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# An 'impossible' macrocyclisation using conformation directing protecting groups

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

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

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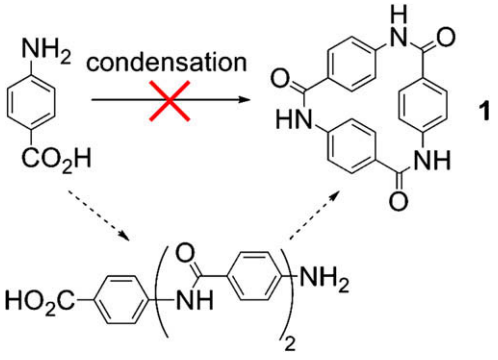
ABSTRACT

A *p*-benzenetricarboxamide macrocycle linked through secondary cis amides is obtained via cyclisation and subsequent deprotection of a folded linear precursor. Secondary benzamides strongly prefer the trans conformation, therefore this synthesis can be considered 'impossible' without recourse to protecting groups.



The efficient synthesis of macrocyclic scaffolds is the cornerstone on which modern supramolecular chemistry is built. Macrocyclisation reactions are typically carried out under conditions of high dilution and/or pre-organisation through non-covalent interactions. These can be introduced via a template or are inherently present in the linear precursor to macrocyclisation. Cyclisation of aromatic oligoamide[1–3] foldamers,[4,5] represents an example of the latter whereby cyclisation is commonly promoted through intramolecular hydrogen bonding.[6–9] In contrast, conformation-directed macrocyclisation reactions are less well studied.[10] In the course of our studies on aromatic oligoamides,[11,12] we exploited the conformational bias of N-alkylated oligobenzamides[13–16] to synthesise N-alkylated benzene tricarboxamide macrocycles functionalised regiospecifically at the periphery.[12] N-Alkylated benzene tricarboxamide macrocycles derived from *ortho*-, *meta*- and *para*-aminobenzoic acids have been the target of numerous synthetic efforts.[17–21] However, the corresponding secondary benzamide macrocycles are unknown. As illustrated in Scheme 1, a direct synthesis of the *para*-derivative could be considered 'impossible' due to the preferred trans-conformation of the secondary amide bonds present in the linear precursor to macrocyclisation that would be formed via iterative monomer additions or a one-pot approach.

In our prior work[12] we obtained N-alkylated benzene tricarboxamide macrocycles by exploiting the folded conformation of linear N-alkylated aromatic oligoamide precursors functionalised with simple alkyl groups. Herein we demonstrate that the synthesis of




**Scheme 1.** Direct route to macrocycle **1**.

*para*-derivative **1** can be achieved by applying this method to precursors possessing cleavable *N*-alkyl groups. Throughout the synthesis, the *cis*-secondary benzamide of the product is protected as a *cis*-tertiary benzamide. Whereas protecting group tuning is often necessary during synthesis to facilitate a cyclisation,[22] the primary role of such groups is to prevent unwanted reactions. The concept presented here differs in the fact that the protecting group serves no other purpose than to act as a structure directing force. Such an approach could be described as exploiting a 'protected conformation' and is similar to protection by conformationally restricted mobility where the steric congestion of a protecting group prevents unwanted side reactions during cyclisation.[23]

The synthesis of the N-alkylated cyclic trimer **2** is shown in Scheme 2. The elegance of our approach centres on an iterative

