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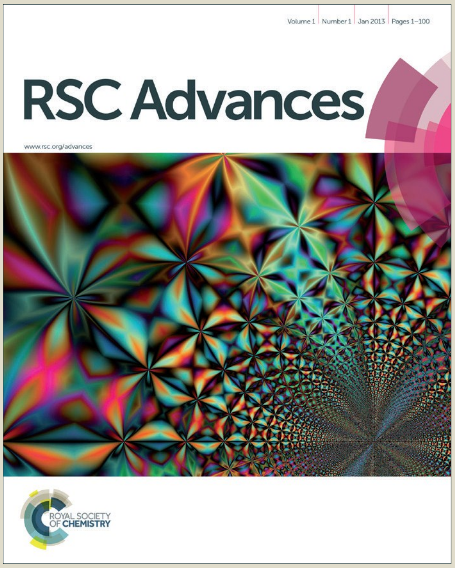

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ARTICLE

Cation Templated Improved Synthesis of Pillar[6]arenes

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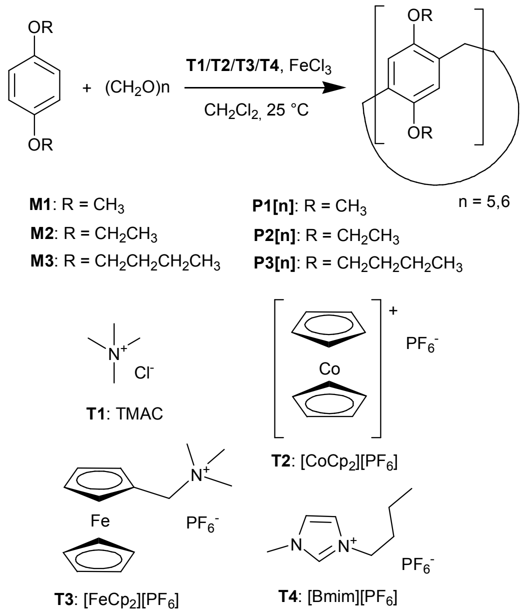
Improved high yield syntheses of the larger pillar[6]arenes (P[6]) bearing different alkoxy substituents through cation templated syntheses using a series of small organic and organometallic cations is reported. Yields of P[6] up to 38% and P[6]/P[5] ratio as high as 5:1 were achieved

In the last decade a new class of macrocyclic aromatic host molecules called pillararenes has been disclosed by Ogoshi based on the condensation reaction between para *bis*-alkoxy benzene derivatives and paraformaldehyde. The reaction is catalyzed by the presence of a Lewis or Brønsted acid, leading to the formation of macrocyclic structures containing five[1] or six[2] arene rings. Since its discovery, this class of molecules showed impressive host-guest properties due to the semi-rigid, symmetric and electron-donating cavity that promotes selective binding of unusual neutral molecules,[3] observing important effects due to both size and length of the alkoxy substituents. Similarly to cyclodextrins, resorcin[n]arenes and calix[n]arenes, the recently discovered pillar[n]arenes represent a new class of molecules with great potentialities[4,5] ranging from preparation of supramolecular polymers,[6] pseudorotaxanes,[7] application as channel for direct methanol fuel cells,[8] inhibition of acetylcholine hydrolysis[9] and other biological applications[10] to mention most recent achievements. Therefore a great attention has been focused on the optimization of the syntheses of pillar[5]arenes (**P[5]**), pillar[6]arenes (**P[6]**)[11] and more recently on 7-15 membered arenes.[12] Most of the procedures reported higher yields for the smaller macro-cycle, with ratios **P[5]**/**P[6]** ranging from 30 to 1.5. Only few very recent examples in the literature reported an inversion of the ratio, with the formation of higher amounts of **P[6]** derivatives using i) particularly bulky *para* disubstituted *bis*-alkoxy-benzene units with chloro-cyclohexane as templating solvent[13] or ii) polar solvents[14] or iii) solvent free conditions[15] as well as iii) naphthalene diimide as templating electron poor unit.[16]

