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Microwave-assisted synthesis of resorcin[4]arene and pyrogallol[4]arene macrocycles

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ABSTRACT

A series of resorcin[4]arene and pyrogallol[4]arene macrocycles have been synthesized efficiently within 5 min, affording crystalline products suitable for single crystal X-ray diffraction, utilising microwave irradiation in a 'one-pot' reaction whilst controlling the selective formation of the *rccc* cone stereoisomer.

Resorcin[4]arene and pyrogallol[4]arene are subgroups of calixarene macrocycles containing eight and twelve hydroxy groups at the upper rim of their cup-like structure, respectively. This abundance of potential hydrogen bonding sites plays an essential role in the self-assembly of these molecular building blocks into supramolecular carcerants,[1,2] cavitands[3,4] and nanometre scale capsules.[5–7] Subsequently, they have been investigated and developed for a wide variety of applications including metal extraction,[8,9] sensors,[10,11] phase transfer of hydrocarbon gases[12] and as novel stationary phases.[13–15]

Despite the rapid emergence and utilisation of these materials, the original synthesis remained relatively unchanged for over 130 years and is based on the cyclocondensation of resorcinol or pyrogallol with an aldehyde under acidic conditions, for up to 7 days at reflux.[16] This condensation reaction predominantly affords the cyclic tetramer over the pentamer and hexamer.[17] Generally, the all *cis*-tetramer, *rccc*, precipitates during the course of the reaction, due to its low solubility in acidic aqueous media and thereby drives the reaction to the macrocyclic product. This thermodynamically preferred cone conformation exhibits four intramolecular H-bonding interactions, which are not accessible in the three other *rccc* conformations. The formation of the other relative configurations (Scheme 1) is sterically driven by the axial subsistent, R′, but can also result from the presence of electron-withdrawing groups at the α-position of the phenolic residue.

Greener approaches, such as our own solvent-free method,[18] using a catalytic amount of *p*-toluenesulfonic acid (*p*TSA), have been reported for aryl resorcin[4]arenes and alkyl pyrogallol[4]arenes.[19] However, isomeric control and scale-up of these methods are problematic. The host–guest chemistry that drives the majority of the research and applications of these materials relies on the formation of the *rccc* cone conformer. Herein, we report a versatile green synthetic route that demonstrates selective control over the stereoisomer formation of both the resorcin[4]arene and pyrogallol[4]arene.

Microwave irradiation has emerged as a versatile tool for organic synthesis and is used for its ability to reach high temperatures rapidly via electromagnetic waves.

By utilising microwave irradiation, the reaction times can often be significantly reduced and, therefore, the energy efficiency is greatly increased. It has recently been demonstrated that a tungstophosphoric acid Keggin-type can be combined with microwave irradiation to synthesise resorcin[4]arenes.[20] This work was later developed to include the pyrogallol[4]arene macrocycles.[21] However, when highly hindered substituted aldehydes, such as aryl or tolyl are used, the favoured stereomer is *rctt*.[18]

The following method has been tuned to produce the *rccc* stereoisomer, as the major product, independently of the pendant R′ group length or steric hindrance; thereby, substantially increasing accessibility to a wider range of diverse macrocycles via greener technologies. Additionally, by controlling the reaction conditions and using a sealed vessel, the work-up procedure has been reduced to simple filtration.

The general procedure consists of premixing equimolar quantities of resorcinol or pyrogallol with an aldehyde in an acidic reaction medium. The reaction vessel is sealed and subjected to microwave irradiation for five minutes at a constant temperature of 100 °C using a CEM Discovery SP instrument. Upon cooling, the *rccc* product crystallises from the solution, whereupon it can be collected by filtration as the pure product.

