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Expedient synthesis of benzene tricarboxamide macrocycles derived from *p*-aminobenzoic acid

Fred Campbell [a], Colin A. Kilner [a,b], Andrew J. Wilson [a,b,*]

[a] School of Chemistry, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, UK
[b] Astbury Centre for Structural Molecular Biology, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, UK

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ABSTRACT

The synthesis of macrocycles functionalized at the periphery in a regiospecific fashion is considered challenging. This Letter describes a six-step synthesis of N-alkylated benzene tricarboxamide macrocycles derived from *p*-aminobenzoic acid via the iterative coupling of Fmoc-protected monomers and cyclization of the resultant linear foldamers.

The efficient syntheses of highly functionalized macrocyclic scaffolds are the basis of numerous studies in the area of molecular recognition, including supramolecular self-assembly[1] and bioactive ligand discovery.[2] However, whilst this ultimately requires scaffolds possessing different functional groups in a defined sequence, rather than symmetrical presentation of functional groups—with the exception of cyclic peptides[3] and a few other examples[4–8]—the construction of such scaffolds is synthetically challenging. Statistical approaches[9] have proven successful but purification is challenging. Cyclization of foldamers[10,11]—of which aromatic oligoamides[12–14] are one class—represents an alternative to this challenge. Hydrogen-bonding is commonly used as a directing force to promote cyclization of the constituent building blocks of aromatic oligoamide foldamers[15–21] and this approach has been extended to the synthesis of macrocycles functionalized regiospecifically at the periphery.[4] We recently outlined a strategy for the synthesis of regiospecifically functionalized benzentricarboxamide macrocycles **1**.[5] In contrast to many aromatic oligoamide macrocycles where hydrogen-bonding is used as a structure-directing force, the approach exploits the conformational bias of N-alkylated aromatic oligobenzamides[22–25] to promote cyclization of iteratively assembled linear trimers with a pre-programmed sequence of monomers. We subsequently extended the approach to the first synthesis of the parent macrocycle **2** by employing a cleavable 2,4-dimethoxybenzyl-protecting group as the macrocyclization-directing *N*-alkyl group.[26]

In our original syntheses, we employed a nitro-masked amine as the building block and so both alkylation and acylation were performed in a linear sequence that extended to nine steps. In this Letter, we report a more convergent and shorter six-step approach in which N-alkylated Fmoc-protected aminobenzoic acid monomers are iteratively coupled and deprotected—an approach conceptually similar to Kilbinger's solid-phase synthesis of oligo(*p*-benzamide foldamers).[27]

Our synthesis of the cyclic trimers **1a** and **1b** is shown in Scheme 1. Following each amide bond formation, cleavage of the Fmoc-protecting group using a secondary amine affords an aniline ready for the next iterative step of the synthesis. Monomers were prepared as shown in Scheme 2 via a simple reductive amination using borane·picoline with unoptimized yields ranging from 72–80%. This was followed by reaction with Fmoc-chloride in the absence of base, again in good yield, to afford the protected building blocks. With a suitable collection of monomers in hand, we applied our synthetic approach to macrocycle **1a** with three identical dimethoxybenzyl (DMB) side chains and then to an example in which three different substituents are incorporated—macrocycle **1b**. As in our earlier work,[5] we employed in situ formation of the acid chloride using dichlorotriphenylphosphorane for amide bond formation. However, in this work, we found that the prolonged heating resulted in some cleavage of the DMB group during coupling and so carried out all amide bond forming reactions in the presence of sodium hydrogen carbonate. Unoptimized yields for

* Corresponding author. Tel.: +44 (0)113 3431409; fax: +44 (0)113 3436565.
E-mail address: A.J.Wilson@leeds.ac.uk (A.J. Wilson).

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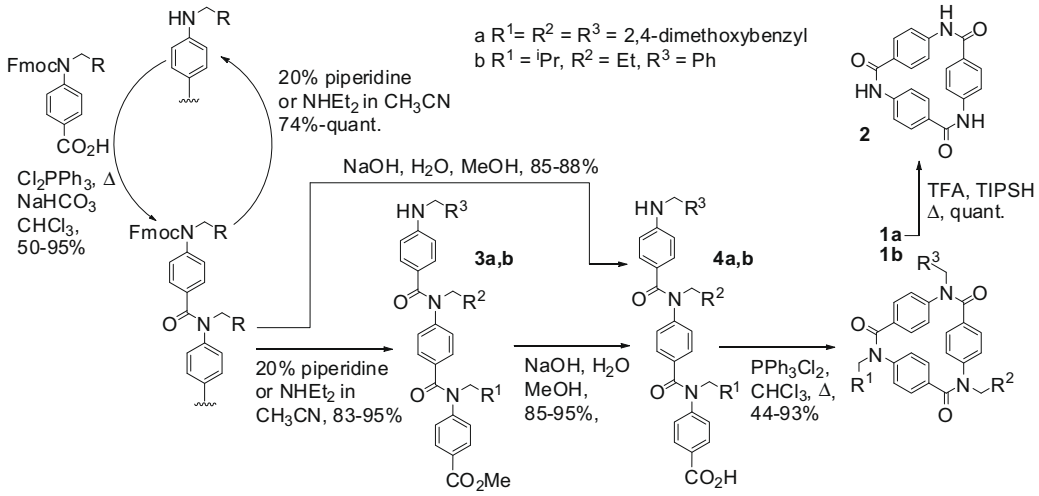
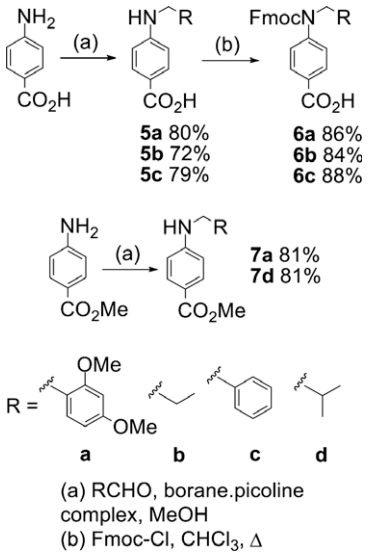


