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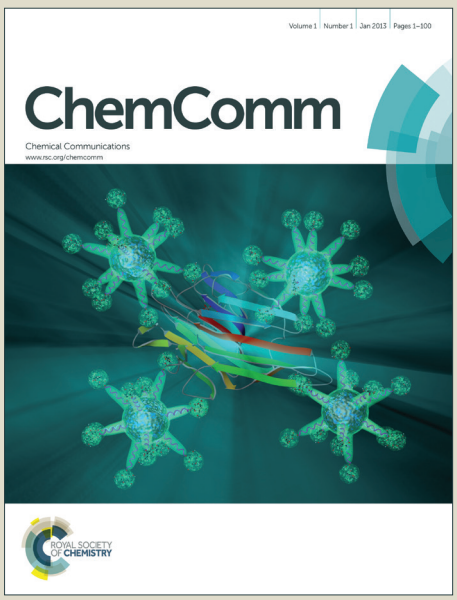

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Continuous Flow Synthesis of a Carbon-Based Molecular Cage Macrocycle *via* a Three-Fold Homocoupling Reaction

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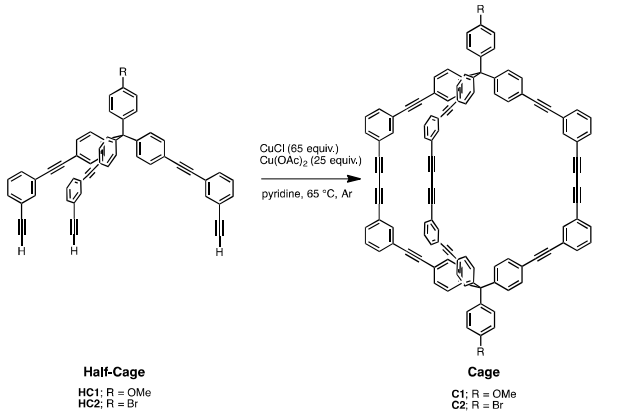
The facile synthesis of the cage molecule ($C_{110}H_{56}Br_2$) *via* a remarkable three-fold homo-coupling macrocyclization reaction using continuous flow methodology is reported. Synthesis *via* continuous flow chemistry improves the residence time, safety, and environmental profile of this synthetically challenging reaction. Further, the new cage possesses halogen atoms at its apex that serve to expand the potential reaction space of these, intrinsically porous, all carbon-carbon bonded molecular cage molecules.

Shape-persistent cage molecules are of broad interest due to their unique photophysical properties,[1,2] host-guest chemistry[3,4] and remarkable permanent porosity.[5,6] Such porous molecular solids have recently emerged as attractive materials for application to gas adsorption and separation science,[7] as whilst they possess comparable porosity[8] to extended framework materials such as metal-organic frameworks and covalent-organic frameworks, they are also soluble. This solubility facilitates processing and incorporation into extended molecular architectures[9] such as mixed-media technologies[10] and porous polymers.[11,12] Importantly though, to fully realise the potential of these materials in emerging applications[13] efficient synthetic protocols must be developed. We have previously reported the synthesis and characterisation of a novel cage, Cage **C1** (R = OMe)[14] (Scheme 1), with a molecular architecture constructed entirely from carbon-carbon bonds. Furthermore, we demonstrated that Cage **C1** can be controllably processed into a solid of high surface area. To promote the use of molecular species like Cage **C1** as building blocks for novel materials, however, synthetically versatile functional groups need to be incorporated into their structures to enable further elaboration. In this respect, the extensive reactivity of aryl halides is well documented in the literature.[15,16,17] In particular, we note the potential for transition metal-catalyzed processes such as the Sonogashira-,[18,19] Suzuki-,[20,21] Stille-,[22,23] Heck-[24,25] and Ullmann-[26,27] type coupling reactions. Accordingly, replacement of the terminal methoxy group with a halogen would allow access to reactive halides, thereby increasing the potential utility of Cage **C1** as a molecular building block. We were therefore encouraged to pursue the synthesis of Cage **C2** (Br), a bromo-terminated analogue of Cage **C1**, *via* a three-fold oxidative homocoupling macrocyclization.[28]

The exploration of chemically robust cage materials is usually limited by low-yielding transformations,[29] and in connection with Cages **C1** and **C2**, this synthetic challenge is due to the irreversible nature of C-C covalent bond formation that favours kinetically driven reaction products. Thus, in cases where the desired 3-dimensional macrocycle is ultimately formed by a multifold cross- or homocoupling step, the reactions are performed under high dilution conditions to minimize the production of oligomers and polymeric species.[30] As such, in addition to decorating the cage with functional groups, a general synthetic methodology that affords significant quantities of the cage product in a facile manner, and in a workable reaction volume, is highly desirable.



Scheme 1. General scheme for the preparation of molecular cage macrocycles.