Templated synthesis is a common strategy to steer product selectivity in a chemical reaction towards a particular molecule exploiting its recognition properties towards the templating unit. Examples of this strategy are the synthesis of crown ethers[17] or catenanes[18] based on metal ion chelates, cyclotrimers[19] with a porous coordination framework, paracyclophanes[20] with covalently bond template as well as materials like mesoporous silica MCM-41 using surfactants.[21]

In the present contribution we report an improved synthesis of **P[6]** carried out with the templating approach based on the right selection of cationic guests characterized by proper size and shape to bind through cation-π interaction preferentially into the electron rich cavity of **P[6]** rather than **P[5]** (Scheme 1).



Scheme 1. Synthesis of **P[5]** and **P[6]** with $FeCl_3$ as catalyst in the presence of different cationic templating units **T1**-**T4**.

Starting from simple reagents like *para-bis*-alkoxy-benzene derivatives with formaldehyde and $FeCl_3$ as catalyst in the presence of tetramethylammonium chloride (**TMAC**) and *bis*(cyclopentadienyl)cobalt (III) hexafluorophosphate (**[CoCp$_2$][PF$_6$]**) as templating units, **P[6]** was obtained as main

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Electronic Supplementary Information (ESI) available: experimental synthetic procedures and NMR titrations. See DOI: 10.1039/x0xx00000x product with isolated yields up to 38% and **P[5]**/**P[6]** as low as 0.2.

In order to select possible templating guests, we investigated by ^{1}H NMR the interaction of a series of cationic species like **T1**, **T2**, **T3**, **T4**, with both **P2[5]** and **P2[6]** following the effect of the addition of the templating species on the resonances of the two pillararenes (see supporting information). We observed that **T4** turned out to be a suitable guest for the smaller macrocycle **P2[5]** with no evidence of binding to **P2[6]** in agreement with recent reports for other similar ionic liquids.[22] On the contrary, **T2** and **T3** turned out to bind into the cavity of **P2[6]** and not to that of **P2[5]**, as reported in Figure 1.

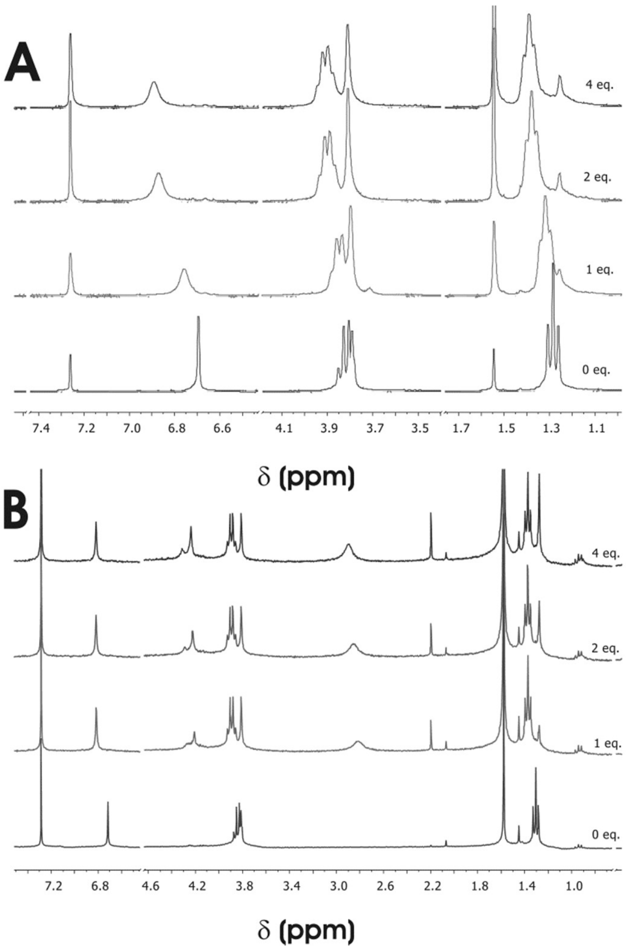

Figure 1. A) Bottom to top, ^{1}H NMR spectra of the progressive addition of equivalent amounts of **T2** to **P2[6]**, B) Bottom to top, ^{1}H NMR spectrum of a progressive addition of equivalent amounts of **T**3 to **P2[6]**.