A library of calixarene macrocycles **1**–**10** (Table 1) were chosen as a representative sample. All reactions were conducted on a gram scale and the products were characterised using ^{1}H and ^{13}C NMR techniques and MALDI-TOF mass spectrometry. In order to isolate any potential *rctt* isomer, distilled water was added to the reaction medium and the precipitate was subsequently collected and characterised. Potentially, any unreacted starting materials and solvent can then be readily recycled.

The NMR chemical shifts for macrocycles **1**–**10** were consistent with the literature values for the isolated stereoisomers synthesised

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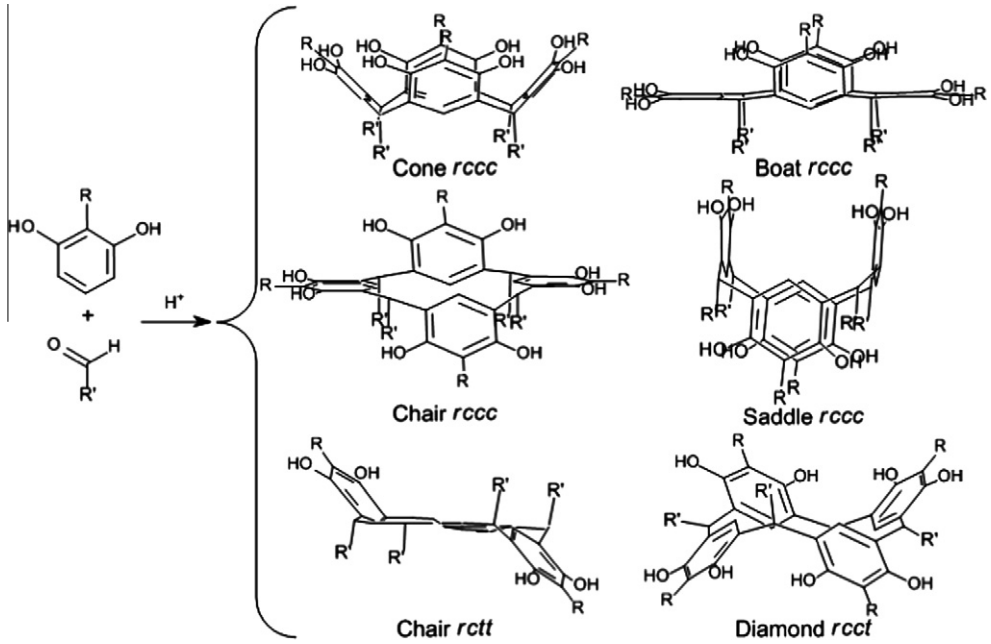


Scheme 1. Macrocycle stereoisomers. (Resorcinol, R = H and pyrogallol R = OH; R′ = alkyl or aryl chain, equatorial functional groups have been omitted for clarity).

Table 1
Microwave-assisted synthesis of calixarene macrocycles

Macrocycle	R	R′	Yield (%)	*m/z* [M+Na]$^+$
1	OH	$(CH_2)CH(CH_3)_2$	85	799
2	OH	$(CH_2)_2CH_3$	61	743
3	OH	$(CH_2)_3CH_3$	62	799
4	OH	$(CH_2)_4CH_3$	68	855
5	OH	C_6H_5	66	879
6	H	$(CH_2)CH(CH_3)_2$	90	735
7	H	$(CH_2)_2CH_3$	96	679
8	H	$(CH_2)_3CH_3$	67	735
9	H	$(CH_2)_4CH_3$	84	791
10	H	C_6H_5	72	805
11	OH	*o*-tolyl	84	935
12	OH	*m*-tolyl	94	935
13	OH	*p*-tolyl	87	935
14	H	*o*-tolyl	86	848
15	H	*m*-tolyl	96	848
16	H	*p*-tolyl	94	848

Table 2
Conformational study of the microwave-assisted synthesis of *c*-butylpyrogallol[4]arene

