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A family of C-(4-substituted phenyl)calix[4]pyrogallolarene hosts was synthesized through the acid-catalyzed condensation of pyrogallol with a series of para*-substituted benzaldehydes at different reaction temperatures. The effect of reaction temperature and substitution pattern on the benzaldehyde was investigated. Different isomers of C-(4-substituted phenyl)calix[4]pyrogallolarene were observed at room temperature or under reflux conditions as indicated in the solid-state structures of compounds* **1** *and* **2**. *The conformational rigidity of the resulting C-(4-substituted phenyl)calix[4]pyrogallolarene was also affected by the halogen substitution. X-ray analyses of single crystals of C-(4-substituted phenyl)calix[4]pyrogallolarene revealed the formation of inclusion complexes with different stoichiometries.*

Keywords: cocrystal; conformational analysis; host–guest complexes; hydrogen bond; self-assembly; X-ray crystal structures

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INTRODUCTION

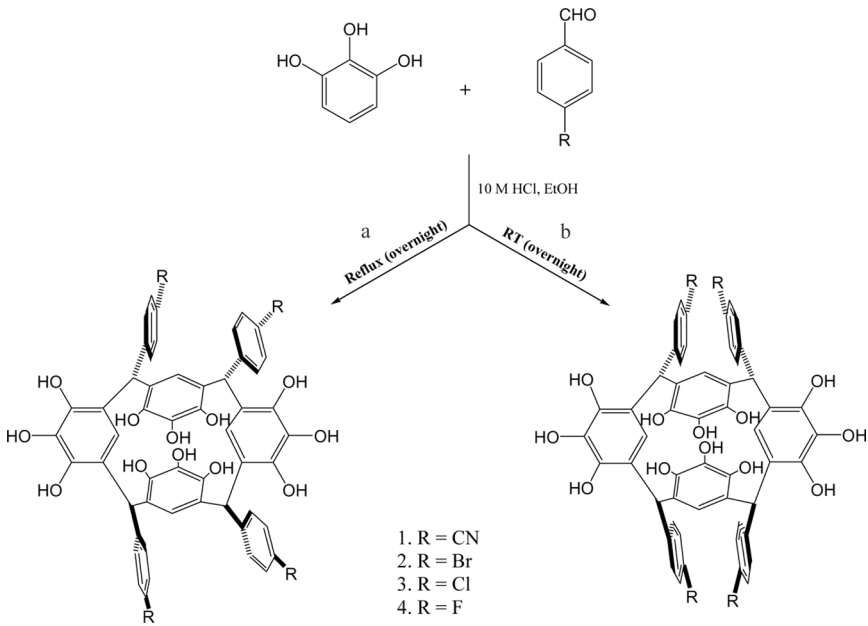
Calix[4]arenes are self-assembling systems possessing large cavities and are able to trap large molecules in the crystal lattice. These materials have found many applications, including their use in High Performance Liquid Chromatography (HPLC) as stationary phases for separation [1], gas purification, and storage materials [2,3] nanofiltration-complexation systems to extract heavy metals [4], rapid synthesis of dendrimers [5], protein activators [6], antiviral and anticancer compounds [7–9], and nanocapsules for drug delivery [10]. For example, in the area of drug delivery, Shahgaldian et al. [11] reported that *p*-sulfonatocalix[n]arenes showed no haemolytic effects and no toxicity and did not provoke immune reactions compared to cyclodextrins, which show unfavourable haemolytic properties [12]. These observations provide promising signs that calix[4]arenes could be used as nanocapsules and cocrystal formers in pharmaceutical industry. By making use of molecular recognition properties, they can be tailored to allow targeting of biological receptors. In host–guest chemistry, Ma et al. [14] reported on several crystal structures of benzil in calix[4]resorcinarene host matrixes to explore the influence of the host environment on the properties of the guest benzil. There is also work done to synthesize calix[4]arenes as host molecules with chiral recognition [14].

Recently, we have been interested in designing new systems of calix[4]arenes to explore their ability as potential host molecules for industrial applications. Our strategy involved investigating the effect of temperature on the formation of different isomers and hence exploring the supramolecularity of each isomer. The variation of the reaction temperature played a crucial factor in the structural isomer of the formed compounds [15]. For example, reaction temperature has a great effect [16] on the product conformation, which was found to be either cone (rccc-isomer) or chair (rctt-isomer). In this article, we present the synthesis of several *C*-phenylcalix[4]pyrogallolarenes under different reaction temperatures and report on the conformational rigidity of these hosts. The crystal structures of *C*-(4-cyanophenyl)calix[4]pyrogallolarene **1** and *C*-(4-bromophenyl)calix[4]pyrogallolarene **2**, *C*-(4-chlorophenyl)calix[4]pyrogallolarene **3**, and *C*-(4-fluorophenyl)calix[4]pyrogallolarene **4** are reported. Although the synthesis of compounds **2** and **4** has been reported [7,8], to the best of our knowledge their X-ray crystal structures have not been published, underlining difficulties involved in their crystallization.

RESULTS AND DISCUSSION

Synthesis of *C*-Phenylcalix[4]pyrogallolarene Hosts

C-Phenylcalix[4]pyrogallolarenes were synthesized as shown in Scheme 1. A solution of para-substituted-benzaldehyde (0.0198 mol, 1 equiv) in ethanol (25 mL) was added dropwise to an ice-cooled solution of pyrogallol (2.5 g, 0.0198 mol) in a mixture of ethanol (15 mL) and conc. HCl (10 M, 3 mL). The reaction mixture was stirred at either room temperature or heated at reflux for 24 h. The precipitated solid was collected by suction filtration and washed successively with water (25 mL) and ethanol (25 mL) and dried under vacuum. Compound **1a** has formed an inclusion compound with Dimethylsulphoxide (DMSO), which was used as a crystallization solvent to obtain pure **1a**. Because of the high boiling point of DMSO, traces of the solvent were trapped in the cavity of **1a** and were difficult to remove despite using a high vacuum dessicator. Therefore, it might have affected the elemental analysis.



SCHEME 1 Synthetic route for compounds **1–4** at two different conditions.

