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Stereospecific synthesis of resorcin[4]arenes and pyrogallol[4]arenes in dynamic thin films†

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Acid catalysed condensation of resorcinol and pyrogallol with aromatic aldehydes using a microfluidic vortex fluidic device (VFD) under continuous flow conditions results in the selective formation of resorcin[4]arenes and pyrogallol[4]arenes as predominantly their C_{4v} isomers. Notably C_{2v} isomers and C_{2h} isomers can be also prepared with the latter being converted to the C_{4v} isomer when the VFD operates in confined mode.

Resorcin[4]arene and pyrogallol[4]arene macrocycles are a versatile sub-class of calixarenes with 8 or 12 upper rim hydroxyl groups, respectively. These versatile molecules can be used for further chemical elaboration, for H-bonding and for metal ion complexation in building complex materials. These materials include the formation of hexameric or dimeric capsules,[1–3] tubular arrays,[4] and organic nanotubes.[5] The traditional synthesis of these macrocycles involves acid-catalyzed condensation of resorcinol or pyrogallol with aromatic or aliphatic aldehydes in an alcoholic medium under reflux. The reaction times for these reactions vary from hours to several days,[6–8] nature of the aldehydes also affecting reaction conditions.[9–14]

Resorcin[4]arene and pyrogallol[4]arenes macrocycles are non-planar and can exist in different forms,[6,7] which include the crown (C_{4v}) boat (C_{2v}), chair (C_{2h}), diamond (C_s) and saddle (D_{2d}) arrangements. The relative positions of the substituents at the methylene bridges can be all *cis* (*rccc*), *cis–trans–cis* (*rctc*), *cis–cis–trans* (*rcct*) and *cis–trans–trans* (*rctt*).[15] The C_{4v} symmetry has the *rccc* configuration and simple torsion of this gives C_{2v} symmetry. The chair (C_{2h}) isomer has *rctt* configuration. Critically, the reaction conditions and the nature of the side chains at the bridging carbon atoms affect the stereoselectivity of the cyclization. Hoegberg[16] described the condensation of various benzaldehydes with resorcinol and found that only two different stereoisomeric octols were formed, namely, the chair (C_{2h}) and the crown (C_{4v}) conformers. In these specific cases, the kinetically favoured chair isomer is converted into the thermodynamically more stable crown isomer after longer reaction times.

Herein we report the synthesis of resorcin[4]arenes and pyrogallol[4]arenes involving different aldehydes using a microfluidic vortex fluidic device (VFD), in controlling chemical reactivity and selectivity, as part of a program on developing more efficient and alternative synthetic protocols for targeted organic reactions. This system has already demonstated capability in organic reactions,[17] fabricating nanoparticles,[18,19] exfoliating graphene,[20] and wrapping graphene, graphene oxide and polymers ladden with superparamagnetic magnetite nanoparticles, around algal cells.[21–23]

The design of the VFD is simple with variation in the rotational speed, angle of inclination and feed flow rates effective at fine tuning the outcome of the reaction being conducted.[17] The device is designed to have jet feeds which direct liquid to the end of a tube and with the intense micromixing in the resulting dynamic thin film, the residence time can be controlled by varying both the feed rate and the length of the tube. The thin liquid film created inside the rotating tube produces a very high heat and mass transfer rate.[24] It also has a longer residence time than the related spinning disc processing apparatus (SDP)[24] which allows the organic reaction to occur efficiently in a single pass within a few minutes. The effectiveness of the VFD in controlling chemical reactivity in the continuous flow mode[17] is explored in the present work for the synthesis of the resorcin[4]arene and pyrogallol[4]arene macrocycles, with optimisation dependent on the choice of the extended operating parameters relative to traditional batch processing, which include flow rates, rotational speeds and inclination angles.

The general procedure for using the VFD in continuous flow mode for the preparation of calix[4]arenes **4a–i** involved treating resorcinol **1** or pyrogallol **2** and aldehydes **3a–e** in a 20 : 1 mixture of ethanol and concentrated hydrochloric acid (Scheme 1). This is in contrast to earlier studies using traditional batch processing which typically involve a 4 : 1 ratio of solvents.[7] The acidic ethanol solution was delivered through one feed jet to a 10 mm diameter standard NMR tube at a flow rate of 1 mL min^{-1}. The rotational speed, angle of inclination of the tube and temperature were set at 7000 rpm,

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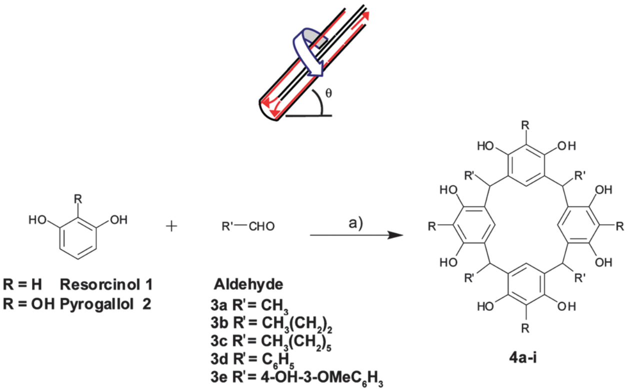


Scheme 1 General reaction procedure for the preparation of calix[4]arenas. (a) Ethanol, conc. HCl, 80 °C, 7000 rpm, 45° inclination angle, 1 mL min^{-1}.