Time (min)	*T* (°C)	Solvent	Yield (%)	*rccc*[a] (%)	Time (min)	*T* (°C)	Solvent	Yield (%)	*rccc*[a] (%)
1			Oligomer[a]			40		Oligomer[b]	
2			57	77		60		Oligomer[b]	
3			65	79	5	80	EtOH	77	85
4			60	80		120		Decomposed[b]	
5	100	EtOH	73	83		140		Decomposed[b]	
6			76	86	5	100	MeOH	56	66
7			79	86			*n*PrOH	40	88
8			66	83			*n*BuOH	76	96
9			72	86			EtOAc	25	96
10			70	86			H_2O	56	4

[a] Stereoisomer yields based on ^{1}H NMR integration.
[b] Product was not isolated. Constant power (100 W) and HCl ratio (25%).

using traditional techniques.[22,23] Macrocyles **11**–**16** were isolated and characterised as the *rccc* isomers following a recrystallization of the crude product from methanol.[24] Crystalline materials isolated from the crude reaction media were further investigated by single crystal X-ray analysis. In all cases, the molecular structure was that of the *rccc* isomer as a solvated clathrate, with crystallographic measurements consistent with literature values.[16]

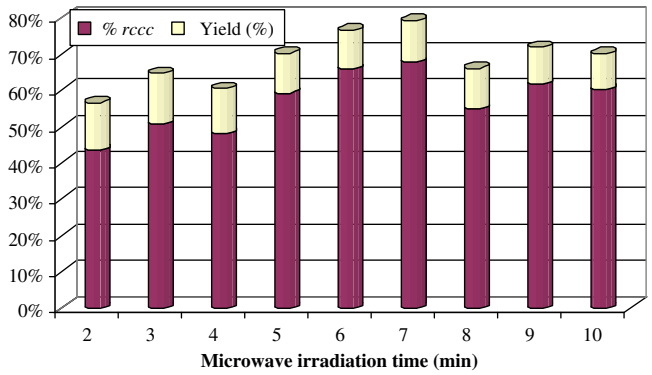
The rapid synthesis of the macrocycles using this microwave technique has enabled us to explore and study the effects of varying the reaction conditions on the formation of the different stereoisomers. These studies were conducted on *c*-butylpyrogallol[4]arene as a model synthesis. The effects of changing reaction conditions including time, temperature, solvent and acid catalyst were assessed and are summarised in Table 2.

To assess the stereoisomer control of the varying synthetic parameters, the crude product of the reaction was isolated via precipitation with water. The ^{1}H NMR spectra of the precipitates, in DMSO-d_6, displayed three triplets with a chemical shift between 4 and 6 ppm. This is indicative of the presence of both the *rccc* cone (single triplet, 4*H*) and the *rctt* (two inequivalent triplets, $2H_{axial}$ and $2H_{equatorial}$) stereoisomers. There was no evidence of the *rcct* isomer in any of the crude products. The relative percentages of both stereoisomers present in the crude product were assessed by ^{1}H NMR integration techniques. Integration of the characteristic singlet for the pyrogallol aromatic proton at 6.85 ppm was normalised to one and the integrations of the characteristic triplets of the *rctt* conformation were measured. In all cases, the *rccc* product was observed to be the predominant configuration.

Following the reaction over time revealed that exposure time did not influence significantly the formation of the *rctt* chair conformer, as it remained constant after 6 min. However, higher yields were obtained on longer reaction times (Graph 1).

Although there does not appear to be a linear relationship between time and yield over ten minutes, the overall formation of the *rccc* stereoisomer can be seen to be favoured with prolonged exposure to microwave irradiation.

The macrocyclic product was only observed when the temperature was allowed to increase above 80 °C. Below this temperature only linear oligomers could be isolated. As the temperature increases, the relative percentage yield of the *rccc* stereoisomer remained constant. However, when the temperature was further increased to 120 °C and above the reaction mixture decomposed.



Graph 1. Overall yield (total) and *rccc* stereoisomer yield depending on microwave irradiation time (min).

