK molecular models reveals that to accomplish the interconversion between stereoisomers **3a**–**3c** the aliphatic side chain would be required to pass between the methoxy groups of the neighbouring resorcinol units, thus producing an unfavourably crowded high-energy transition state.[4] The same substitution pattern of the side chains had already been observed in cyanoresorc[4]arenes **2b** and **2c**, as substantiated by DIF NOE experiments.[5]

The calculated energies for the three stereoisomers were: 96.3 kcal·mol^{-1} (partial cone, **3b**), 92.2 kcal·mol^{-1} (partial 1,3-alternate, **3a**) and 102.5 kcal·mol^{-1} (partial 1,2-alternate, **3c**). Notably, a geometry optimization (in the gas phase) carried out by starting from the X-ray molecular structure gave the same 1,3-alternate structure as obtained from the conformational analysis, and allowed the energy required for the molecular rearrangement during the gas–solid phase transition to be calculated. The calculated single-point energies for macrocycle **3a** in the solid and the gas phase (166.7 and 92.2 kcal·mol^{-1}, respectively) indicate that 74.5 kcal·mol^{-1} are spent for the conformational change, which does not, however, change the torsion angles Φ and χ to the point of affecting their signs.

In summary, on consideration of the X-ray structure of **3a** (Figure 2), of the three novel stereoisomers in the gas phase as calculated by MM, and of the NMR spectroscopic data, the three compounds were attributed the architectures of partial 1,3-alternate (**3a**), partial cone (**3b**) and partial 1,2-alternate (**3c**).

Closer examination of the progress of the first experiment [involving the pure (*E*) isomer of **1**] over time revealed that the cyanoresorc[5]arenes **3a**–**3c** are the first to form (kinetic products), while the tetrameric analogues **2a**–**2c** develop later (thermodynamic products). After a 6 h reaction time, we found 45% of tetramers and 50% of pentamers. The overnight formation of white crystals, corresponding exclusively to the three cyanoresorc[4]arenes (**2a**, 7%; **2b**, 62%, **2c**, 31%), as judged by their HPLC profiles, clearly directs the reaction toward the tetrameric species. In the second experiment [involving the pure (*Z*) isomer of **1**], we observed mainly the formation of cyanoresorc[4]arenes (75%), while the pentameric analogues were obtained in lower yield (20%) after the same reaction time. When the crude (*E*/*Z*) mixture (3:2) was treated with BF_3·Et_2O, the same series of products was obtained: again, cyanoresorc[5]-arenes **3a**–**3c** are the first to form (25% after 6 h), while the tetrameric analogues **2a**–**2c** develop with time (68%); in particular, **3a** is the first to disappear, in favour of **3b** and **3c** (of the cyanoresorc[5]arenes) and of **2b** and **2c** (of the cyanoresorc[4]arenes). It is worthy noting that under our HPLC conditions (see Supporting Information), we were also able to monitor the disappearance of the starting materials and to observe that the (*Z*) isomer of **1** reacted towards the cyclization reaction more rapidly than the (*E*) isomer. In previous experiments[4] we demonstrated that a series of C-alkylcalix-resorc[4]arenes could interconvert into the thermodynamically stable cone stereoisomers in the presence of BF_3·Et_2O. To confirm the conversion of pentamers into tetramers, compound **3a** was heated at reflux in chloroform in the presence of BF_3·Et_2O (molar ratio 1:1.5), to give a mixture of **2b** (5%) and **2c** (75%), but also **3b** (15%) and **3c** (5%) stereoisomers. A plausible explanation for the conversion of pentamer **3a** into tetramers (mainly **2c**) might involve a BF_3·Et_2O-catalysed ring-opening by two subsequent scissions of the methine-aryl C–C bonds through a "protodealkylation process",[12] followed by elimination of the fifth aromatic nucleus prior to a new ring closure.

Conclusions

The above results demonstrate that the formation of resorc[5]arene decamethyl ethers is possible under appropriate reaction conditions. Three different, novel, highly flexible stereoisomers were obtained instead of the cone conformations previously obtained for resorc[5]arenes[2] and [5]cavitands.[3] Furthermore, although tetramer formation affords distinct conformations, pentamer formation gives more complex and less defined architectures, both in solid and in gas phases. NMR spectra, however, revealed that cyanoresorc[5]arenes in solution achieve a C_S symmetry by appropriate oscillations of the aromatic rings oriented on opposite sides of the symmetry plane.

We also demonstrated that the cyclization reaction of 2-(2,4-dimethoxyphenyl)acrylonitrile gives rise to a complex mixture of cyanoresorc[4]arenes and cyanoresorc[5]arenes, the (*E*/*Z*) geometry of the starting monomer playing a role only in their different proportions.

Finally, we have applied a UPLC system to the direct analysis of a crude calixarene reaction mixture for the first time. This could be of general applicability for reaction monitoring in very short times.

