Rod–coil copolymers from oligo(*p*-benzamide) foldamers†‡

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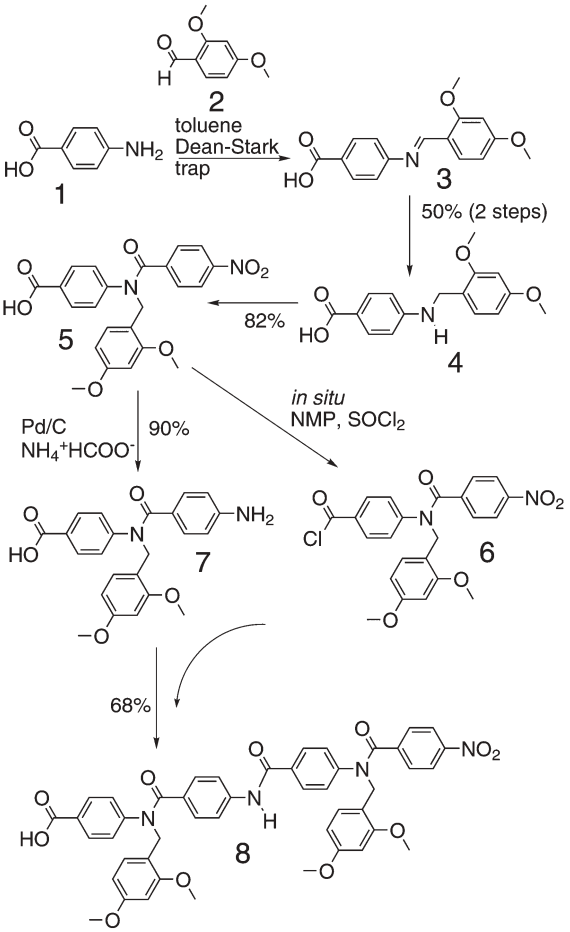
Self assembling rod–coil copolymers were synthesized in which oligo(*p*-benzamide) rods up to the octamer were prepared *via* iterative solution synthesis employing the acid labile 2,4-dimethoxybenzyl amide protective group.

Rod-like molecules with nanometre dimensions have recently attracted increased attention.[1] Most of these shape persistent molecules gain rigidity from either helix formation[2] or π-conjugation.[3] Molecular rods offer the possibility to position reactive centres at known distances from each other which is, for example, important for the study of electron and energy transfer. On the other hand they are useful nano-scaffolds used in the construction of larger shape persistent molecules as well as in supramolecular chemistry.[4] Oligo(*p*-benzamide)s (OPBAs) are particularly interesting molecular rods as they combine chain stiffness with the ability to form multiple hydrogen bonds. This combination of shape persistence and directionality in non-covalent bond formation makes them interesting building blocks for the construction of supramolecular objects such as rod–coil copolymers. Rod–coil copolymers are an important class of supramolecular polymer. They offer the possibility of creating defined nano-structures in solution or the solid state on length scales much smaller than typically accessible using coil–coil block copolymers.[5] We recently described the synthesis and aggregation behaviour of rod–coil copolymers in which the rod-segments are based on shape persistent OPBA.[6,7]

The greatest challenge in synthesizing OPBA for use in supramolecular chemistry is their strong aggregation and hence low solubility in most organic solvents.[8] We previously reported a precursor route[9] as well as a solid supported synthesis protocol[10,11] that overcomes these limitations. Here we describe a new synthetic route to OPBA up to the octamer using *N*-2,4-dimethoxybenzyl (*N*-DMB) protection on every second amide group.

As shown in Scheme 1, *p*-aminobenzoic acid (**1**) was reductively alkylated using 2,4-dimethoxy benzaldehyde (**2**) and sodium borohydride to give the secondary amine **4** (50% over two steps). Acylation of **4** with *p*-nitrobenzoyl chloride gave the *N*-DMB protected dimer **5** (82%). The nitro group of **5** could be reduced to the amine using Pd/C and ammonium formate to give amino acid **7** (90%). The nitro reduction at rt was found to be slow and completion of reaction was monitored by RP-HPLC (reversed phase-HPLC, see ESI‡). Using an activation protocol described by Zollinger and co-workers[12] and more recently by Ueda and co-workers,[13] **5** could be transformed into the acid chloride **6** using thionyl chloride in NMP without any detectable loss of the DMB-protective group. Acylation of **7** with **6** gave the tetramer **8** (68%).



Scheme 1 Synthesis of OPBA dimers (**5**, **7**) and the tetramer (**8**).

We were fortunate to grow single crystals of **8** from an ethanol–water (20 : 1 v/v) mixture which allowed X-ray crystallographic analysis (see crystal data§[14]). Of particular interest was the conformation of the three amide bonds in **8**.