TABLE 1 Crystal Data and Structure Refinements

Compound	1a	1b
Empirical formula	$C_{68}H_{76}N_4O_{20}S_6$	$C_{36}H_{44}N_2O_{11}S_4$
Formula weight	1461.66	808.97
Temperature, K	223(2)	223(2)
λ, Å	0.71073 Å	0.71073
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a, Å	11.204 (3)	10.5219 (4)
b, Å	12.562 (4)	13.5056 (6)
c, Å	13.526 (4)	15.8152 (7)
α,°	76.865 (6)	66.7000 (10)
β,°	84.890 (6)	80.6250 (10)
γ,°	75.758 (6)	73.0740 (10)
V, Å^3	1795.8 (9)	1971.80 (14)
Z	1	2
D_c, Mg/m^3	1.348	1.363
μ, mm^{-1}	0.264	0.301
F(000)	764	852
Crystal size, mm^3	$0.36 \times 0.10 \times 0.08$	$0.40 \times 0.14 \times 0.10$
θ range for data collection, °	1.55 to 22.50	1.40 to 27.50
Index ranges, h, k, l	$-12/12$, $-13/13$, $-14/14$	$-13/13$, $-17/17$, $-20/20$
Reflections collected	15289	25994
Independent reflections	4697 [R(int) = 0.0553]	9047 [R(int) = 0.0305]
Completeness to θ_{max}, %	100	99.9
Max. and min. transmission	0.9792 and 0.9108	0.9705 and 0.8891
Data/restraints/parameters	4697/75/568	9047/9/504
Goodness of fit on F^2	1.152	1.05
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0982$, $wR2 = 0.2279$	$R1 = 0.0674$, $wR2 = 0.1820$
R indices (all data)	$R1 = 0.1182$, $WR2 = 0.2167$	$R1 = 0.0805$, $WR2 = 0.1920$
Largest diff. peak and hole, e. Å^{-3}	0.401 and -0.380	1.891 and -0.630

Crystallization of Compounds 1–4

Single crystals were obtained by dissolving (at room temperature or by heating) compounds **1**, **2**, **3**, or **4** (*ca*. 20 mg) in DMSO (1 mL). The solution was allowed to stand while slowly evaporating at room temperature. This method produced single crystals suitable for X-ray analysis. Table 1 illustrates the crystal data and structure refinements of compounds **1–4** as well as data for the conformational isomers (**a** and **b**, Scheme 1) of compounds **1** and **2**, and

2a	2b	3	4
$C_{68}H_{84}Br_4O_{20}S_8$	$C_{60}H_{64}Br_4O_{18}S_4$	$C_{64}H_{76}Cl_4O_{20}S_6$	$C_{64}H_{74}F_4O_{19}S_6$
1797.47	1520.96	1499.41	1415.59
223(2)	223(2)	223(2)	223(2)
0.71073	0.71073	0.71073	0.71073
Triclinic	Monoclinic	Triclinic	Triclinic
$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
11.4535(18)	11.2558(7)	10.7744(5)	11.9911(5)
12.2052(19)	20.0529(12)	13.0428(6)	12.0902(5)
16.204(3)	14.1088(9)	14.1038(7)	13.5470(6)
91.869(4)	90	64.2370(10)	64.7340(10)
106.209(4)	95.427(2)	77.9610(10)	85.2510(10)
116.002(4)	90	75.0880(10)	69.7910(10)
1923.2(5)	3170.2(3)	1714.17(14)	1661.91(12)
1	2	1	1
1.552	1.589	1.452	1.412
2.378	2.741	0.428	0.289
920	1536	784	740
$0.30 \times 0.12 \times 0.04$	$0.50 \times 0.06 \times 0.04$	$0.60 \times 0.30 \times 0.20$	$0.38 \times 0.26 \times 0.20$
1.89 to 25.00	1.77 to 25.00	1.61 to 27.50	1.67 to 27.50
−11/13, −14/14, −19/19	−13/13, −23/12, −16/16	−13/13, −16/16, −18/18	−15/15, −15/15, −17/17
10996	18336	22500	21865
6768	5594	7843	7622
[R(int) = 0.0698]	[R(int) = 0.0792]	[*R(int)* = 0.0258]	[*R(int)* = 0.0274]
99.8	100	99.8	99.8
0.9109 and 0.5356	0.8983 and 0.3411	0.9193 and 0.7833	0.9445 and 0.8982
6768/56/469	5594/14/459	7843/2/448	7622/0/448
0.939	0.997	1.046	1.015
$R1 = 0.0774$, $wR2 = 0.1391$	$R1 = 0.0809$, $wR2 = 0.2127$	$R1 = 0.0632$, $wR2 = 0.1673$	$R1 = 0.0581$, $wR2 = 0.1465$
$R1 = 0.1620$, $WR2 = 0.1677$	$R1 = 0.1603$, $WR2 = 0.2520$	$R1 = 0.0728$, $WR2 = 0.1746$	$R1 = 0.0726$, $WR2 = 0.1557$
0.948 and −0.454	0.605 and −0.748	1.459 and −0.481	0.808 and −0.364

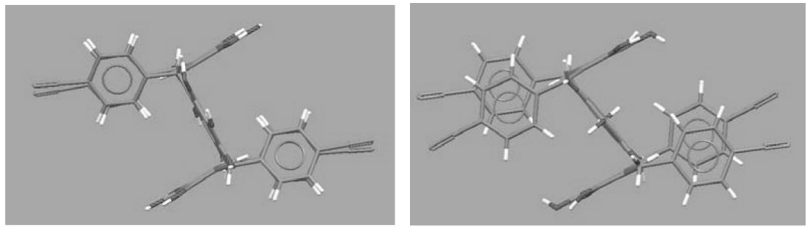
Table 2 shows the type of interactions present in the inclusion compounds. Single-crystal analysis revealed that the compounds were either binary (**2a**) or ternary systems (**1**, **2b**, **3**, and **4**). The binary system consisted of **2a** host and DMSO guests, and the ternary system consisted of **1**, **2b**, **3**, or **4** hosts, DMSO guests, and water. Compounds **1** and **2** had two structural isomers (**a** and **b**) with different crystal packing, host–host, and host–guest interactions. Meanwhile, compounds **3** and **4** did not exhibit such structural changes.

TABLE 2 Interactions Present in the Crystal Structures

	Interactions	Type of interaction	Ring size, no. atoms	No. motifs per molecule	Assembly type[a]	Distance, Å[b]	Angle,°	Dihedral angle,° conformation
1a	Ar-H...CN-Ar...H-Ar	bifurcated	14	2	h-h dimer	2.63, 2.75	72.17	5.07
	Ar-CN...Ar-H...CN-Ar	bifurcated	16	2	h-h dimer	2.63, 2.96	85.17	eclipsed
	CH...CN-Ar...HC	bifurcated	—	2	g-h-g	2.44, 2.82	53.77	
	CN-Ar...HC	single	—	2	g-h	2.88	—	
	Ar-OH...SO...HO-Ar	bifurcated	—	2	h-g-h	2.74, 3.01	136.38	
	SO...HO-Ar	single	—	2	g-h	2.62, 2.71	—	
	SO...HO-Ar	single	—	2	g-h	3.30, 3.24	—	
1b	Ar-CN...HO-Ar	cycle	28	2	h-h dimer	2.36	—	21.31
	CH...CN-Ar...HC	bifurcated	6	2	g-h-g	2.80, 2.81	57.58	staggered
	CN-Ar...HC	trifurcated	—	2	g-h	2.82, 2.90 2.90, 2.99	89.60, 54.22	
	Ar-OH...SO...HO-Ar	bifurcated	—	4	h-g-h	2.69, 2.73	114.61	
	SO...H_2O...HO-Ar	bifurcated	—	2	g-g-h	2.68, 2.77	106.89	
	SO...H_2O...HO-Ar	bifurcated	—	2	g-g-h	2.64, 2.68	106.26	
2a	Ar-Br...H-Ar	cycle	28	2	h-h dimer	3.11	—	1.36
	Ar-Br...H-Ar	cycle	28	2	h-h dimer	3.16	—	eclipsed
	Ar-OH...SO...HO-Ar	bifurcated	5	2	h-g-h	2.64, 2.70	65.33	
	SO...HO-Ar	single	—	2	g-h	2.63, 2.71 2.76	—	