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

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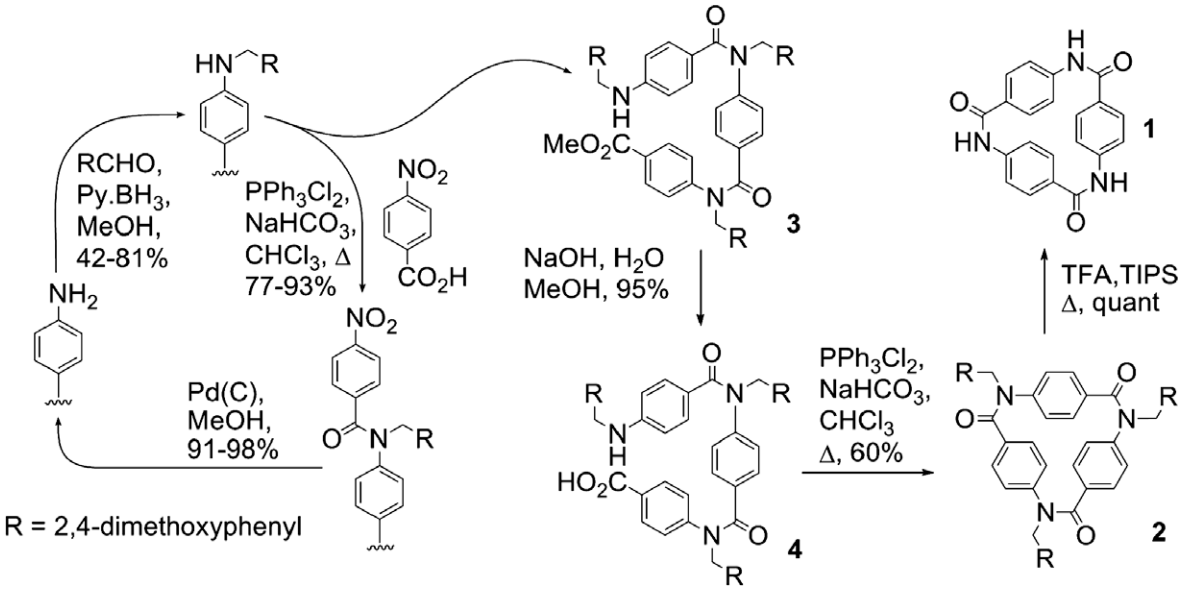


**Scheme 2.** Synthetic route to macrocycle **1** employing protecting groups.

sequence of amide bond formation followed by unmasking and subsequent alkylation of the latent N-terminal amine via reductive amination. We retained the in situ imine formation and reduction using borane·picoline complex from our original work[12] to introduce the 2,4-dimethoxybenzyl (DMB) groups in unoptimised yields ranging from 42% to 81%. Similarly, we retained the in situ formation of the acid chloride using dichlorotriphenylphosphorane from the prior work of ours[12] and others[18] for amide bond formation. However, in this work, we found that prolonged heating in the presence of dichlorotriphenylphosphorane resulted in some cleavage of the DMB group during coupling and so we carried out all amide bond-forming reactions in the presence of sodium hydrogen carbonate. Again, unoptimised yields for this step ranged from 77% to 93%. Hydrolysis of the C-terminal ester of **3** afforded acid **4**, which underwent ring closure using dichlorotriphenylphosphorane to afford the macrocycle **2** in 60% yield. This is a lower yield than that reported in our earlier work[12] and presumably reflects the greater steric bulk of the three DMB groups relative to simple alkyl substituents. Similarly, in our hands, direct formation of macrocycle **2** from *N*-(2,4-dimethoxybenzyl)-4-aminobenzoic acid using dichlorotriphenylphosphorane[19] or from methyl *N*-(2,4-dimethoxybenzyl)-4-aminobenzoate using lithium hexamethyldisilazide (LHMDS)[24] was unsuccessful. In contrast to the facile removal of the DMB groups during the synthesis of the linear precursor **4**, cleavage of the DMB groups on macrocycle **2** proved more challenging. A range of test reactions, including various acidic conditions and scavengers or the use of ceric ammonium nitrate were attempted, however, the isolation of macrocycle **1** proved elusive. Nonetheless, we could achieve the transformation in quantitative yield by refluxing the macrocycle in neat trifluoroacetic acid (TFA) for 14 h with triisopropylsilane (TIPS) as a scavenger.