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‡ Electronic supplementary information (ESI) available: Experimental; X-ray structure of **8**; HPLC elugrams; mass and NMR spectra. See DOI: 10.1039/b617598h

§ CCDC reference number 629491. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b617598h

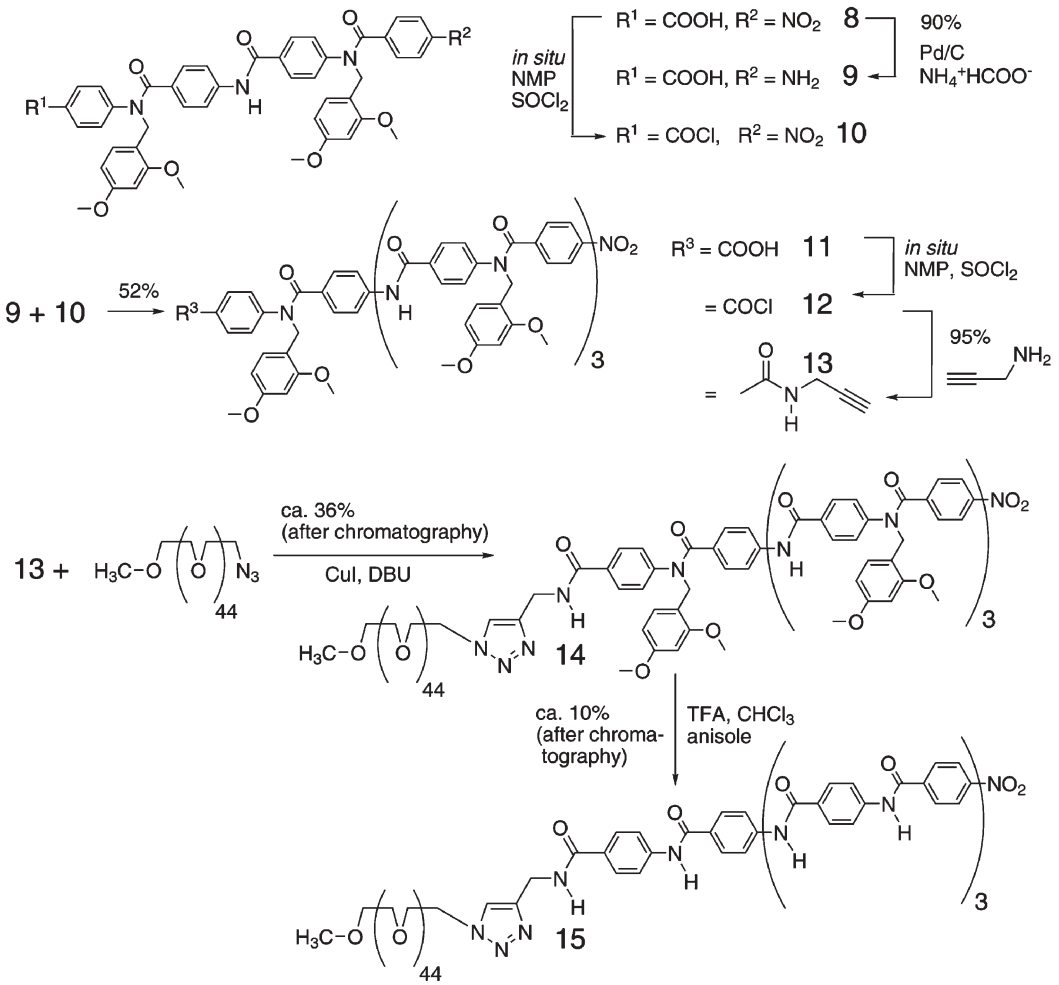
It has been well established that secondary aromatic amides (Ar–CONH–Ar) exist predominantly in the *trans* conformation while the tertiary aromatic amides of the type Ar–CONR–Ar (R = alkyl) prefer the *cis* conformation (with respect to the phenyl rings).[15] In a previous report we could show that this was also true for OPBA dimers in solution as well as in the solid state.[10]

Of the three amide bonds present in **8** only the centre one exists in the *trans* conformation while the outer ones are in the *cis* conformation. This confirms the previous assumption that this conformational preference persists in longer OPBAs. COSY and NOESY-NMR spectroscopy of solutions of **8** allowed the complete peak assignment of the ^{1}H-NMR spectroscopic data and showed that at least one tertiary amide existed exclusively in the *cis* conformation (the conformation of the other amide group could not be assigned due to overlapping peaks; see ESI‡).