Scheme 1. Synthesis of *p*-benzenetricarboxamide macrocycles.



Scheme 2. Synthesis of Fmoc-protected monomers used in the synthesis of macrocycles **1a** and **1b**.

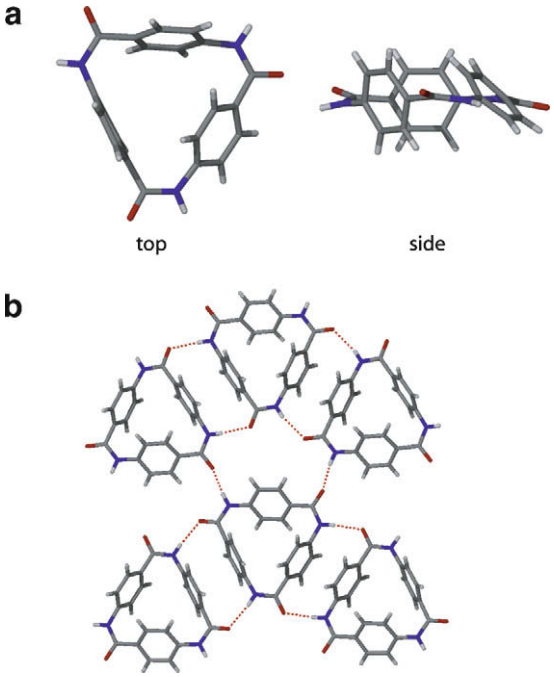


Figure 1. X-ray crystal structure of macrocycles **1a** and **2**.

this step ranged from 50–95%. Hydrolysis of the C-terminal esters **3a** and **3b** afforded free acids **4a** and **4b**. Both underwent ring closure using dichlorotriphenylphosphorane to afford the macrocycles **1a** and **1b** in yields of 44% and 93%, respectively. We were also able to proceed directly to **4a**,**b** by hydrolysis of the Fmoc-protected precursor (Fmoc-**3a**,**b**) and reduce the length of the synthesis by a further step to give a linear sequence of only six steps. Similarly to our previous report, cleavage of the 2,4-dimethoxybenzyl-protecting groups in **1a** using refluxing trifluoroacetic acid (TFA) in the presence of triisopropylsilane (TIPSH) as scavenger afforded the parent *p*-benzene tricarboxamide macrocycle **2** in good yield.

Single crystals of macrocycle **2** suitable for X-ray diffraction studies were obtained from ethyl acetate in dimethylsulfoxide. As anticipated, and consistent with earlier modelling studies, the secondary amide bonds in macrocycle **2** adopt a *cis* geometry with each of the three benzene rings twisted from a perpendicular orientation relative to the amide bond (Fig. 1a). Individual macrocycles then self-assemble through intermacrocycle hydrogen-bonding interactions (Fig. 1b). In contrast to the R_2^2 (8) hydrogen-bonding motif that might be expected for self-assembly of *cis*-amides, H-bonding occurs between amide bonds separated by the aromatic ring with offset π–π stacking in between to generate tapes. The remaining donor and acceptor sites are satisfied through intertape H-bonding.

In conclusion, we have described the synthesis of N-alkylated tricarboxamide macrocycles derived from *para*-aminobenzoic acid. Tricarboxamide macrocycles derived from *ortho*-, *meta*- and *para*-aminobenzoic acid have been the target of synthetic efforts for nearly 30 years[28–32] and this approach should be equally applicable to these compounds. Importantly, this robust method should allow rapid access to macrocycles possessing diverse functionality in a regiospecific manner for use in areas such as protein surface recognition[33] and macrocycle self-assembly.[34] Our ongoing studies are focused towards this endeavour.

Acknowledgements

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Supplementary data

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 752786. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.137.

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