2b	Ar-OH. . .Ar-Br. . .H-Ar	bifurcated	—	2	h-h-h	3.27, 3.26	69.71	0.08
	Ar-Br. . .HO-Ar	single	—	2	h-h	3.25	—	eclipsed
	SO. . .Ar-Br. . .HC	bifurcated	—	2	g-h-g	3.06, 3.14	109.61	
	Ar-OH. . .SO. . .HO-Ar	bifurcated	5	2	h-g-h	2.62, 2.99	60.22	
3	Ar-Cl. . .H-Ar	cycle	8	2	h-h dimer	3.19	—	9.47
	CH. . .Cl-Ar. . .HC	bifurcated	—	2	g-h-g	3.16, 3.15	74.08	staggered
	CH. . .Cl-Ar	single	—	2	g-h	3.07	—	
	SO. . .Cl-Ar	single	—	2	g-h	3.24	—	
	Ar-OH. . .SO. . .HO-Ar	bifurcated	5	2	h-g-h	2.69, 2.72	64.81	
	SO. . .HO-Ar	single	—	2	g-h	2.74, 2.83	—	
	SO. . .HO-Ar	single	—	2	g-h	2.99	—	
	SO. . .H_2O. . .HO-Ar	bifurcated	—	2	g-g-h	2.97, 2.99	66.07	
	SO. . .H_2O. . .HO-Ar	bifurcated	—	2	g-g-h	2.97, 2.74	126.86	
4	Ar-F. . .H-Ar	cycle	8	2	h-h dimer	2.53	—	13.70
	Ar-F. . .HO-Ar	cycle	22	2	h-h dimer	2.78	—	staggered
	CH. . .F-Ar. . .HC	bifurcated	—	2	g-h-g	2.66, 2.95	92.16	
	Ar-OH. . .SO. . .HO-Ar	bifurcated	5	2	h-g-h	3.03, 2.79	54.61	
	Ar-OH. . .SO. . .HO-Ar	bifurcated	5	2	h-g-h	2.76, 2.85	61.06	
	Ar-OH. . .SO. . .HO-Ar	bifurcated	5	2	h-g-h	2.70, 2.76	63.52	
	H_2O. . .HO-Ar	single	—	2	g-h	2.87	—	

[a] h = host, g = guest.
[b] All hydrogen positions were calculated values.

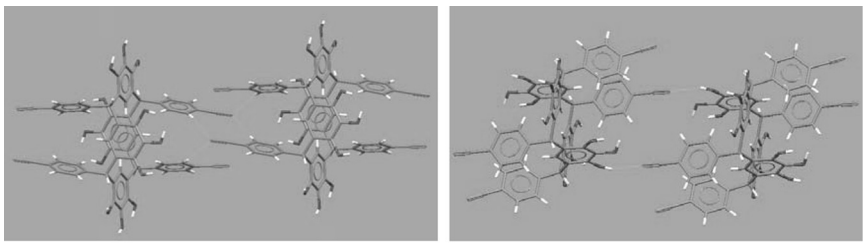


(a) (b)

FIGURE 1 Twist angles of host *C*-(4-cyanophenyl)calix[4]pyrogallolarene **1** synthesized under (a) room temperature and (b) reflux conditions. Color code: C, grey; N, blue; O, red; H, white.

Crystal Structure of *C*-(4-Cyanophenyl)calix[4]pyrogallolarene 1

Compound **1a**, prepared at room temperature, showed an eclipsed conformation of the two benzene rings on each side with a slight twist of the CN groups (Fig. 1). The twist angle of the two eclipsed benzene-ring stack was 5.07° (Fig. 1a). However, compound **1b** prepared under reflux conditions showed the two benzene rings in a staggered conformation. This arrangement forced the CN groups to be further apart from each other, where the twist angle of the two staggered benzene-ring stack became 21.31° (Fig. 1b). The host–host interactions were established through different forms of hydrogen bonds. In case of **1a**, a hydrogen bond between the nitrogen atom of the CN group and a hydrogen atom from the aromatic ring (Ar-C$\underline{N}$...$\underline{H}$-Ar) occurred to form a centrosymmetric dimer with a distance of 2.63Å. The other Ar-C$\underline{N}$...$\underline{H}$-Ar distances were 2.75 Å and 2.96 Å (Fig. 2a). Compound **1b** displayed a hydrogen bond between the nitrogen atom



(a) (b)

FIGURE 2 CN interactions found in host *C*-(4-cyanophenyl)calix[4]pyrogallolarene **1** synthesized under (a) room temperature and (b) reflux conditions.

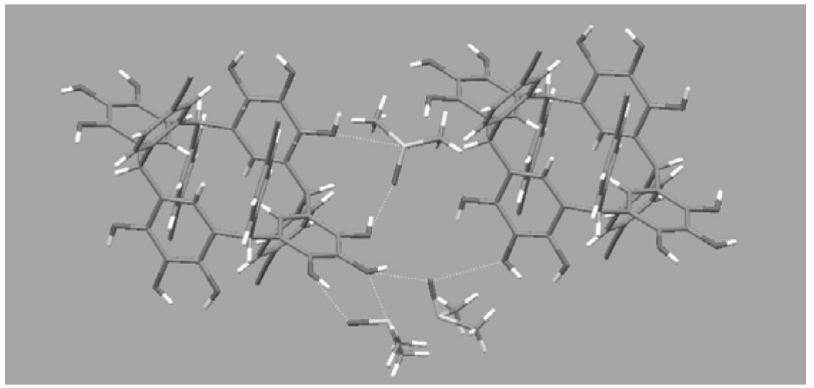


FIGURE 3 Host–guest interactions observed for the room temperature product **1a**. Color by element: C, grey; N, blue; O, red; H, white; S, yellow.

of the CN and the hydrogen atom of the phenolic group to form a centrosymmetric dimer with a distance of 2.36 Å (Fig. 2b).

