Pillar[n]arene macroroycles are a class of cylindrical macroroycles made up of dialkoxybenzene rings linked by methylene bridges. Although they were first reported as recently as 2008,1 they have already become established as a vital part of the modern supramolecular chemistry toolbox.2 This is largely due to their rich host–guest chemistry, which has allowed their incorporation into interlocked structures,3,4 use in molecular separation,5,6,7 and binding and sequestration of biologically important guests.8–11

The synthesis of pillar[5]arenes (P5s) is generally straightforward and high-yielding, and commonly uses a long and thin molecule such as dichloromethane (DCM) or 1,2-dichloroethane (DCE) as the reaction solvent (Scheme 1). It has been shown that these molecules can bind to P5s,12 which presumably provides a thermodynamic driving force for cyclisation to this macroring rather than other possible ring sizes.2 Additionally, a recent computational study indicates that the interaction between the cationic pre-macroring and the solvent is a major factor in determining the product distribution.13

In contrast, while P6s are very promising for a number of applications—particularly binding biologically relevant guests8–11—their synthesis is often non-trivial. When large alkoxy substituents such as hexyl14 or CH2–cyclohexyl15 are incorporated into the macroring (i.e. P6Me and P6(OC2H5)), synthesis proceeds smoothly and in high yields in the relatively bulky solvents chloroform or chlorocyclohexane as templates. Unfortunately, the hexyl/cyclohexyl substituents can be difficult to remove for subsequent derivatization and so there is a need for access to P6s bearing smaller derivatives such as P6Me and P6Et. To the best of our knowledge, the direct synthesis of P6Me has only been reported once as part of a mixture of products from a cation-templated reaction.16,17 In contrast, P6Et has been reported many times, although there are numerous different procedures reported for its synthesis.

Briefly, a solvent-free synthesis of P6Et,18 as well as one that uses polar solvents such as acetonitrile19 and one that uses a deep eutectic solvent20 have been reported, although despite the reported high yields these have not been widely adopted. Other authors have used chloroform as templating solvent in combination with either a Brønsted14 or Lewis16,21,22 acid. In all cases, mixtures of P5Et and P6Et are obtained, which require chromatographic separation. While the current work was underway, Hof and co-workers published an Organic Syntheses paper describing a chromatography-free route to P6Et.23 This route uses similar conditions to those used by Ogoshi to prepare P6Me, namely BF3OEt2 in chlorocyclohexane, and impressively can be scaled up to give > 14 g of pure P6Et in 34% yield.

We have recently begun a research project investigating pillararene derivatives as biomimetic organocatalysts. As part of this, we needed a route to large quantities of a P6 derivative that could be readily mono-dealkylated to give a free hydroxy group for subsequent functionalization (i.e. P6Me or P6Et). In this work we describe our difficulties reproducing literature syntheses of P6Et, and highlight some of the variabilities with these procedures. We demonstrate that P6 yields are very dependent on reaction rate and show that this can be tuned using sub-stoichiometric amounts of Brønsted acids.

Attempts to repeat literature syntheses of P6Et: We were initially attracted to Wang and co-workers’ reported synthesis of P6 derivatives including P6Et using methanesulfonic acid in chloroform due to its operational simplicity.14 While we found this procedure very effective as a method of preparing P6Me from 1,4-dihexyloxybenzene, when we attempted to use the same method to prepare P6Et from 1,4-diethoxybenzene we obtained large amounts of insoluble material, both during the reaction and after work-up. While some conversion to P6Et was apparent, the vast majority of the product was insoluble. We also investigated several other methods but found these gave little product in our hands. These included using H2SO4 or BF3OEt2 in acetonitrile,19 using H2SO4 in a solventless reaction,18 and using FeCl3 or BF3OEt2 in
CHCl$_3^{21,22}$ (more information about attempted repeats of literature syntheses is given in the Supporting Information). We stress that this is not a criticism of the original authors of these papers, but rather highlights the temperamental nature of P6 formation reactions (as discussed later).

**Chlorocyclohexane-templated synthesis of P6**: Having struggled to synthesize P6 using a chloroform template, we next investigated the solvent chlorocyclohexane, which has been reported to give good yields of a cyclo-hexyl substituted P6,\textsuperscript{15} and has been predicted by a computational study to be an effective template for P6.\textsuperscript{13} Initial BF$_3$·OEt$_2$-mediated reactions indicated that this gave P6\textsuperscript{23} in reasonably good yields (~35–40%) with only very small amounts of P5\textsuperscript{23} formed (these conditions are very similar to those developed by Hof,\textsuperscript{23} see later). After several successful reactions under these conditions, the (old) bottle of cyclohexane that we had been using ran out and so we switched to a new bottle. At this point, the reaction stopped working and instead gave only oligomeric products. Comparing the two bottles by H NMR spectroscopy suggested that the newer bottle had a slightly higher water content, but drying the solvent did not improve the reaction. However, pH testing revealed that the old bottle of chlorocyclohexane was notably acidic (presumably due to decomposition), while the new bottle was neutral.