Experimental Section

General Remarks: Melting points were recorded on a Büchi B-545 microscope, and are uncorrected. ^{1}H and ^{13}C NMR spectra: 300 MHz and 75 MHz, respectively (TMS = 0 ppm as internal standard in $CDCl_3$ solutions). Analytical HPLC separations were performed on a Waters 2690 Separation Module (Waters, Milford, MA, USA), fitted with a Rheodyne Model 8125 20 μL injector, including a Model M486 programmable multi-wavelength detector. Semipreparative HPLC separations were carried out on a Waters Delta Prep 3000 chromatographic system, fitted with a Rheodyne Model 7010 5 mL loop injector and a Knauer variable wavelength

monitor (Berlin, Germany). Chromatographic data were collected and processed with the Millennium 2010 Chromatography Manager software. Mass spectra (MS) were obtained by electrospray ionization (ESI) on a Waters ZMD single quadrupole instrument, fitted with a Model 75-72 nitrogen generator (Whatman Inc., Haverhill, MA, USA) and a Model "Pump 11" microprocessor single syringe (Harvard Apparatus Inc., South Natick, MA, USA) for direct sample infusion. Chromatographic and MS data were collected and processed with the MassLynx Version 3.4 software (Micromass UK Ltd., Manchester, UK). FT-IR spectra were recorded as KBr pellets on a Jasco FT/IR 430 spectrometer (Jasco Europe). The chiral stationary phase used [(1*R*,2*R*)-DACH-DNB] was based on Kromasil Si 100, 5 μm spherical silica gel. Details on the synthetic procedure have already been published.[7] Column dimensions were 250 × 4.5 mm i.d. and 250 × 10 mm i.d. for analytical and semipreparative applications, respectively. UPLC analyses were performed on a Waters Acquity Ultra Performance LC system. Chromatographic conditions are given in the Supporting Information.

Synthesis of 2-(2,4-Dimethoxyphenyl)acrylonitrile (1): Compound **1** was synthesized as described previously.[5] The residue was purified on silica gel by gradient elution with CH_2Cl_2/*n*-hexane 70:30 (initial) to CH_2Cl_2/*n*-hexane 50:50 (final) to give **1** as two separate isomers (97–98% purities, checked by HPLC).

Synthesis and Isolation of Cyanoresorc[5]arene Decamethyl Ethers 3a–3c: $BF_3{\cdot}Et_2O$ (0.2 mL, 1.5 mmol) was added to a solution of 2-(2,4-dimethoxyphenyl)acrylonitrile [**1**, either as (*E*), (*Z*) or (*E*/*Z* = 3:2) forms, 192 mg, 1 mmol] in $CHCl_3$ (5 mL), and the mixture was transferred by syringe into a tubular stainless-steel reactor of 5 mL capacity. The reactor was placed in a preheated (50 °C) aluminium block, and periodic withdrawals of the reaction mixture were made through a stainless-steel needle for the HPLC monitoring. After 6 h, all the monitored reactions were stopped, the mixtures were cooled and diluted with MeOH, and the solvents were evaporated to dryness. The product of the reaction starting from the mixture (*E*/*Z* = 3:2) of compound **1** was purified on silica gel with CH_2Cl_2/*n*-hexane/EtOAc (85:10:5) to give fractions I–IV. Fractions I, II and IV were identified as tetramers **2a** (29 mg, 15% yield), **2b** (23 mg, 12% yield) and **2c** (77 mg, 40% yield), respectively. Conversely, fraction III (60 mg) was processed by semipreparative HPLC (see Supporting Information), affording fractions III-I and III-II. The latter fraction was identified as compound **3a** (18 mg, 10% yield, 99% purity), while fraction III-I (40 mg) was processed further, affording two more fractions, coincident with compounds **3b** (8 mg, 4% yield, 99% purity) and **3c** (5 mg, 3% yield, 95% purity). The purities of the isolated products were checked by analytical HPLC, under gradient elution conditions (see Supporting Information).

***r*-2,*t*-8,*t*-14,*t*-20,*c*-26-Pentakis(cyanomethyl)hexacyclo[27.3.1.1^{3,7},1^{9,13},1^{15,19},1^{21,25}]pentatriaconta-1(31),3,5,7(35),8,11,13(34),15,17,19(33),21,23,25(32),27,29-pentadecaene-4,6,10,12,16,18,22,24,28,30-decaol Decamethyl Ether (3a):** M.p. 241–243 °C. ^{1}H and ^{13}C NMR signals as given in Table 1. FT-IR: $\tilde{\nu}_{max}$ = 2965, 2929, 2856, 1616, 1580, 1507, 1261, 1204, 1152, 1104, 1036, 804 cm^{-1}. ESI-MS (pos.): *m*/*z* found 968.4 $[M + Na]^+$, $C_{55}H_{55}N_5O_{10}Na$ requires 968.3847. FAB-MS: *m*/*z* (rel. int.) found: 968 $[M + Na]^+$ (88), 946 $[M + H]^+$ (13), 945 $[M]^+$ (16), 905 $[M - CH_2CN]^+$ (100). $C_{55}H_{55}N_5O_{10}$ (968.38): calcd. C 69.83, H 5.86, N 7.40; found C 69.57, H 5.82, N 7.39.