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Continuous flow chemistry was recently demonstrated to be an effective strategy for substantially improving the yield of the final Glaser-Hay coupling step in the formation of carbon-based macrocycles.[31, 32] Similar benefits were realised for a macrocyclization utilising an azide-acetylene cycloaddition reaction at high temperature, which did not proceed under batch conditions.[33] To our knowledge, however, there have been no reports to date regarding the use of continuous flow chemistry in two- or three-fold homocoupling macrocyclizations. On the basis of the precise control of reagent concentration, mixing *via* static mixing devices and efficient heat and mass transfer achievable in flow microreactors, we contend that continuous flow methodology provides optimal conditions for conventionally slow macrocyclization reactions.[15,7]

Here we demonstrate the development of a three-fold oxidative homocoupling macrocyclization under both batch and continuous flow conditions for the preparation of a new molecular cage derivative, Cage **C2**. We assert that continuous flow synthesis can be successfully employed as a strategy to dramatically increase the efficiency of multifold carbon-carbon bond coupling reactions and, as a result, greatly expand the field of porous molecular solids.

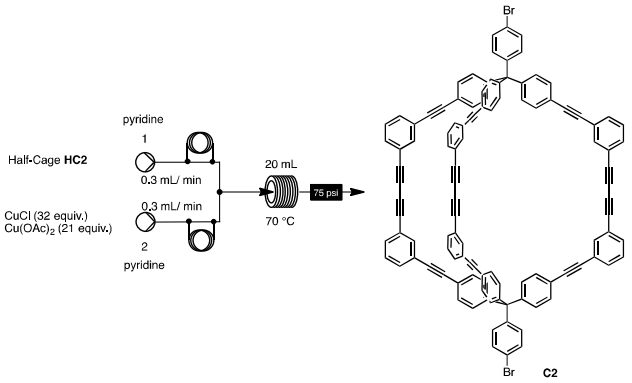

Figure 1. A schematic representation of the synthesis of Cage **C2** through a three-fold Eglinton homocoupling.

As a control, Cage **C2** was synthesised under traditional batch synthesis conditions *via* the homocoupling of Half-Cage **HC2**. High dilution conditions and a large excess of copper coupling reagents were required in order to minimise oligomer formation, with the reaction proceeding in a 20% yield. The formation of Cage **C2** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy, the latter showing aromatic resonances consistent with the cage molecule appearing in the range 7.15-7.76 ppm, with the alkyne peak of the brominated half cage notably absent at 3.09 ppm. Electrospray ionization mass spectrometry (ESI-MS) revealed a peak for the parent ion at m/z 1537, and a peak isotope pattern that corresponds to an ionized dibromo cage. Promisingly, in terms of further modifications, Cage **C2** was found to be soluble in common organic solvents, such as dichloromethane and chloroform.

The limiting step for the synthesis of Cage **C2** is the final homocoupling reaction of the rigid, alkyne-terminated precursors. Under traditional Glaser[34] and Eglinton[35] conditions, the coupling reaction was unsuccessful. Rather, the Breslow modification[36] to the Glaser-Eglinton conditions were the only conditions found to lead to any product. The rotational flexibility of the tetraphenylmethane backbone of the half cage (Scheme 1, Half Cage **HC2**) allows for oligomer formation and therefore, in order to promote the formation of the cage, the reactants must be present at very low concentrations. Additionally, in batch conditions, a large excess of copper(II)/(I) reagents are required to facilitate the coupling reaction thereby maximising the probability of cage formation with respect to oligomers (Fig. 2, Table S1). As a result, performing these reactions on large scales in a laboratory setting represents a significant operational challenge. The rapid and efficient heat and mass transfer offered by the laminar flow of reagents under continuous flow conditions allows for shorter reaction times that, in this reaction, should favour the desired kinetic product.[37] With respect to the above dimerization, the continuous flow of reactants would also enable the synthesis of large quantities of product whilst maintaining the high dilution factor of half cage and a large excess of copper species.

Flow synthesis conditions were chosen based on the reaction time and concentration of half cage required for the batch synthesis. However, the molar ratio of copper reagents was significantly reduced, to 32% of $Cu(OAc)_2$, and 71% of CuCl used in the traditional batch synthesis to ensure solubility. Two separate reagent streams were used, that were combined at a T-mixing piece before entering the first of two 10 mL, 1.0 mm inner diameter (ID) perfluoroalkoxypolymer (PFA) microreactor coils. The first flow stream contained a pre-mixed solution of anhydrous $Cu(OAc)_2$ (21 eq.) and CuCl (32 eq.) in dry pyridine. The second flow stream contained a 1 mmol solution of Half Cage **HC2** in dry pyridine. The solutions were continuously pumped through two reaction coils, which were heated to 70 °C. The most successful flow rate was found to be 0.6 mL min^{-1}, equating to a residence time of 33.3 min, and which produced Cage **C2** in a yield comparable to batch chemistry (20% batch chemistry *vs.* 21% flow chemistry). This represents a significant decrease (92.5%) in reaction times when compared with the corresponding batch synthesis. (Fig 2, Table S1). The observed decrease in residence time gave rise to an appreciable increase in the space-time yield (STY) of Cage **C2**. STY is a concept gaining increasing traction in industrial and process chemistry, and gives a measure of the mass of product per m^3 of reaction mixture per day.[38, 39] For Cage **C2**, the STY achieved under flow conditions amounted to 104.6 g m^{-3} day^{-1} . A limitation of the flow method relative to batch howver, relates to the increased dilution of Half Cage **HC2** and copper reagents (c.a. 4-fold solvent increase for Half Cage **HC2** and 2-fold for copper.