We initially investigated the effect of HCl on the reaction by bubbling HCl gas through chlorocyclohexane to give an HCl-saturated solution, before diluting to give a range of HCl concentrations. These initial reactions showed clearly that there was a “Goldilocks” region for acid content, as no acid or very small amounts of acid gave negligible product (and instead formed oligomers), moderate amounts gave good yields of product of high purity, and larger amounts gave very little product (instead returning mainly starting material, see Supporting Information for full details). These experiments were subsequently repeated using a 1.0 M solution of HCl in Et$_2$O instead of HCl$_\text{atm}$-saturated chlorocyclohexane to allow for a more quantitative determination of the effect of acid.

Relatively small-scale reactions (2.0 mmol of diethoxybenzene) were conducted in chlorocyclohexane (10 mL) using 1.0 equivalents of BF$_3$·OEt$_2$, 3.0 equivalents of paraformaldehyde and varying amounts of HCl in Et$_2$O solution. After stirring at room temperature for 2 hours under a nitrogen atmosphere, the reaction was precipitated using methanol, and filtered through a short plug of silica gel using a methanol/chloroform mixture as eluent to remove insoluble impurities. Figure 1 shows the effect of acid on estimated yield and purity of this crude product. As can be seen, when no HCl was used, almost no P6\textsuperscript{23} was formed instead returning mainly insoluble oligomeric/polymeric material. Between 0.5–5 mol % HCl gave P6\textsuperscript{23} in reasonable yields as the major product, while a higher mol% HCl returned mainly unreacted starting material.

When scaled-up to a 10–20 mmol scale, relatively good yields (~50%) of P6\textsuperscript{23} were reproducibly obtained. While we have not investigated scaling the reaction up to the impressive scales reported by Hof and co-workers,\textsuperscript{23} we note that this methodology gives access to significant quantities of P6\textsuperscript{23} (1–2 g) in purity sufficient for most subsequent reactions very rapidly (3 hours from starting reaction to isolation of product).

**HCl slows formation of P6**: As we were conducting this work, Hof and co-workers published an *Organic Syntheses* procedure giving access to large quantities of P6\textsuperscript{23}. Their optimized procedure is broadly very similar to that which we had developed, but does not use HCl. We repeated this procedure as described (although on a smaller scale) but initially did not obtain significant amounts of P6\textsuperscript{23} instead finding that on addition of BF$_3$·OEt$_2$ clumps of dark precipitate were immediately formed, which upon work up gave primarily oligomeric material. We wondered whether the source of this discrepancy may be that the solvent used by Hof may also contain an acid impurity. However, the authors kindly checked the solvent they used and found it to be neutral.\textsuperscript{24} Given Hof’s procedure has been independently verified by the *Organic Syntheses* checkers, we were particularly puzzled by our inability to reproduce the results.

Hof’s *Organic Syntheses* paper helpfully includes photographs of the reaction mixture, which shows that the initially white suspension takes on a blueish-green color within one minute and a dark green color within two minutes.\textsuperscript{23} In contrast, when we used small quantities of HCl we found that it took significantly longer to reach these colors. For example, using 7.5 mol % HCl, it took about 80 minutes to reach the deep green color (Figure 2). This, and the fact that using larger amounts of HCl resulted in significant quantities of unreacted diethoxybenzene suggested to us that the primary role of the HCl was to slow the reaction. At 15 mol% HCl, no change in appearance was observed after the 2-hour reaction window; however, leaving the reaction longer (24 hours) saw the mixture darken, but with no apparent increase in yield or purity above the shorter reaction time.

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Figure 1. Estimated yields (triangles) and purity (circles) of small test-scale P6 reactions using BF$_3$·OEt$_2$ in chlorocyclohexane and various mol % HCl (added as 1.0 M HCl in Et$_2$O). Yields are corrected for purity, and are approximate and based on the product obtained after precipitating the reaction mixture with methanol and flushing through a short pad of silica. Purity estimates are based on integration of the crude $^1$H NMR spectrum.
Figure 2. Photographs of reaction mixture during synthesis of \( \text{P6} \) in the presence of 7.5 mol\% HCl (chlorocyclohexane, BF\(_3\)·OEt\(_2\), room temperature). Hof and co-workers report reaching a deep green color within 2 minutes when no HCl is included in the reaction.\(^{23}\)