45° and 80 °C respectively, with the choices of speed and angle based on earlier work using this instrument.[17] In most cases the reaction produced a precipitate, which was collected using simple filtration. The solid products were washed with water to remove any acid and purified, by crystallisation from ethanol, to give the desired compounds **4a–i** in good yields (Table 1). All compounds obtained had ^{1}H and ^{13}C NMR spectra that were consistent with literature values[6,7,10,13] previously reported for C_{4v} isomers (see ESI†). Of note is that in all cases the reactions were conducted using a single pass on the VFD which translates to 10 min processing for 10 mL of solution, at the designated flow rate of 1 mL min^{-1}.

The macrocycles **4a–f** were characterised as their *rccc* crown (C_{4v}) isomer, which is the favoured isomer formed using traditional batch processing for aliphatic aldehydes with resorcinol **1** and pyrogallol **2**. There were no signs of the formation of the other isomers, in particular the kinetically favoured *rctt* chair (C_{2h}). Of note was the preparation of the resorcin[4]arene **4g** which was isolated exclusively as the *rccc* crown isomer. Previous traditional literature preparations[7] of **4g** were found to only form the *rctt* chair isomer (C_{2h}) after short reaction times and only after longer reaction times did the formation of the *rccc* crown isomer result. Of interest was that the reaction of pyrogallol **2** with vanillin afforded exclusively the pyrogallol[4]arene macrocycle **4i** as its C_{2v} (boat) isomer in high yield.

The calix[4]arene macrocycle **4h** (synthesised from vanillin and resorcinol **1**) was prepared in both the *rccc* C_{4v} and *rctt* C_{2h} isomers under VFD continuous flow conditions with the ratio of C_{4v} and C_{2h} being 3 : 4. Possible reasons for the formation of this mixture lie in the substitution pattern of vanillin which may cause steric hindrance during the cyclization and so the amount of the C_{4v} isomer may therefore increase. Interestingly, the VFD significantly reduces the reaction time for the preparation of **4h**, which is consistent with the microfluidic platform providing a 'soft' form of energy to increase molecular collisions for reactions under diffusion control.[17] As a comparison the C_{2h} isomer is usually prepared in 5 days using traditional method processing with no formation of the C_{4v} isomer.[10]

Table 1 Synthesis of calixarene macrocycles using continuous flow VFD operating at 7000 rpm, 45° tilt angle and 80 °C at a flow rate of 1 mL min^{-1}

Product	–R′	–R	Yield (%)	Isomer
4a	**3a**	H	32	C_{4v}
4b	**3b**	H	43	C_{4v}
4c	**3c**	H	40	C_{4v}
4d	**3a**	OH	42	C_{4v}
4e	**3b**	OH	42	C_{4v}
4f	**3c**	OH	75	C_{4v}
4g	**3d**	H	56	C_{4v}
4h	**3e**	H	99	C_{4v} and C_{2h}
4i	**3e**	OH	84	C_{2v}

We further investigated whether the percentage conversion of the stereoisomers found using vanillin and resorcinol **1** could be controlled by changing the different reaction parameters for the VFD. Systematic variation of rotational speed, temperature, flow rate, angle of tilt and acid used, resulted in formation of both the C_{4v} and C_{2h} stereoisomers in all cases, albeit with different percent conversions and different ratios of the isomers (Table 2). The rotational speed is a key processing parameter of the VFD, in controlling the thickness of the dynamic thin film.[24]

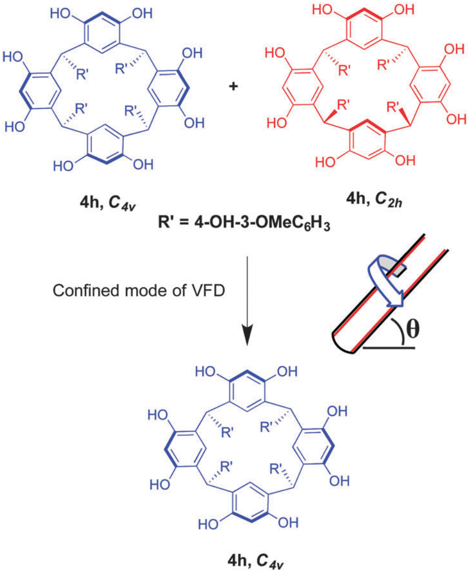
At high speed (7000 rpm) the conversion to **4h** was high yielding with a mixture of the C_{4v} and C_{2h} isomers whereas at lower speed (3000 rpm) the ratio was more in favour of the C_{2h} isomer. The angle of tilt of the VFD was also seen to play an important role in the reactions. At an angle of 45°, where both gravitational and centrifugal forces create shear within the resulting thin film formed, a higher conversion to C_{4v} was observed compared to an angle of 0° where only centrifugal forces are present.[17]