Both **1a** and **1b** were found to be ternary systems. Compound **1a** incorporated three pairs of crystallographically independent and disordered DMSO molecules, and compound **1b** included four pairs of crystallographically independent and nondisordered DMSO. Both compounds **1a** and **1b** included two water molecules. Part of host–guest interactions of both **1a** and **1b** inclusion compounds are shown in Figs. 3 and 4; almost all phenolic groups were hydrogen bonded to sulfur or oxygen of DMSO molecules. In addition, N...H interactions

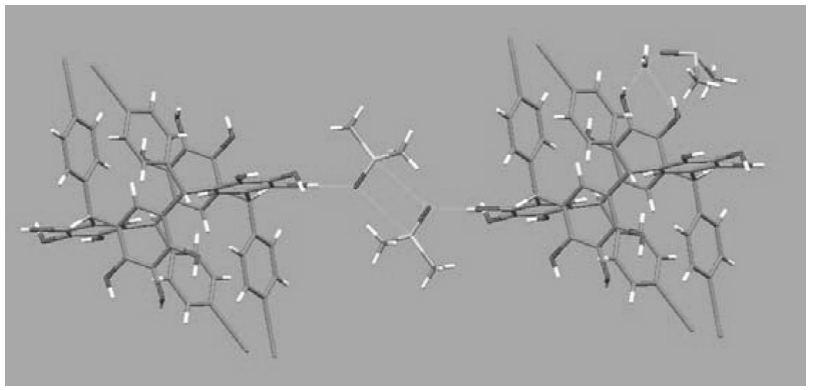
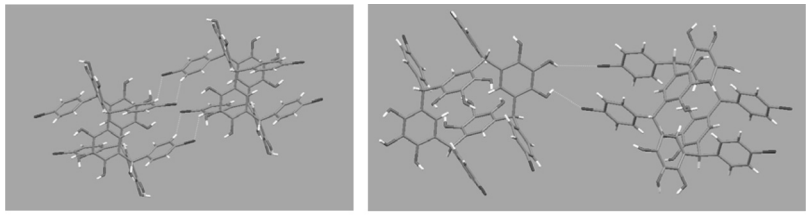


FIGURE 4 Host–guest interactions observed for the reflux product **1b**. Color by element: C, grey; N, blue; O, red; H, white; S, yellow.



(a) (b)

FIGURE 5 Br...H interactions found in host *C*-(4-bromophenyl)calix[4]pyrogallolarene **2** synthesized under (a) room temperature and (b) reflux conditions. Bromine atoms participating in interactions are indicated in red.

were also observed between the host and guest molecules. In case of compound **1b**, water molecules were essential for linking two DMSO molecules to the host molecule; this situation was not observed for compound **1a**.

Crystal Structure of *C*-(4-Bromophenyl)calix[4]pyrogallolarene 2

When the CN group was replaced with bromine, the resulting compounds **2a** and **2b** showed a different crystal system, space group, packing, supramolecularity, and molecular interactions, as illustrated in Tables 1 and 2. Both **2a** and **2b** exhibited eclipsed conformation albeit with different twist angles. The twist angle of the two eclipsed benzene-ring stack in **2a** obtained at room temperature was 1.36°,

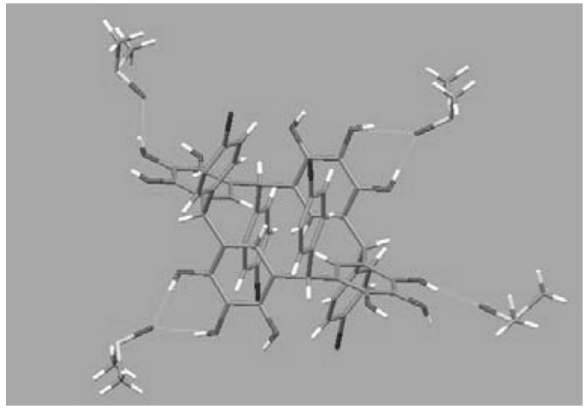


FIGURE 6 Host–guest interactions of the room-temperature product **2a**. Color by element: C, grey; O, red; H, white; S, yellow; Br, purple.

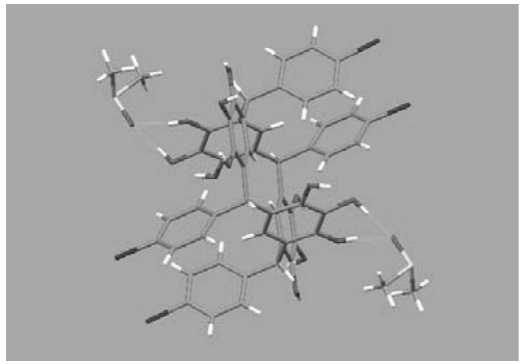


FIGURE 7 Host–guest interactions of the reflux product **2b**. Color by element: C, grey; O, red; H, white; S, yellow; Br, purple.

whereas that in **2b**, obtained under reflux conditions, was 0.08°. In the case of **2a**, the Br atom displayed a hydrogen bond with the hydrogen atom from the aromatic ring of the other calix[4]arene molecule to form centrosymmetric dimers with distances of 3.11 Å and 3.16 Å (Fig. 5a). Compound **2b** showed the Br atom bonded to the hydrogen atom of the phenolic group (Fig. 5b).

Compound **2a** was found to be a binary system, incorporating four pairs of crystallographically independent DMSO molecules with three pairs having the sulfur atom disordered into two positions. Compound **2b** was found to be a ternary system, because it included two pairs of crystallographically independent DMSO molecules of which one pair was disordered, in addition to two water molecules into two positions at 50:50 occupancy ratios. A number of intra- and intermolecular hydrogen bonds were present in the crystal structure (Fig. 5). In Fig. 6, almost all of the phenolic OH groups of host **2a** were hydrogen bonded to oxygen of DMSO molecules. Compound **2b** showed different modes of host–guest interactions as partially presented in Fig. 7.

Crystal Structure of *C*-(4-Chlorophenyl)calix[4]pyrogallolarene 3

Only one isomer of **3** was observed when bromine was replaced with chlorine. Contrary to previous examples, both reactions run at room temperature and reflux conditions produced the thermodynamically more stable staggered conformation with a twist angle of the two staggered benzene-ring stack of 9.47° (Fig. 8). Host molecules were linked via Cl...H centrosymmetric dimers with a distance of 3.19 Å (Fig. 9). Compound **3** was found to be a ternary system, incorporating three

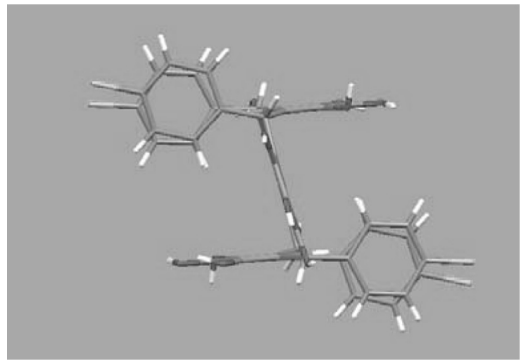


FIGURE 8 Twist angle of host *C*-(4-chlorophenyl)calix[4]pyrogallolarene **3**. Color code: C, grey; O, red; H, white; Cl, green.

pairs of crystallographically independent DMSO molecules with one disordered pair and two water molecules. The host molecules interacted with the guest molecules through Cl. . .O interactions and interaction of the phenolic group to either sulfur or oxygen of DMSO. In addition, water molecules also played a bridging role, linking the host molecule to DMSO (Fig. 10).