Balancing on a knife’s edge, macrocyclization vs. oligomerization/polymerization: Pillar[n]arene formation occurs via a series of reversible Friedel-Crafts alkylation reactions\(^{25,26}\) (Scheme 2). This involves loss of a proton in each condensation step\(^{13}\) (the reaction is overall neutral due to formal removal of OH\(^-\) as \(\text{HOBF}_3^-\)). We suggest that the small quantities of HCl added act as a catalyst for the back reaction, slowing down both oligomerization and macrocyclization. Using FeCl\(_3\) and catalytic HCl gave similar results to BF\(_3\)·OEt\(_2\) with catalytic HCl, as did using BF\(_3\)·OEt\(_2\) with catalytic MeSO\(_3\)H, suggesting that in general a small percentage of a strong Brønsted acid can be used to slow a Lewis acid-promoted macrocyclization. In addition to varying the amount of HCl, we also investigated the effect of varying the number of equivalents of BF\(_3\)·OEt\(_2\) and paraformaldehyde.\(^{12,27}\) Increasing the amount of BF\(_3\)·OEt\(_2\) or decreasing the amount of paraformaldehyde both increased the reaction rate, leading to a larger amount of insoluble material.

It appears that \( \text{P6} \) formation balances on a knife’s edge where macrocycle formation is in competition with oligomerization/precipitation. If too much oligomer forms too rapidly, this precipitates from the chlorocyclohexane solvent and thus cannot equilibrate to form the thermodynamically-favored macrocycle. Once precipitation has begun, this acts as a sink removing the material from equilibrium. Adding a trace of HCl slows the reaction preventing rapid build-up of oligomer and thus keeping all species in solution.

Scheme 2. Proposed mechanism for formation of \( \text{P6} \) highlighting the role of H\(^+\). Mechanism based in part on those suggested by Nierengarten and co-workers,\(^{25}\) and by Zuilhof and co-workers.\(^{13}\) Note that formation of numerous other cyclic/oligomeric/polymeric species is also possible.
We are unsure why Hof and co-workers’ (and the Organic Syntheses checkers) reactions\textsuperscript{23} did not precipitate oligomer while ours did, but suspect it may be due to something as trivial as slight differences in the “room” temperature used to conduct the reactions, or slight differences in the purity of one or more reagents (e.g., BF\textsubscript{3}OEt\textsubscript{2} can contain traces of HF due to hydrolysis). In support of this theory, repeating our unsuccessful attempt to repeat Hof and co-workers’ synthesis but halving the reaction concentration gave clean product in good yield, as reported by the authors.\textsuperscript{23} Several months later, we re-attempted Hof and co-workers’ procedure as reported by the authors (i.e. at the original concentration); in this case the reaction was successful. However shortly after this, we were unable to repeat the procedure either at the original concentration, or at half concentration. This variability emphasizes just how unpredictable the reaction is!

Our suggestion that there is very thin line between the reaction staying soluble leading to substantial amounts of macroyclic product or precipitating insoluble oligomer/polymer is consistent with other findings on P6 synthesis. The fact that P6Me\textsubscript{4} has never been synthesized as the major product of a reaction is to be expected given that the smaller methyl groups result in less soluble products (i.e. favoring rapid precipitation of oligomeric/polymeric material). Similarly, P6 derivatives with larger solubilizing groups such as hexyl or cyclohexyl appear to be significantly easier to make, which is consistent with these substrates keeping the oligomers in solution long enough for cyclisation to occur. In our hands we could obtain P6Me\textsubscript{4} readily using methanesulphonic acid in CHCl\textsubscript{3},\textsuperscript{14} but were unable to prepare P6Et\textsubscript{4}, which we attribute to the solubility afforded by the hexyl substituents. In the original paper describing these conditions, the authors note that conducting the reaction to form P6Me\textsubscript{4} at 40 °C rather than 20 °C resulted in “a large amount of insoluble polymerized product.” We suggest that even this small increase in temperature is enough to cause very rapid production of oligomer/polymer and in this case even the solubilizing hexyl groups are not sufficient to prevent precipitation. While we have not investigated the effect of temperature in this study, we note that changing temperature will affect both reaction rate and solubility so is likely to be another critical variable.

Effect of HCl on synthesis of P6Me\textsubscript{4} and P6Et\textsubscript{4} To the best of our knowledge, P6Me\textsubscript{4} has never been observed as a major reaction product, although it has been prepared in relatively low yields (up to 13\%) from a cation-templated reaction of 1,4-dimethoxybenzene and paraformaldehyde.\textsuperscript{16} Presumably this is due to poor solubility of oligomeric intermediate products in the reaction. Given that HCl slows the reaction and appears to minimize the build-up of oligomers, we wondered whether it would be possible to prepare P6Me\textsubscript{4} as a major product using HCl to control reactivity. Unfortunately, even when large quantities of HCl were used, we obtained large quantities of insoluble oligomeric/polymeric material. When we used 1,4-diethoxybenzene to form P6Et\textsubscript{4} in chlorocyclohexane, we observed no effect of 5 mol\% HCl addition, which is consistent with this more soluble compound remaining in solution for macrocyclization of the initially-formed oligomer to occur without the need for an HCl “brake.” Interestingly, in this case the major product is P5Et\textsubscript{4} rather than P6Et\textsubscript{4} (see Supporting Information).