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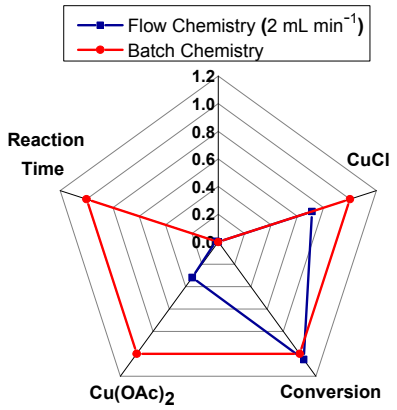

Figure 2. A comparison of the reaction conditions required for the synthesis of Cage **C2** *via* Flow Chemistry (0.6 mL min^{-1}) *vs.* Traditional Batch Chemistry. The conditions for traditional batch chemistry have been normalised for clarity.

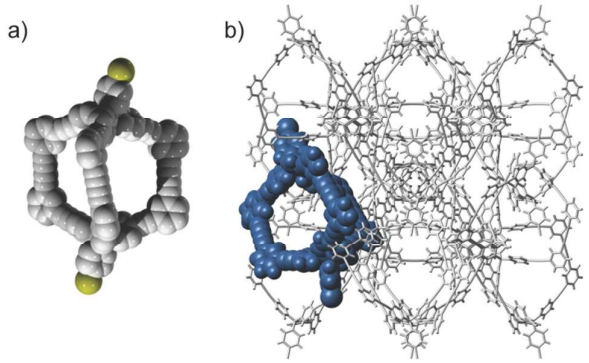

Figure 3. a) Space-filling depiction of Cage **C2**, carbon and bromine atoms are pale grey and yellow, respectively. b) A view of the crystal packing of Cage C2, a single cage molecule is highlighted in a space-filling representation. In a) and b) hydrogen atoms have been omitted for clarity.

The increase in solvent-to-reagent ratio was necessary to ensure complete solubilisation of the reagents in pyridine, thereby avoiding potential blocking of the flow apparatus. It is clear however, that the increase in dilution is compensated by the higher throughput and reduced reaction times of the flow method relative to batch. Finally, it should be noted that any unwanted oligomerization products, were removed during the purification process and analysis of the crude ^{1}HNMR did not reveal the presence of de-halogenated cage products.

Crystals of Cage **C2** suitable for X-ray diffraction were grown from diffusion of petroleum spirits into a benzene solution of the cage. Single crystals grown under these conditions, and a variety of others, were very weakly diffracting; even for the best quality crystals obtained, using synchrotron X-ray sources, diffraction data was only obtained to $2\theta = 37.32°$. As such only basic structural parameters will be described. Nonetheless, the formation of the bromo-functionalised cage could be readily confirmed. Cage **C2** crystallises in the tetragonal space group $I4_1/acd$ with half a cage molecule in the asymmetric unit. As it possesses an identical carbon-bonded backbone, the cage adopts a very similar structure (Fig. 3a) to that encountered for the previously reported, methoxy-derivatised cage C1,[14] with similar bond lengths, angles and internal dimensions to the previously reported entity. Viewed down the axis of the cage the phenyl rings of the tetraphenylmethane head groups are eclipsed with subtle twists of the alkyne arms; interestingly two are twisted in one direction and the third in the opposite direction which attests to the flexibility of the tetraphenylmethane moiety. Cage **C2** packs to form an open, potentially porous structure that is filled with disordered solvent. Due to the lack of functional groups, packing interactions are dominated by numerous weak C-H···π and π-stacking interactions. Despite the presence of a halogen, no halogen bonding interactions are observed in the crystal packing and the bromine moiety extends into the void of an adjacent cage entity.

In summary, we have developed a new process to access the novel porous organic cage compound, Cage **C2**, through continuous flow technology *via* a three-fold oxidative homocoupling macrocyclization. A benefit of our approach derives from the inherent scalability of continuous flow synthesis, in which the macrocyclization can be readily scaled in the laboratory without the impracticality associated with scaling macrocyclization reactions *via* traditional batch techniques. Furthermore, although we have demonstrated a reduction in the use of $Cu(OAc)_2$ and CuCl reagents relative to batch synthesis, we believe that this will be further reduced to sub-stoichiometric amounts through the use of immobilised copper species. This approach is currently being investigated. As such, we have shown that continuous flow methods offer a realistic, feasible and economic route to the scaling-up of shape-persistent organic cage synthesis. This work demonstrates the potential for using flow chemistry methods to readily and rapidly generate multi-gram quantities of complex molecules that are of interest in contemporary technologies such as polymer chemistry, and microelectronics where materials synthesised *via* multifold carbon coupling reactions are common. Furthermore, the Br-substituted cage is now a synthetic starting point of efforts to understand the role capping substituents play in the packing of these carbon-bonded cage molecules.

Notes and references

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