The effect of flow rate was also investigated by varying the input rate from 1 mL min^{-1} to 3 mL min^{-1}, over 1 mL increments. We found that the best rate for the conversion to **4h** of C_{4v} isomers was 1 mL min^{-1} (43%), with higher flow rates resulting in lower conversions. This could be attributed to the reduced residence time of the liquid in the VFD and therefore less chance for conversion. The optimal temperature was found to be 80 °C and switching the acid used from hydrochloric acid to *p*-toluene sulfonic acid or acetic acid in ethanol resulted in reduced conversion and no conversion, respectively.

The VFD is unique in that it has two formats under which chemical reactions can take place, continuous flow and confined mode.[17] To evaluate the effects of performing chemical reactions in the confined mode we took the mixture of isomers of **4h**

Table 2 Investigation into the conformation of **4 h** using different parameters of reaction in VFD under continuous flow conditions

Parameters	Variation of parameters	C_{4v} (%)	C_{2h} (%)	Yield (%)
Rotational speed (rpm)	7000	43	57	99
	3000	30	70	96
Angle of inclination (degrees)	45	43	57	99
	0	27	73	81
Flow rate (mL min^{-1})	1	43	57	99
	3	25	75	74
Temperature (°C)	80	43	57	99
	60	14	86	37
Acid	HCl	43	57	99
	p-TSA	37	63	90
	Acetic acid	0	0	0



Scheme 2 VFD conditions: confined mode, ethanol, conc. HCl, 60 °C, 7000 rpm, 45° inclination angle, 1 mL solution of **4h** (1 mmol, C_{4v} and C_{2h}) treated for one hour.

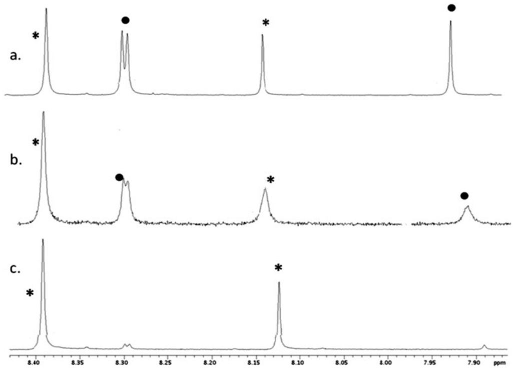


Fig. 1 Part of the 400 MHz ^{1}H NMR spectrum of (a) compound **4h** (3 : 4 mixture of C_{4v} and C_{2h} isomers), (b) intermediate product **4h** (30 min) and (c) compound **4h** (predominating C_{4v} isomer). * corresponds to the C_{4v} isomer and ● corresponds to the C_{2h} isomer.

(C_{4v} and C_{2h}) and treated them in the VFD in an acidic medium at 60 °C for one hour (Scheme 2). After this time and isolation of the material we found that the ratio of the two isomers had changed to a point that the C_{4v} isomer was almost exclusively present, with this conversion being confirmed by ^{1}H NMR spectroscopy (Fig. 1). We rationalise that in the original continuous flow mode reaction conditions, the reaction time (residence time) is insufficient for conversion of the lower symmetry C_{2h} isomer to the thermodynamically more stable C_{4v} isomer. Only after treatment in the confined mode in the VFD was this conversion able to proceed. Notably when the same mixture was treated using the same reaction conditions as in batch mode, there was only 46% conversion of the C_{2h} isomer to the C_{4v} isomer after one hour, and extended reaction times did not improve this conversion. This also provides further evidence that intense shear is present under confined mode operation of the VFD, and arises from the cross vector of centrifugal force and gravity.[20] Of interest is that compound **4i** in the C_{2v} isomer cannot be converted to the C_{4v} isomer using the same approach.

In conclusion, we have established a novel and facile method for the synthesis of different resorcin[4]arenes and pyrogallol[4]arenes as the C_{4v} isomer, with one exception, using the microfluidic VFD under continuous flow conditions. The type of isomers that can be formed, as well as conversion between them, can be controlled by varying the parameters of the VFD, with an added advantage of significantly reducing the reaction times and the amount of catalyst required. This method has potential for controlling for formation of other calixarenes, and a plethora of chemical reactions.

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