In summary, we have studied the formation of pillar[6]arene derivatives, particularly the very commonly used compound P6Et\textsuperscript{4}. We have shown that synthesis of this compound is extraordinarily capricious, which may explain the plethora of different methods reported for its preparation. We report conditions that are optimal in our hands in our laboratory, and which minimize the use of the relatively expensive solvent chlorocyclohexane (i.e. conduct the reaction at higher concentrations than other procedures reported in this solvent). However, the broader aim of this work is to highlight the unpredictability of P6 synthesis, and suggest general strategies that may be used to minimize this.

We propose that product formation is highly dependent on initial reaction rate and solubility. If the reaction occurs too quickly, oligomeric/polymeric material precipitates and thus prevents subsequent rearrangement to the thermodynamically favored macrocyclic product. In the case that precipitation is observed, conducting the reaction at lower concentration can favor macrocyclization. Additionally, for syntheses promoted by a Lewis acid, we have demonstrated that a small percentage of a Brønsted acid can slow the reaction, reducing the likelihood of precipitation of insoluble oligomers/polymer.

Experimental section

**General remarks:** The known compounds 1,4-diethoxybenzene and 1,4-dihexyloxybenzene were synthesized by alkylating hydroquinone with bromoethane or bromohexane in ethanol in the presence of KOH and then recrystallized (see Supporting Information). Other compounds were bought from commercial suppliers and used as received.

**General procedure for reactions to investigate effect of HCl on P6Et\textsuperscript{4} formation:** Under a nitrogen atmosphere, paraformaldehyde (0.18 g, 6.0 mmol) was added to a solution of 1,4-diethoxybenzene (0.33 g, 2.0 mmol) in chlorocyclohexane (10 mL), which had been acidified using either HCl\textsubscript{aq} or HCl in Et\textsubscript{2}O (1.0 M). This was stirred at room temperature to give a fine white suspension. BF\textsubscript{3}OEt\textsubscript{2} (0.25 mL, 0.28 g, 2.0 mmol) was added causing the colour changes shown in Figure 2, although the time to reach these colours varied depending on the amount of HCl. After 2 hours, the reaction was quenched by the addition of methanol (2 mL) and then poured into methanol (50 mL) to give a white precipitate. This collected using a fine sintered funnel and then dissolved in 96:4 chloroform:methanol and filtered through a short plug of silica (washing through with more of the same solvent mixture) to remove any polymer and other insoluble impurities. The filtrate was taken to dryness under reduced pressure to give white powders.

**P6Et\textsuperscript{4}:** Under a nitrogen atmosphere, 1,4-diethoxybenzene (3.32 g, 20.0 mmol) was dissolved in chlorocyclohexane (100 mL) and HCl\textsubscript{aq} (0.20 mL, 0.20 mmol, 1 mol\%) added. Paraformaldehyde (1.80 g, 60.0 mmol) was slowly added to avoid clumping, and the resulting suspension stirred at room temperature for 5 min. BF\textsubscript{3}OEt\textsubscript{2} (2.50 mL, 2.84 g, 20.0 mmol) was added slowly, dropwise, causing the mixture to change in color to deep green over approximately 5 min. After 2 hours, the reaction was
quenched by the addition of methanol (10 mL) and then poured into methanol (200 mL) to give an off-white precipitate. This was collected using a fine sintered funnel and then dissolved in 96:4 chloroform:methanol and filtered through a short plug of silica (washing through with more of the same solvent mixture) to remove any polymer and other insoluble impurities. The filtrate was taken to dryness under reduced pressure to give P6\textsuperscript{8} as an off-white powder of purity suitable for subsequent reactions; the major impurity at this point is residual chlorocyclohexane (see Figures S5 and S6 for \textsuperscript{1}H and \textsuperscript{13}C NMR spectra). Yield: 1.98 g (1.85 mmol, 56\%), not accounting for impurities.

If further purification is required to remove residual chlorocyclohexane, the product may be recrystallized by methods developed by the Hof group\textsuperscript{23} all of the material was dissolved in chloroform/acetone (40 mL/40 mL) and the solution cooled to 
\(-18\) °C for 48 hours during which time crystals formed. These were isolated by filtration, air dried, then dried under high vacuum.


References