As the formation of the macrocycle is an equilibrium, it can be displaced by selecting the reaction media that precipitates the desired product (Graph 2).

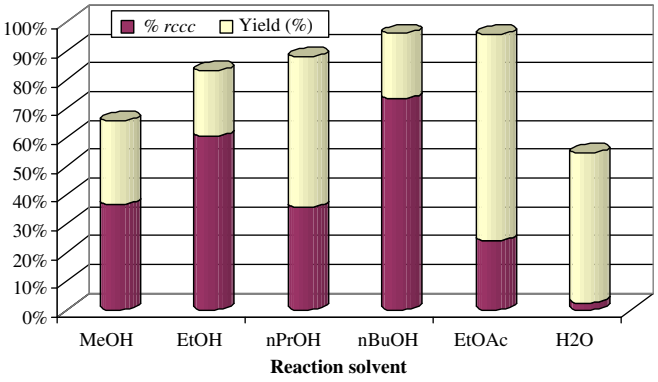
Switching the solvent from ethanol to water resulted in a negligible isolated yield. This is due to the equilibrium of this condensation reaction being driven to the left, thereby preventing the reaction from going to completion. In contrast, the insolubility of the *rccc* cone conformer in ethanol drives the equilibrium towards the product. Remarkably, when ethyl acetate was used as the solvent system the *rccc* isomer crystallised from the reaction media on cooling as the nanometre scale hexameric assembly.[22]

The formation of the macrocycle is reported to proceed via the acetal of the aldehyde in situ,[17] which subsequently reacts with the phenol. Hence, the steric bulk of the acetal function plays a predominant role in influencing the formation of one conformation over the other. As the length of the alcohol chain was increased from ethyl to butyl, the yield of the *rccc* macrocycle was increased, hence by increasing the bulkiness of the acetal, the possibilities to interchange conformations were lowered.

The solid state molecular structure obtained from slow diffusion of water into a solution of macrocycle **3** in DMSO shows that the solvent coordinates to the upper rim hydroxy groups of the pyrogallol.[25] (Fig. 1).

It was anticipated that this hydrogen bonding interaction would disturb the preorganisation of the cone *rccc* stereoisomer during the condensation reaction. DMSO was, therefore, introduced to the reaction solvent (ethanol) to reduce the possibilities of intramolecular H-bonding in the tetramer leading to the formation of the *rctt* stereoisomer. Surprisingly, the addition of DMSO had no significant effect on the overall yield or stereoisomer ratio.

Changing the acid catalyst from hydrochloric acid to acetic acid, in the absence of any additional solvent, prevented the reaction from proceeding to the desired product. However, when *p*TSA was used as the acid catalyst in ethanol, over 70% of the *rctt* product was isolated. The addition of acetic and formic acid to a 25% hydrochloric ethanolic solution resulted in lower overall yields, whilst retaining the *rccc* conformation as the predominant stereoisomer.



Graph 2. Overall yield (white) and %*rccc* (red) depending on the solvent system.