The affinity between **T2** and **P2[6]** was investigated in detail by means of ^{1}H-NMR titration following the aromatic resonance of host that changed from 6.47 ppm in the absence of the guest up to 6.85 ppm under saturation conditions with excess of guest. The fitting of the $\Delta\delta$ as a function of the ratio between the concentration of the guest and the host was interpolated with a 1:1 binding mode observing a K_{ass} of $1.2 \cdot 10^4$ M^{-1} (supporting information). The value observed is indicative of a good affinity between the cationic guest and the larger host **P2[6]** and it is comparable to what observed for the interaction between a similar pillar[6]arene and ferrocenium.[23]

In order to better investigate the contact between T2 as guest and the two host structures **P2[5]** and **P2[6]** at a semiempirical PM3 level (supporting information). According to symmetry considerations it would be expected a better templating effect imparted by the pentagonal **T2** on the pentagonal **P2[5]** rather than on the hexagonal **P2[6]** analogue. Nevertheless, molecular modelling of **T2@P$_2$[5]** and **T2@P$_2$[6]** show that the templating molecule **T2** barely fits in the cavity of **P$_2$[5]** and this is further evidenced by the forced eclipsed conformation that the cobaltocenium guest has to assume in order to fit within the cavity. Conversely, the larger cavity of **P$_2$[6]** allows the more favoured staggered conformation of **T2**, without contacts with the inner walls of the cavity (Figure 2).

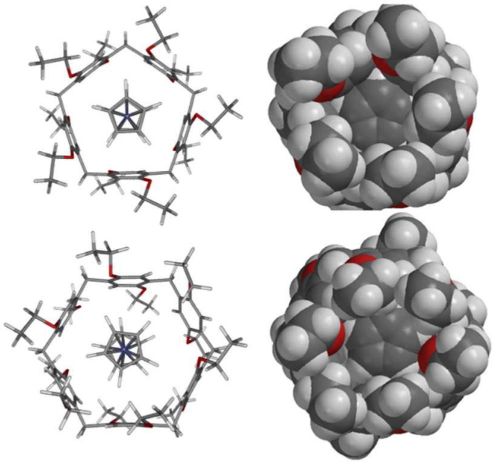

Figure 2. Minimized (semiempirical PM3) structures of **T2@P$_2$[5]** (top left: front view stick; top right: front view space filling) and of **T2@P$_2$[6]** (bottom left: front view stick; bottom right: front view space filling).

The recent synthesis of the pillar[n]arenes[24] with $FeCl_3$ as a low cost, environmentally friendly catalyst starting from para-bis-alkoxy-benzene derivatives was investigated in the presence and absence of the selected templating cationic species **T1**-**T4**. Reactions carried out without templates with all the para-bis-alkoxy-benzene derivative employed led to conversions comparable to that reported in the literature but not in terms of isolated yields (Table 1).[25]

Subsequently, all the cationic guests **T1**-**T4** were employed as templating species in the reaction between **M1**-**M3** derivatives and paraformaldehyde with $FeCl_3$. Using **M1** as substrate and in the presence of **T1** the reaction led to quantitative conversion of the aromatic substrate and formation of **P1[5]** and **P1[6]** in 30% and 13% isolated yields, respectively (Table 1, entry 4).

