Macrocyclic scaffolds derived from *p*-aminobenzoic acid†

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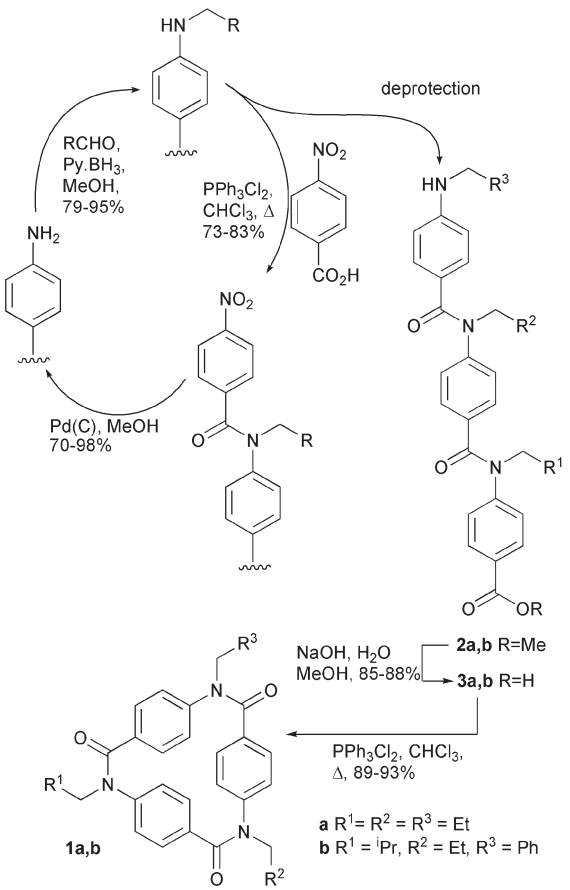
The regiospecific synthesis of C_3 macrocyclic scaffolds possessing multiple different functional groups is described.

The efficient synthesis of macrocyclic scaffolds such as cyclodextrins, calixarenes and porphyrins is the foundation on which modern supramolecular receptors are built. However, with the exception of cyclic peptides,[1] their syntheses are not amenable to construction of scaffolds possessing different peripheral functional groups in a defined sequence. This is a requirement for modern applications such as protein surface recognition.[2] Although statistical approaches[3] often prove useful, there is a need for synthetic methods that lead to scaffolds with these features. Cyclisation of *foldamers*[4,5]—of which aromatic oligoamides[6–8] are one class—represents a means of achieving this goal. Indeed, hydrogen-bonding has been used to promote cyclisation of the constituent building blocks of aromatic oligoamide foldamers[9–12] and more recently to synthesise tetramers with a defined sequence of functional groups at the periphery.[13] Herein we report a different strategy that exploits the conformational bias of *N*-alkylated aromatic oligobenzamides[14–17] to achieve this goal *via* an iterative synthesis of linear trimers and subsequent cyclisation to yield macrocycles. Although cyclic trimers of this nature[18,19] can be made with identical substituents our approach leads to regiospecific incorporation of functional groups.

Our synthesis of the cyclic trimers **1a** and **1b** is shown in Scheme 1. The elegance of our approach derives from the fact that after each amide bond formation is carried out, the latent amine can be unmasked and then monoalkylated utilising reductive amination conditions. We first applied this synthesis to macrocycle **1a** with three identical propyl side chains and then to an example in which three different substituents are incorporated— macrocycle **1b**. Of a panel of different methods, we found *in situ* imine formation and reduction using borane–pyridine or borane–picoline complex to be ideal with unoptimised yields ranging from 79–95%. Other reducing agents such as sodium cyanoborohydride gave progressively poorer yields on chain elongation whilst isolation of the imine and reduction using sodium borohydride gave poor yields. As has previously been observed, we found that *in situ* formation of the acid chloride using dichlorotriphenylphosphorane[20] was a convenient method of amide bond formation. Many other peptide bond forming reagents including PyBOP, EDCI and TFFH failed to give any reaction. Again unoptimised yields for this step ranged from 73–83%. It is also noteworthy that direct addition of 4-nitrobenzoyl chloride to a refluxing solution of the secondary aniline and triethylamine also afforded decent yields of product. Hydrolysis of the C-terminal esters **2a** and **2b** afforded free acids **3a** and **3b**. These both underwent ring closure using dichlorotriphenylphosphorane to afford the macrocycles **1a** and **1b** in yields of 89 and 93% yield respectively. In our hands, direct formation of macrocycle **1a** from the *N*-propyl-4-aminobenzoic acid using dichlorotriphenylphosphorane resulted in poor yields and difficult purification.



Scheme 1 Synthesis of cyclic trimers **1a** and **1b**.

The cyclisation yields are remarkable, given that no special high dilution conditions or templates are used. The reaction is so efficient because the linear trimers adopt a folded conformation enforced by the known preference of *N*-alkylphenylbenzamides for the *cis* conformation.[14–17] This is confirmed by single crystal

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studies of compound **1a** and **2a** and ^{1}H NMR and 2D NOESY experiments for **1b** and **2b**.