***r*-2,*t*-8,*t*-14,*t*-20,*c*-26-Pentakis(cyanomethyl)hexacyclo[27.3.1.1^{3,7},1^{9,13},1^{15,19},1^{21,25}]pentatriaconta-1(31),3,5,7(35),8,11,13(34),15,17,19(33),21,23,25(32),27,29-pentadecaene-4,6,10,12,16,18,22,24,28,30-decaol Decamethyl Ether (3b):** Vitreous solid. ^{1}H and ^{13}C NMR signals as given in Table 1. FT-IR: $\tilde{\nu}_{max}$ = 2963, 2928, 2855, 1615, 1582, 1508, 1261,1202, 1150, 1099, 1029, 801 cm^{-1}. ESI-MS (pos.): *m*/*z* found 968.4 $([M + Na]^+)$, $C_{55}H_{55}N_5O_{10}Na$ requires 968.3847. $C_{55}H_{55}N_5O_{10}$ (968.38): calcd. C 69.83, H 5.86, N 7.40; found C 69.80, H 5.87, N 7.41.

***r*-2,*t*-8,*t*-14,*t*-20,*c*-26-Pentakis(cyanomethyl)hexacyclo[27.3.1.1^{3,7},1^{9,13},1^{15,19},1^{21,25}]pentatriaconta-1(31),3,5,7(35),8,11,13(34),15,17,19(33),21,23,25(32),27,29-pentadecaene-4,6,10,12,16,18,22,24,28,30-decaol Decamethyl Ether (3c):** Vitreous solid. ^{1}H and ^{13}C NMR signals as given in Table 1. FT-IR: $\tilde{\nu}_{max}$ = 2965, 2929, 2855, 1615, 1580, 1508, 1261,1204, 1150, 1103, 1032, 803 cm^{-1}. ESI-MS (pos.): *m*/*z* found 968.4 $([M + Na]^+)$, $C_{55}H_{55}N_5O_{10}Na$ requires 968.3847. $C_{55}H_{55}N_5O_{10}$ (968.38): calcd. C 69.83, H 5.86, N 7.40; found C 69.60, H 5.85, N 7.42.

Crystallographic Data for Compound 3a: $C_{55}H_{55}N_5O_{10}{\cdot}C_7H_8{\cdot}0.5\,H_2O$, M = 1047.214, crystal size: 0.4 × 0.3 × 0.4 mm^3, crystal system: monoclinic, space group: $P2_1/c$, a = 14.494(5), b = 30.884(5), c = 15.008(5) Å, β = 110.95(1)°, volume: 6274(3) Å^3, Z = 4, T = 295 K, ρ(calcd.) = 1.103 g·cm^{-3}, 26533 reflections collected, 9067 unique (R_{int} = 0.0899). Additional crystallographic data, experimental and refinement parameters are given in the Supporting Information (Table 1S). Intensity data and cell parameters were recorded on a Bruker AXS Smart 1000 single-crystal diffractometer (Mo-K_α radiation) fitted with a CCD area detector. The SMART program package[13a] was used to determine the unit cell parameters and for data collection (30 s/frame scan time for a sphere of diffraction data, 20 s/frame scan time for a sphere of diffraction). The raw frame data were processed with SAINT[13b] and SADABS[13c] to yield the reflection data file. The structure was solved by direct methods by use of the SIR92 program[13d] and refined by full-matrix, least-squares procedures (based on F_o^2), by use of the SHELXL-97 program.[13e] All non-hydrogen atoms were refined with anisotropic atomic displacements (with the exception of the solvents molecules) while the hydrogen atoms were introduced into the geometrically calculated positions and refined "riding" on the corresponding parent atoms. The weighting scheme used in the last cycle of refinement was $w = 1/[\sigma^2(F_o^2) + (0.1472\ P)^2]$ where $P = (F_o^2 + 2\ F_c^2)/3$. Molecular geometry calculations were carried out with the PARST97 program.[13f] Drawings were obtained by use of ORTEP3 in the WinGX suite.[13g] All calculations were carried out on a DIGITAL Alpha Station 255 computer.

CCDC-244934 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

Supporting Information (see footnote on the first page of this article): Crystallographic data, experimental and refinement parameters for compound **3a** (Table 1S). Chromatographic conditions for the HPLC and UPLC monitoring of reactions. Structure of the (1*R*,2*R*)-DACH-DNB chiral stationary phase (Scheme 1S).

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