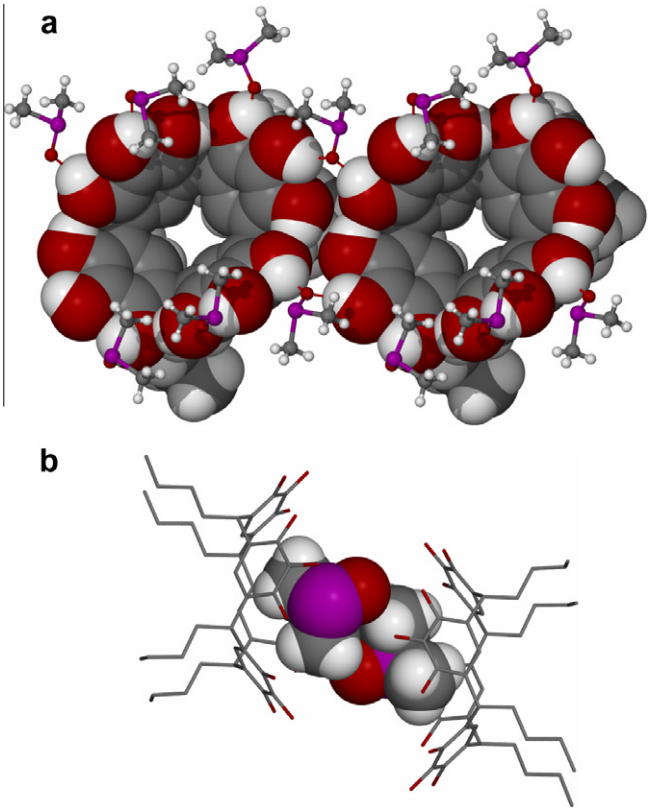


Figure 1. Molecular projection of the *c*-butylpyrogallol[4]arene DMSO clathrate (**3**): (a) top view of two *rccc* symmetrical cone-configured macrocycles, hydrogen bonded together via two DMSO bridges, (b) compound **3** DMSO clathrate (macrocycle hydrogen atoms omitted for clarity).

To facilitate both the recycling of the catalyst and towards developing a flow reactor,[26] a switch from homogeneous to heterogeneous conditions was investigated. Preliminary experiments involving solid acidic zeolites, including K10-Montmorillonite, HMFI, HFAU, Na-MOR as well as aluminium oxide, were far from comparable to the heterogeneous acid conditions but are still under investigation.

In implementing this new technique, the energy required and the waste production are considerably reduced compared to the traditional open vessel synthesis. In conclusion, we have demonstrated that this greener synthesis of both resorcin[4]arene and pyrogallol[4]arene macrocycles can be tuned to predominantly yield the *rccc* stereoisomer. Moreover, it can be applied to an extensive range of products, including alkyl chains and aromatic substituents, as a one-pot reaction without any further purification. We are continuing to investigate safer greener routes to these materials and are focusing our research on switching to a benign heterogeneous system that can potentially be scaled-up to a continuous flow reactor.