Crystal Structure of *C*-(4-Fluorophenyl)calix[4] pyrogallolarene 4

Similar to compound **3**, the reaction temperature had no effect on the conformation of compound **4** when chlorine was replaced with fluorine.

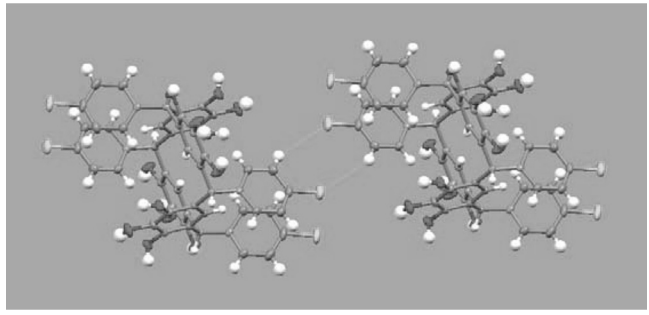


FIGURE 9 Cl. . .H centrosymmetric dimerobserved in host *C*-(4-chlorophenyl)-calix[4]pyrogallolarene **3**. Color by element: C, grey; O, red; H, white; S, yellow; Cl, green.

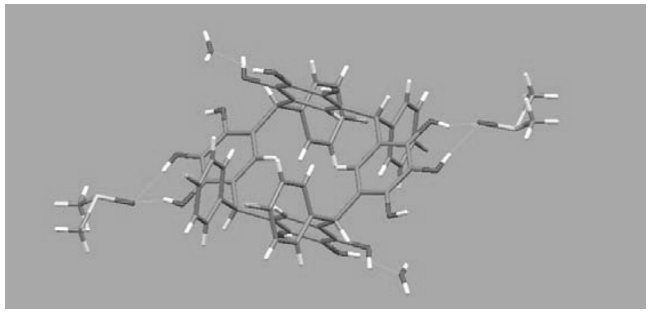


FIGURE 10 Host-guest interactions of compound **3**. Color by element: C, grey; O, red; H, white; S, yellow; Cl, green.

The thermodynamically stable staggered conformation with a twist angle of the two staggered benzene-ring stack being 13.7° was obtained (Fig. 11). Centrosymmetric dimers of F...H interactions, namely Ar-F...H-Ar with distances of 2.53 Å, were observed (Fig. 12).

Compound **4** was also found to be a ternary system, incorporating three pairs of crystallographically independent DMSO molecules with two disordered pairs and one water molecule. Hydrogen bonding was observed between the various phenolic OH groups of the host molecule and the oxygen of the DMSO and water molecules. Bifurcated F...H host–guest interactions were also observed (Fig. 13).

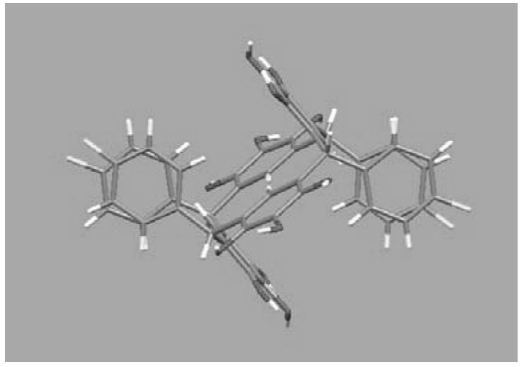


FIGURE 11 Twist angle of host *C*-(4-fluorophenyl)calix[4]pyrogallolarene **4**. Color code: C, grey; O, red; H, white; F, green.

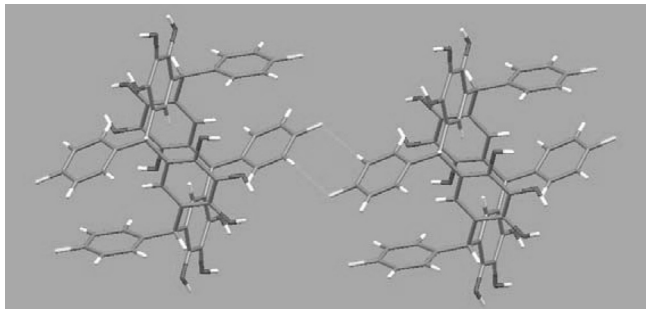


FIGURE 12 Two centrosymmetric dimer F…H interactions of host *C*-(4-fluorophenyl)calix[4]pyrogallolarene **4**. Color by element: C, grey; O, red; H, white; S, yellow; F, pale green.

Isomerization of Compounds 1–4

Compounds **1–4** exhibited mainly staggered and/or eclipsed conformations depending upon the reaction temperature. Indeed, when the condensation reactions of *para*-substituted benzaldehydes and pyrogallol were performed at room temperature or reflux conditions, two different isomers (**a** and **b**) were observed for **1** and **2**. The conversion of one isomer to another was investigated. Accordingly, compound **1a** (0.10 g) was dissolved in ethanol (50 mL), and the solution was heated under reflux for 2 days. After 1 day of reflux, a sample was collected and dried to yield a mixture of the two compounds (**a** and **b**) as indicated by the X-ray diffraction (XRD) results (Fig. 14). The powder XRD of the product obtained after 2 days of reflux was found to correspond to pure **1b** (Fig. 12). This indicated a complete transformation of

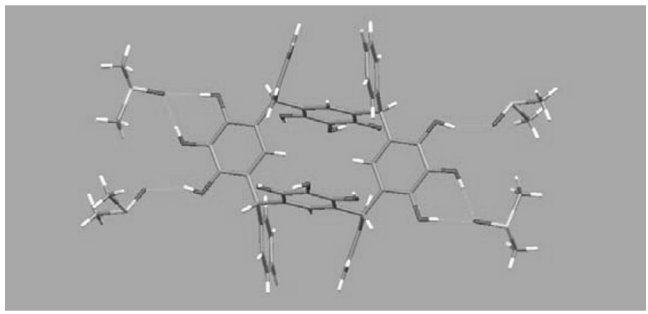


FIGURE 13 Host–guest interactions of compound **4**. Color by element: C, grey; O, red; H, white; S, yellow; F, pale green.