Figure 1 shows the $^1$H NMR spectra of macrocycles **1** and **2** illustrating the anticipated symmetrical spectra indicative of a single defined conformation in solution. We also obtained IR spectra (KBr disks) of the macrocycles **1** and **2**, the linear precursor **3** and benzanilide for comparison. Whereas the N-H stretch of benzanilide appears at 3343 cm$^{-1}$ characteristic of a trans amide, the N–H stretch of **1** appears at 3188 cm$^{-1}$ more characteristic of a cis amide. The amide I CO stretching frequency of macrocycle **1** at 1648 cm$^{-1}$ is similar in wavelength to that observed for both **3** (1642 cm$^{-1}$) and **2** (1643 cm$^{-1}$), whereas for benzanilide this peak appears at 1654 cm$^{-1}$ suggesting that a similar conformation is present for **1**, **2** and **3**. Molecular modelling also indicated that

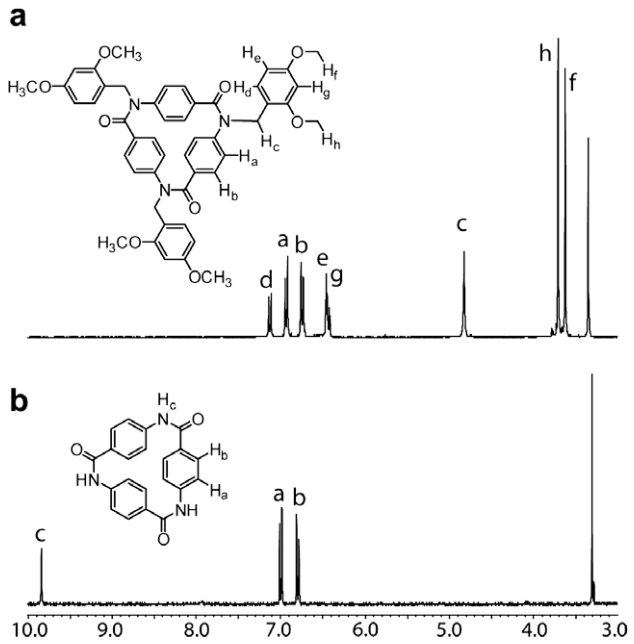


**Figure 1.** $^1$H NMR spectra (500 MHz, DMSO-$d_6$) of (a) macrocycle **2** and (b) macrocycle **1**.

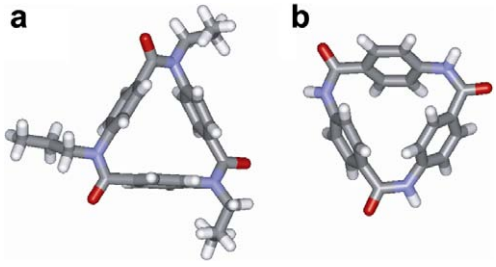


**Figure 2.** (a) X-ray crystal structure of the tris-*N*-propyl-*p*-benzene tricarboxamide macrocycle[12] and (b) molecular model of macrocycle **1**.

macrocycle **1** adopts a cis conformation at each of the amides. A full *Monte Carlo* search and minimisation in MacroModel[25] using the MMFF force-field revealed the lowest energy conformer to be the structure shown in Figure 2b. This structure is similar in nature to the solid state structure of an N-alkylated trimer reported previously by us (Fig. 2a)[12] and confirms that despite the preference for a trans conformation at each of the amides, the less favourable cis conformation is preserved in the macrocycle.

In conclusion, we have exploited the stereoelectronic effects[16] of a protecting group to direct the synthesis of a *p*-benzenetricarboxamide macrocycle. The synthesis of amides that adopt non-standard conformations, for example, quinuclidonium[26] represents an ongoing area of interest due to the conferred dramatic differences in reactivity that plays a key role in biological processes, for example, β-lactam antibiotics. We are therefore interested in the properties and reactivity that this new macrocycle exhibits given that it possesses three amides that are constrained in a undesirable cis geometry within a rigid but large ring. Our future efforts will focus on studies to this effect.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.186.

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