#	**Monomer**	**Template**	**Conversion (%)**	**P[6]^a/P[5]^a**

1	**M1**	-	27	7/3
2	**M 2**	-	29	6/3
3	**M 3**	-	12	5/traces
4	**M1**	**T1**	100	13/30
5	**M 2**	**T1**	100	19/24
6	**M 3**	**T1**	27	15/12
7	**M 1**	**T2**	100	6/5
8	**M 2**	**T2**	100	38/7
9	**M 3**	**T2**	59	32/28
10	**M 1**	**T3**	100	1/22
11	**M 2**	**T3**	100	6/19
12	**M 3**	**T3**	8	7/10
13	**M 1**	**T4**	10	2/8
14	**M 2**	**T4**	94	13/13
15	**M 3**	**T4**	<2	-

Table 1. Synthesis of **P[5]** and **P[6]** with different starting monomers (**M1** methoxy-, **M2** ethoxy-, **M3** butoxy-) and different templating agents: **T1** and **T4** 15 mol%, **T2** and **T3** 25 mol%. a) Isolated yields.

The presence of the cationic template favored both the reaction, since higher overall yields of macrocycles were observed as well as the selectivity towards **P1[6]**. Switching from the dimethoxy **M1** to the diethoxy **M2** reagent, an increase of the amount of the corresponding **P2[6]** product was observed. The longer butoxy **M3** substrate displayed incomplete conversion, but the amount of **P3[6]** isolated was slightly higher than that of **P3[5]**. The same trend was observed with the cationic species **T3** observing quantitative conversions with the smaller aromatic substrate and a **P[6]**/**P[5]** ratio that increased with the longer substituted substrates. Nevertheless, in all cases the corresponding **P[5]** was isolated as the major isomer, with a maximum 7% yield. The use of **T4** as templating unit did not provide good results, since for all the substrates investigated the yield of the corresponding macrocycles were rather low, in some cases due also to reduced conversions of the reagents.

When the reaction was carried out with **T2**, the best result was obtained employing **M2** as substrate with quantitative conversion of the reagent and 38% and 7% yields for **P2[6]** and **P2[5]**, respectively. With the longer **M3** quite good yields but with lower selectivity towards **P3[6]** were obtained (Table 1, entry 9).

Since **T2**, as anticipated from ^{1}H NMR titration experiments, turned out to be the best templating unit to favour the synthesis of the larger macrocycles **P2[6]**, the effect of its amount on the reaction was further investigated using $\mathbf{M_2}$ as substrate (Table 2). It was observed that conversion and even more importantly yields of **P2[6]** and **P2[5]** were not much affected by the mol% amounts of the templating cation. Overall, the best conditions were observed using 25 mol% of **T2** leading to 38% isolated yield of **P2[6]**.

#	Template (mol%)	Conversion (%)	P2[6]^a/P2[5]^a
1	20	93	37/6
2	25	100	38/7
3	30	83	34/5

Table 2. Synthesis of **P2[5]** and **P2[6]** with different molar amounts of **T2**. a) Isolated yields.

In order to ascertain the scalability of the reaction, the synthesis of **P2[6]** templated by **T2** under conditions as in Table 2 entry 8 was repeated on 7 mmol of **M2**. The reaction led to quantitative conversion of the aromatic reagent and formation of the corresponding **P2[6]** macrocycle in 38% isolated yield corresponding to isolation of 472 mg of the host. Since the synthesis of **M2** from hydroquinone is a quantitative reaction, the two step synthesis of **P2[6]** from hydroquinone is possible with an overall yield of 38%.

Conclusions

In conclusion, we reported high yielding template syntheses of the hexameric pillararenes **P[6]** from 1,4-disubstituted alkoxy benzene derivatives and paraformaldehyde with $FeCl_3$ as Lewis acid in the presence of templating cationic guests $\mathbf{T_1}$-$\mathbf{T_4}$. Among other **P[6]** selective syntheses,[13-16] our approach is rather straightforward, it uses an economic and environmentally friendly catalyst and requires a templating unit used in substoichiometric amount.

Acknowledgements

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Cation Templated Improved Synthesis of Pillar[6]arenes

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Graphical Abstract