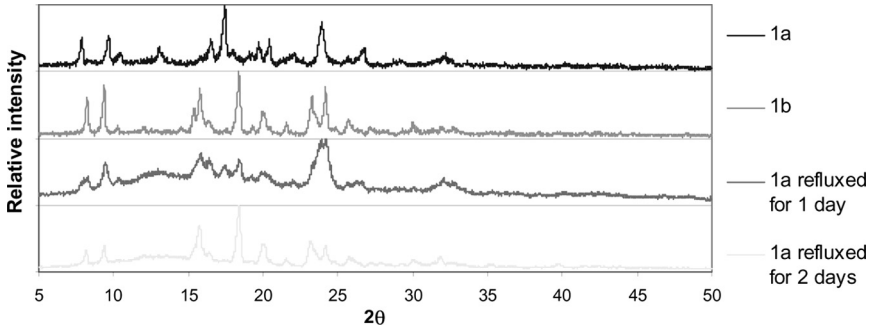


FIGURE 14 Powder X-ray diffraction patterns of the conformational isomers of **1**.

the kinetically favored product **1a** to the thermodynamically favored product **1b**. Attempts were carried out to study the effect of temperature on compounds **2a** and **2b**. However, we were unable to confirm if compound **2a** could be converted to **2b** under reflux, because the powder XRD patterns were closely similar. One plausible explanation could be related to the repulsions between the completely delocalizedπelectrons involving the cyano group and the benzene ring. Such repulsions may increase with temperature, and to minimize these repulsions, the two benzonitrile groups may twist upon temperature increase. The close face-to-face distances are 3.72Å(**1a**) and 3.80Å(**1b**). Therefore, once both isomers are formed, neither one can interchange to the other in case of R = Br.

Substitution Effects

The identity of the R group attached to the *para*-position of the benzaldehyde was crucial in determining the conformation of the host and its inclusion ability. The crystal packing forces were found to be different in relation to the R group, due to stereoelectronic factors. For example, compound **4** (where R = F) showed the strongest and the shortest hydrogen bonding such as Ar-F...H-Ar and Ar-F...H-C (host–guest interactions), respectively(Table 3). When the R group was a halogen, the unit cell volume increased when the size of the halogen increased from F to Br. This behavior affected the number of trapped guest molecules (Table 3). Host **2a** could trap eight DMSO molecules, whereas hosts **3** and **4** trapped only six DMSO molecules. In addition, host **3** trapped an extra molecule of water. When the size of halogen atom decreased from Br to F, the conformation changed from eclipsed to staggered.

TABLE 3 Interactions Present in the Crystal Structures

Compound	**2a**	**2b**	**3a, 3b**	**4a, 4b**
Halogen substituent, X	Br	Br	Cl	F
V, Å^3	1923.2 (5)	3170.2 (3)	1714.17 (14)	1661.91 (12)
No. of DMSO/host	8	4	6	6
No. of water/host	0	2	2	1
Conformation	eclipsed	eclipsed	staggered	staggered
Twist angle	1.36	0.08	9.47	13.70
Ar-X. . .H-Ar	3.111, 3.155	3.263	3.192	2.533
Ar-X. . .H-C	3.211, 3.473, 3.497	3.141	3.072, 3.149, 3.160	2.661, 2.950

CONCLUSIONS

Four members of the *C*-phenylcalix[4]pyrogallolarene [*C*-(4-cyanophenyl)calix[4]pyrogallolarene **1**, *C*-(4-bromophenyl)calix[4]pyrogallolarene **2**, *C*-(4-chlorophenyl)calix[4]pyrogallolarene **3**, and *C*-(4-fluorophenyl)-calixl[4]pyrogallolarene **4**] were synthesized through the condensation of an aldehyde with pyrogallol at different temperatures.When reactions were performed at room temperature, the structural isomerization and conversion of isomers were observed in only compound **1**. The conversion of one isomer to another was possible with certain substituents.

The substitution effects of the R group on the supramolecularity of the *C*-phenylcalix[4]pyrogallolarene were also examined. The crystal packing forces varied according to steric considerations and electronic factors imposed by the R group. By varying the size and the electronic properties of the R group, the inclusion properties (number of DMSO and H_2O molecules) could be controlled. The type of halogen substitution also affected the strength of hydrogen bonding between host and guest molecules. The two isomers of **1** and **2** could be exploited as two potential cocrystal formers. With the same active pharmaceutical ingredient, they could form two types of pharmaceutical cocrystal, with one form perhaps more valuable than the other.

EXPERIMENTAL

Melting points were determined using a Büchi melting-point B-540 apparatus. IR spectra were performed using an Excalibur series Biorad FTS3000MX instrument. NMR spectra were recorded using a Bruker 400 MHz standard bore instrument with Quad Nuclear Probe (QNP) probe and carbon substitution information was determined using the Distortionless Enhancement of Polarisation Transfer (DEPT) procedure. High-resolution mass spectrometry data were

recorded using a Finnigan TSQ 7000 machine. Elemental analyses for C, H, N, Br, Cl, and F were determined using a Perkin-Elmer PE 2400 elemental analyser. Crystals were dried in air and placed in alumina or platinum sample pans. Sample masses in each case were ~10 mg, and the samples were purged by a stream of air flowing at 200 mL/min. min. All experiments were carried out with a temperature program using TA Instruments SDT 2960 starting from room temperature isothermal for 10 min followed by 10°C/min ramp up to 750°C.

Note: in all of the compounds reported, the internal aromatic proton in the cavity could not be observed by NMR in the indicated solvent.

C-(4-Cyanophenyl)calix[4]pyrogallolarene (1)

A solution of 4-cyanobenzaldehyde (2.60 g, 1 equiv) in ethanol (40 mL) was added dropwise to an ice-cold solution of pyrogallol (2.50 g, 0.0198 mol) in ethanol (15 mL) and conc. HCl (10 M, 3 mL). The reaction mixture was then stirred at room temperature for 24 h. The resultant precipitate was collected by vacuum filtration and washed with ethanol and water. Product **1a** was obtained as light pink solid (0.38 g) in 8.1% yield, mp > 400°C.