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24. Compound **11**: yield 84%; ^{1}H NMR (DMSO-d_6; 400 MHz) δ 2.49 (s, 12*H*), 4.83 (s, 4*H*), 5.96 (s, 4*H*), 6.59 (m, 4*H*), 6.69 (m, 8*H*), 6.95 (m, 4*H*), 7.55 (s, 12*H*) ppm; ^{13}C NMR (DMSO-d_6; 100.6 MHz) δ 18.9, 120.5, 121.0, 124.3, 124.4, 128.9, 135.2, 139.8142.0, 142.3, 142.4, 142.9 ppm; MALDI-TOF $C_{56}H_{48}O_{12}$ *m*/*z* 935.97 [M+Na]$^+$; elemental analysis for $C_{56}H_{48}O_{12}$ calcd (found) C 73.67 (73.65), H 5.30 (5.30)%. Compound **12**: yield 94%; ^{1}H NMR (DMSO-d_6; 400 MHz) δ 2.39 (s, 12*H*, CH_3), 4.96 (s, 4*H*), 6.23 (s, 4*H*), 7.00 (m, 12*H*), 7.43 (m, 4*H*), 7.55 (s, 12*H*) ppm; ^{13}C NMR (DMSO-d_6; 100.6 MHz) δ 19.6, 39.2, 124.7, 124.8, 126.1, 125.8, 129.6, 131.2, 137.0, 138.5, 143.0, 144.9 ppm; MALDI-TOF $C_{56}H_{48}O_{12}$ *m*/*z* 935.97 [M+Na]$^+$; elemental analysis for $C_{56}H_{48}O_{12}$ calcd (found) C 73.67 (73.70), H 5.30 (5.30)%. Compound **13**: yield 87%; ^{1}H NMR (DMSO-d_6; 400 MHz) δ 1.49 (s, 12*H*), 4.96 (s, 4*H*), 6.17 (s, 4*H*), 6.89 (AA′XX′, 8*H*), 6.99 (AA 'XX', 8*H*) ppm; ^{13}C NMR (DMSO-d_6; 100.6 MHz) δ 19.1, 46.8, 120.0, 126.3, 127.0, 127.1, 129.8, 131.9, 140.3 ppm; MALDI-TOF $C_{56}H_{48}O_{12}$ *m*/*z* 935.97 [M+Na]$^+$; elemental analysis for $C_{56}H_{48}O_{12}$ calcd (found) C 73.67 (73.70), H 5.30 (5.30)%. Compound **14**: yield 86%; ^{1}H NMR (DMSO-d_6; 400 MHz) δ 2.49 (s, 12*H*), 5.22 (s, 4*H*), 5.67 (s, 4*H*), 6.14 (s, 4*H*), 6.68 (m, 12*H*), 6.72 (m, 4*H*), 6.53 (s, 8*H*) ppm; ^{13}C NMR (DMSO-d_6; 100.6 MHz) δ 20.7, 39.5, 103.1, 120.4, 121.1, 122.0, 125.8, 136.5, 136.7, 144.6, 145.8, 153.8 ppm; MALDI-TOF $C_{56}H_{48}O_8$ *m*/*z* 848.33 [M+Na]$^+$; elemental analysis for $C_{56}H_{48}O_8$ calcd (found) C 79.22 (79.22), H 5.70 (5.65)%. Compound **15**: yield 96%; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 1.35 (s, 12*H*), 4.87 (s, 4*H*), 5.36 (s, 4*H*), 5.44 (s, 4*H*), 6.75 (s, 4*H*), 6.84 (d, ^3J = 7.73 Hz, 4*H*), 6.93 (d, ^3J = 7.73 Hz, 4*H*), 7.07 (t, 4*H*, ^3J = 7.44 Hz) ppm; ^{13}C NMR (DMSO-d_6; 100.6 MHz) δ 19.7, 39.8, 100.7, 119.3, 123.7, 124.2, 127.9, 134.2, 138.9, 143.7, 150.9 ppm; MALDI-TOF $C_{56}H_{48}O_8$ *m*/*z* 848.33 [M+Na]$^+$; elemental analysis for $C_{56}H_{48}O_8$ calcd (found) C 79.22 (79.25), H 5.70 (5.70)%. Compound **16**: yield 94%; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 1.41 (s, 12*H*), 4.79 (s, 4*H*), 5.32 (s, 4*H*), 6.43 (s, 4*H*), 6.82 (AA′XX′, 8*H*), 6.95 (AA′XX′, 8*H*) ppm; ^{13}C NMR (DMSO-d_6; 100.6 MHz) δ 19.1, 39.6, 100.5, 119.2, 125.9, 127.0, 138.9, 140.9, 150.8 ppm; MALDI-TOF $C_{56}H_{48}O_8$ *m*/*z* 848.33 [M+Na]$^+$; elemental analysis for $C_{56}H_{48}O_8$ calcd (found) C 79.22 (79.20), H 5.70 (5.70)%.
25. Crystal data of **3**: $C_{55}H_{89}O_{17.50}S_{5.50}$, M = 1206.59 g mol^{-1}, triclinic, space group $P\bar{1}$ (No. 2), a = 12.7282(3) Å, b = 13.3196(2) Å, c = 19.2932(3) Å, α = 104.3940(10)°, β = 97.5090(10)°, γ = 99.0330(10)°, V = 3079.26(10) Å^3, T = 120(2) K, Z = 2, D_c = 1.301 g cm^{-3}, μ = 0.272 mm^{-1}, F_{000} = 1294, crystal size = 0.19 × 0.17 × 0.08 mm^3, *R*1 = 0.0780, *wR*2 = 0.1859, *GooF* = 1.015 Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 755190.
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