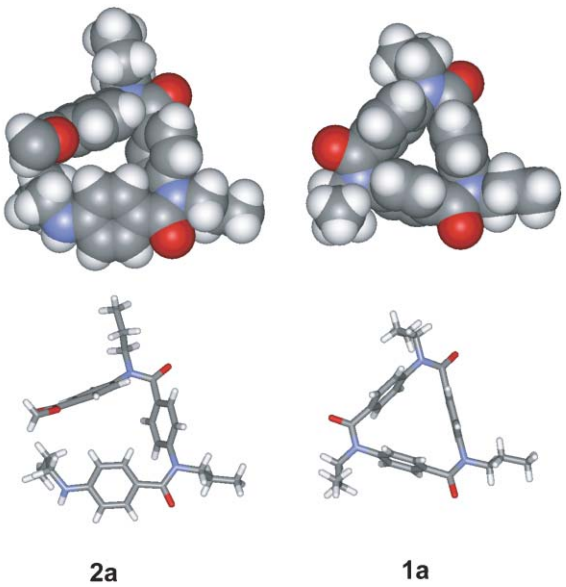

Fig. 1 X-Ray crystal structures of the acyclic protected trimer **2a** and its corresponding cyclic trimer **1a** (above CPK representation, below stick representation). Carbon is shown in grey, hydrogen in white, nitrogen in blue and oxygen in red.‡

Crystals suitable for X-ray diffraction were obtained by cooling a wet solution of methanol and ether of the propyl-appended linear trimer **2a**.‡ The structure (Fig. 1) clearly demonstrates the mutual proximity of the amine and carboxylate groups with both amides adopting a *cis* conformation. Crystals of macrocycle **1a** were obtained by slow evaporation of a toluene–dichloromethane solution.† The asymmetric unit contains 4 molecules of trimer and 4 molecules of toluene which pack into columns of alternate trimer and toluene units held together by edge to face π–π interactions (ESI Fig. S1†). Only one of the macrocycles **1a** in the structure is shown in Fig. 1. Although slight differences are observed for each of the four trimers, the main structural features are the same. Thus, the structure is similar in nature to the previously disclosed *N*,*N*′,*N*″-trimethyl derivative[18] and closely resembles the structure of the linear ester **2a** from which it derives. For **1a** all three amide groups necessarily adopt the *cis* conformation and the amides twist out of conjugation with the aromatic ring—clearly indicating why the structures can form so easily. From the crystal structure, the cavity volume is estimated to be ~15 Å^3. This is too small to be useful for host–guest chemistry and indicates the macrocycles will function exclusively as scaffolds onto which guest binding domains can be added.

The solid state conformational behaviour is maintained in solution. Fig. 2 shows the ^{1}H NMR spectra of compound **2b** and **1b**—NOE cross peaks (ESI Fig. S3) are highlighted for interacting protons.† The ^{1}H NMR spectrum of the acyclic trimer **2b** has only one set of resonances indicative of a strong bias towards one conformation. Observation of through-space correlation between protons situated on aromatic rings at opposing ends of the acyclic trimer indicate that the folded conformation is adopted. These

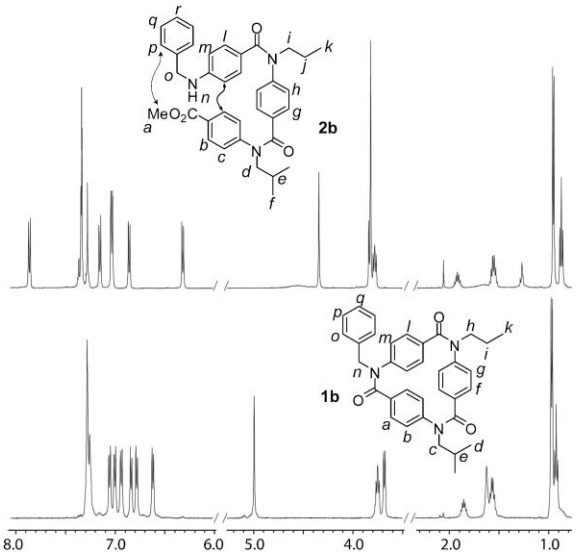

Fig. 2 ^{1}H NMR spectra (500 MHz, $CDCl_3$) of acyclic trimer **2b** and cyclic trimer **1b** (arrows denote NOE cross peaks).

cross peaks are still present in the final macrocycle **1b** (not shown). In the ^{1}H NMR spectrum of **1b**, the amine resonance is lost whilst the aromatic resonances move closer together, although interestingly they remain well resolved despite only subtle differences in alkyl substitution. This is not a conformational issue as little change is observed upon heating a sample in $C_2D_2Cl_4$ to 100 °C. Finally, the ^{1}H NMR and NOESY spectrum of compound **2a** is similarly complicated to that for **2b** but upon cyclisation simplifies to just five resonances consistent with a C_3 symmetric cyclic compound (ESI Fig. S2 and S4).† This again suggests only one conformation is present in solution for these macrocycles.

In summary, we have described a robust method for regiospecific synthesis of differentially substituted C_3 cyclic supramolecular scaffolds. Future studies will focus on incorporation of protected aldehyde fragments that contain useful functional groups for host–guest chemistry. We will report on these results in due course.

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Notes and references

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