1a. IR: 3515–3254 (broad), 2234, 1928, 1805, 1621, 1606, 1501, 1462, 1366, 1282, 1192, 1075, 1017, 943, 868, 829, 789, 752, 709, 573 cm^{-1}; ^{1}H NMR (DMSO) δ: 4.73 (s, 4H), 5.76 (s, 8H), 5.92 (s, 4H), 6.80 and 6.82 (d, $J_{AB} = 8.0$ Hz, 8H), 7.40 and 7.42 (d, $J_{AB} = 8.0$ Hz, 8H); ^{13}C NMR (DMSO) δ: 42.9 (CH), 107.6 (C), 118.7 (C), 119.9 (CH), 120.0 (C), 121.0 (C), 121.8 (CH), 129.8 (CH), 130.9 (CH), 131.8 (C), 132.7 (C), 142.2 (C), 142.7 (C) and 150.2 (C); m/z of >10% intensity (ESI −c): 477.3, 955.3, Elemental analysis: experimental (calculated), %C: 65.79 (70.29), %H: 4.15 (3.79), %N: 5.21 (5.86); DSC: (exotherm) temperature: 293.98, 507.29°C, respective heat flow: 8.10, 31.53 W/g; TGA: weight loss of 16.96% from room temperature up to 200°C , followed by 55.88% weight loss beyond 293.98°C, and remaining weight loss starting at 507.29°C and ending at 626.53°C. When the same reaction was repeated exactly as detailed previously except that it was heated under reflux for 24 h, product **1b** was obtained as a light pink solid (0.93 g) in 19.6% yield, mp > 400°C.

1b. IR: 3407 (broad), 2234, 1605, 1501, 1461, 1364, 1284, 1197, 1076, 1015, 942, 869, 832, 576 cm^{-1}; ^{1}H NMR (DMSO) δ 4.70 (s, 4H), 5.73 (s, 8H), 5.89 (s, 4H), 6.77 and 6.79 (d, $J_{AB} = 8.0$ Hz, 8H), 7.36 and 7.38 (d, $J_{AB} = 8.4$ Hz, 8H); ^{13}C NMR (DMSO) δ 42.9 (CH), 107.6 (C), 118.7 (C), 119.9 (CH), 120.0 (C), 121.0 (C), 121.8 (CH), 129.8 (CH), 130.9 (CH), 131.8 (C), 132.7 (C), 142.2 (C), 142.7 (C) and 150.2 (C); m/z of >10% intensity (ESI −c): 477.2, 842.2, 955.3. Elemental analysis:

experimental (calculated), %C: 70.25 (70.29), %H: 3.82 (3.79), %N: 5.26 (5.37); DSC: (exotherm) temperature: 295.56, 510.49°C, respective heat flow: 10.63, 36.38 W/g; TGA: weight loss of 9.51% from room temperature, followed by 64.56% weight loss starting at 295.56°C, and remaining weight loss starting at 510.49°C and ending at 630.57°C.

C-(4-Bromophenyl)calix[4]pyrogallolarene (2)

A solution of 4-bromobenzaldehyde (3.67 g, 1 equiv) in ethanol (40 mL) was added dropwise to an ice-cold solution of pyrogallol (2.50 g, 0.0198 mol) in ethanol (15 mL) and conc. HCl (10 M, 3 mL). The reaction mixture was then stirred at either room temperature or heated at reflux for 24 h. The resultant precipitate was collected by vacuum filtration and washed successively with water and ethanol. Product **2a** obtained at room temperature as a light pink solid (0.53 g) in 9.1% yield. Product **2b** obtained at reflux was also light pink solid (1.25 g) in 43.0% yield. The melting points of both **2a** and **2b** were more than 400°C.

2a. IR: 3468–3345 (broad), 1910, 1782, 1628, 1606, 1467, 1405, 1366, 1281–1209 (broad), 1072, 1011, 938, 923, 880, 862, 818, 725, 667, 564 cm^{-1}; ^{1}H NMR (DMSO) δ: 5.03 (s, 4H), 5.62 (s, 8H), 5.88 (s, 4H), 6.53 and 6.56 (d, $J_{AB} = 8.4$ Hz, 8H), 7.10 and 7.12 (d, $J_{AB} = 8.4$ Hz, 8H); ^{13}C NMR (DMSO) δ: 42.2 (CH), 117.9 (C), 119.5 (CH), 120.9 (C), 121.1 (C), 122.1 (CH), 129.8 (CH), 131.0 (CH), 131.6 (C), 132.2 (C), 142.1 (C), 142.3 (C) and 143.3 (C). Elemental analysis: experimental (calculated), %C: 53.13 (53.27), %H: 2.91 (3.09), %Br: 26.85 (27.26); DSC: (exotherm) temperature: 298.59, 447.93, 478.20, 503.43, 529.66°C, respective heat flow: 13.14, 16.61, 13.00, 10.21, 7.84 W/g; TGA: weight loss of 21.42% starting room temperature, followed by 42.06% weight loss starting at 298.59°C, then 11.88% starting at 447.93°C, and remaining weight loss starting at 478.20°C, ending at 539.75°C.

2b. IR: 3480 (broad), 3343 (broad), 1913, 1782, 1631, 1606, 1467, 1405, 1369, 1281 (broad), 1070, 1013, 929, 922, 880, 861, 815, 728, 670, 564 cm^{-1}; ^{1}H NMR (DMSO) δ: 5.02 (s, 4H), 5.61 (s, 8H), 5.88 (s, 4H), 6.53 and 6.55 (d, $J_{AB} = 8.4$ Hz, 8H), 7.10 and 7.12 (d, $J_{AB} = 8.4$ Hz, 8H); ^{13}C NMR (DMSO) δ: 42.2 (CH), 117.9 (C), 119.5 (CH), 120.9 (C), 121.1 (C), 122.1 (CH), 129.8 (CH), 131.0 (CH), 131.6 (C), 132.2 (C), 142.1 (C), 142.3 (C) and 143.3 (C). Elemental analysis: experimental (calculated), %C: 53.11 (53.27), %H: 3.05 (3.09), %Br: 27.11 (27.26); DSC: (exotherm) temperature: 281.44, 454.99, 492.33°C, respective heat flow: 14.42, 22.10, 22.54 W/g; TGA: weight loss of 20.54% from room temperature, followed by 45.73% weight loss starting at 281.44°C, then 23.80% starting at 454.99°C, and remaining weight loss starting at 492.33°C and ending at 560.94°C.

C-(4-Chlorophenyl)calix[4]pyrogallolarene (3)

A solution of 4-chlorobenzaldehyde (2.89 g, 1 equiv) in ethanol (40 mL) was added dropwise to an ice-cold solution of pyrogallol (2.50 g, 0.0198 mol) in ethanol (15 mL) and conc. HCl (10 M, 3 mL). The reaction mixture was then stirred at either room temperature or refluxed for 24 h. The resultant precipitate was collected by vacuum filtration and successively washed with water and ethanol. Product **3a** obtained at rt as a pink solid (0.41 g) in 8.3% yield. Product **3b** obtained at reflux was also pink solid (1.81 g) in 36.7% yield. The melting points of both **3a** and **3b** were more than 400°C.

3a. IR: 3477–3352 (broad), 1910, 1782, 1628, 1606, 1492, 1467, 1409, 1371, 1281–1208 (broad), 1070, 1017, 820, 736, 672, 563 cm^{-1} ^1H NMR (DMSO) δ: 4.96 (s, 4H), 5.63 (s, 8H), 5.89 (s, 4H), 6.59 and 6.61 (d, $J_{AB} = 8.4$ Hz, 8H), 6.96 and 6.98 (d, $J_{AB} = 8.4$ Hz, 8H); ^{13}C NMR (DMSO) δ: 42.1 (CH), 119.7 (CH), 120.9 (C), 121.3 (C), 122.2 (CH), 126.8 (CH), 129.5 (C), 130.5 (CH), 131.6 (C), 132.2 (C), 142.0 (C), 142.3 (C) and 142.9 (C). Elemental analysis: experimental (calculated), %C: 62.87 (62.79), %H: 3.52 (3.65), %Cl: 14.15 (14.26); DSC: (exotherm) temperature: 296.57, 452.98, 498.38, 530.67°C, respective heat flow: 11.67, 17.64, 12.40, 7.01 W/g; TGA: weight loss of 15.87% from room temperature, followed by 55.63 % weight loss starting at 296.57°C, then 20.10% starting at 452.98°C, and remaining weight loss starting at 498.38°C and ending at 537.74°C.

3b. IR: 3482, 3466, 3357, 1631, 1606, 1491, 1467, 1411, 1371, 1281, 1246, 1210, 1070, 1016, 817, 737, 674, 564 cm^{-1}; ^1H NMR (DMSO) δ: 4.96 (s, 4H), 5.63 (s, 8H), 5.89 (s, 4H), 6.58 and 6.60 (d, $J_{AB} = 8.8$ Hz, 8H), 6.95 and 6.97 (d, $J_{AB} = 8.4$ Hz, 8H); ^{13}C NMR (DMSO) δ: 42.1 (CH), 119.7 (CH), 120.9 (C), 121.3 (C), 122.2 (CH), 126.8 (CH), 129.5 (C), 130.5 (CH), 131.6 (C), 132.2 (C), 142.0 (C), 142.3 (C) and 142.9 (C). Elemental analysis: experimental (calculated), %C: 62.61 (62.79), %H: 3.49 (3.65), %Cl: 14.13 (14.26); DSC: (exotherm) temperature: 292.54, 488.29°C, respective heat flow: 10.48, 30.89 W/g; TGA: Weight loss of 10.71% from room temperature, followed by 78.46% weight loss starting at 292.54°C, and remaining weight loss starting at 488.29°C and ending at 581.12°C.

C-(4-Fluorophenyl)calix[4]pyrogallolarene (4)

A solution of 4-fluorobenzaldehyde (2.46 g, 1 equiv) in ethanol (10 mL) was added dropwise to an ice-cold solution of pyrogallol (2.50 g, 0.0198 mol) in ethanol (15 mL) and conc. HCl (10 M, 3 mL). The reaction mixture was then stirred at either room temperature or heated

under reflux for 24 h. The precipitate was collected by vacuum filtration and successively washed with water and ethanol. Compound **4a** obtained at room temperature as a pink solid (0.86 g) in 18.7% yield. Compound **4b** obtained at reflux as a pink solid (3.91 g) but with a higher yield of 85.0%. The melting points of both **4a** and **4b** were more than 400°C.

4a. IR: 3476 (broad), 3387 (broad), 1629, 1604, 1506, 1467, 1372, 1286, 1233, 1158, 1069, 1015, 830, 564 cm^{-1}; ^{1}H NMR (DMSO) δ: 4.86 (s, 4H), 5.63 (s, 8H), 5.90 (s, 4H), 6.58–6.61 (m, 8H) and 6.68–6.72 (m, 8H); ^{13}C NMR (DMSO) δ: 42.0 (CH), 113.4 (CH), 113.6 (CH), 119.9 (CH), 121.1 (C), 121.7 (C), 122.3 (CH), 130.3 (CH), 131.6 (C), 132.2 (C), 140.0 (C), 141.7 (C), 142.2 (C), 158.8 (C) and 161.2 (C). One additional CH and one additional quaternary C signal due to ^{13}C–^{19}F coupling [17]. Elemental analysis: experimental (calculated), %C: 67.48 (67.24), %H: 3.66 (3.91), %F: 7.97 (8.18); DSC: (exotherm) temperature: 286.48, 470.13, 502.42°C, respective heat flow: 11.41, 20.06, 6.09 W/g; TGA: weight loss of 13.85% from room temperature, followed by 69.69% weight loss starting at 286.48°C, and remaining weight loss starting at 470.13°C and ending at 552.87°C.

4b. IR: 3482, 3468, 3388, 1630, 1605, 1509, 1467, 1371, 1286, 1234, 1159, 1069, 1018, 830, 565 cm^{-1}; ^{1}H NMR (DMSO) δ: 4.86 (s, 4H), 5.63 (s, 8H), 5.90 (s, 4H), 6.57–6.72 (m, 8H) and 6.69–6.72 (m, 8H); ^{13}C NMR (DMSO) δ: 42.0 (CH), 113.4 (CH), 113.6 (CH), 119.9 (CH), 121.1 (C), 121.7 (C), 122.3 (CH), 130.3 (CH), 131.6 (C), 132.2 (C), 140.0 (C), 141.7 (C), 142.2 (C), 158.8 (C), and 161.2 (C). One additional CH and one additional quaternary C signal due to ^{13}C–^{19}F coupling [17]; m/z of $>10\%$ intensity (ESI –c): 463.2, 927.3. Elemental analysis: experimental (calculated), %C: 67.20 (67.24), %H: 3.78 (3.91), %F: 7.92 (8.18); DSC: (exotherm) temperature: 296.57, 474.17°C; respective heat flow: 13.72, 24.13 W/g; TGA: weight loss of 10.04% from room temperature, followed by 77.92 % weight loss starting at 296.57°C, and remaining weight loss starting at 474.17°C and ending at 573.05°C.

Solution and Refinement of the Crystal Structures

Single-crystal X-ray diffraction experiments were carried out on a Bruker SMART Apex 1000 diffractometer equipped with a CCD detector and Mo-Kα sealed tube at 223(2) K. SMART [18] was used for collecting frame data, indexing reflection, and determination of lattice parameters. SAINT [18] was used for integration of intensity of reflections and scaling. SADABS [19] was used for absorption correction and SHELXTL [20] for space group, structure determination, and

least-square refinements on F^2. All hydrogen atoms were placed in calculated positions for the purpose of structure factor calculation. All nonhydrogen atoms were refined anisotropically [20], and all hydrogen atoms were included in calculated positions with isotropic thermal motion linked to that of the bonded atom.

SUPPORTING INFORMATION AVAILABLE

Crystallographic data (cif) have been deposited with the Cambridge Structural Data Centre (CCDC), CCDC reference numbers 269682–269683 and 280479–280482. See http://www.rsc.org/suppdata/ for crystallographic data in .cif or other electronic format. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223–336033 or E-mail: deposit@ccdc.cam.ac.uk].

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