Continuing with the iterative strategy, **8** could be reduced to the amine **9** using Pd/C and ammonium formate (90%, Scheme 2). *In situ* activation of **8** with thionyl chloride in NMP gave the acid chloride **10**, which was coupled with **9** to give the octamer **11** (52%). **11** could be converted into an acid chloride *in situ* ($SOCl_2$–NMP) and coupled with propargylamine to install a terminal alkyne in **13** (95%). Poly(ethylene glycol) mono-methyl ether mono-azide[16] could be reacted with **13** in a [2 + 3]-cycloaddition under Cu(I)-catalysis[17] to give the block copolymer **14** (40%) in which both blocks are 1,4-linked *via* a 1,2,3-triazole unit.

Block copolymer **14** which most likely adopts a coil–coil-like conformation showed no aggregation in chloroform. The presence of DMB-*N*-protective groups on every second amide effectively disrupted the aggregation process. It is important to note that a virtually identical synthetic strategy using a dimer analogous to **7** carrying a *p*-methoxybenzyl group was unsuccessful when carried out on a solid support. We attributed this to backbone aggregation of the oligomers on the solid phase. For this reason we previously reported that complete *N*-protection is necessary for successful solid supported synthesis of such oligomers.[10] In the case described here, the bulky polymer chain of **14** possibly helps in reducing the aggregation strength *via* steric shielding. **14** could be analyzed by MALDI-TOF mass spectroscopy (Fig. 1, left). The mass spectrum shows only the fully protected block copolymer as the sodium, potassium and lithium adduct.

The DMB-protective group was removed by dissolving **14** in a mixture of trifluoroacetic acid (TFA), chloroform and



Scheme 2 Synthesis of an OPBA octamer (**11**) and conjugation with poly(ethylene glycol) to yield a coil–coil copolymer (**14**) or rod–coil copolymer (**15**) after DMB-deprotection.

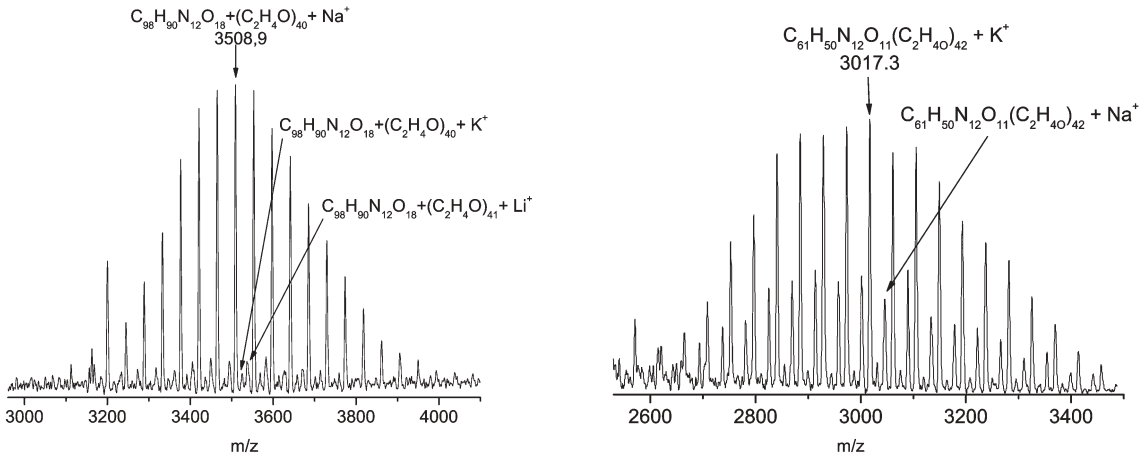


Fig. 1 MALDI-TOF mass spectrum of protected **14** (left) and unprotected **15** (right).

anisole at rt for 15 h. The ease of protective group removal could be demonstrated by addition of polymer **14** to neat TFA. This immediately gave a purple coloured solution, indicative of the successfully cleaved DMB cation. Polymer **15**, in which all aromatic amides are assumed to exist exclusively in the all-*trans* conformation was further purified by silica gel chromatography in THF and DMF. Fig. 1 (right) shows the MALDI-TOF mass spectrum of **15**. Two mass distributions, one for the potassium and one for the sodium adduct of **15** can be observed.

Fig. 2 (top, middle) shows the chloroform GPC traces for **14**, **15** as well as for the parent PEG–azide. A shift to higher mass is clearly visible going from PEG–N_3 to the *N*-DMB-protected block copolymer **14**. The elugram of **14** showed the molecularly dissolved polymer eluting at the poly(styrene) equivalent hydrodynamic radius (M_n = 3500 g mol^{-1}, M_w = 3800 g mol^{-1}; PDI = 1.07).

The GPC trace of **15** in chloroform showed the presence of molecularly dissolved polymer as well as high molecular weight aggregates. The non-covalent aggregates elute at very high molecular weight (>2 × 10^6 g mol^{-1}) outside the calibration limit of the GPC setup. Similar behaviour has previously been observed by us for other rod–coil copolymers in chloroform solution.[9]

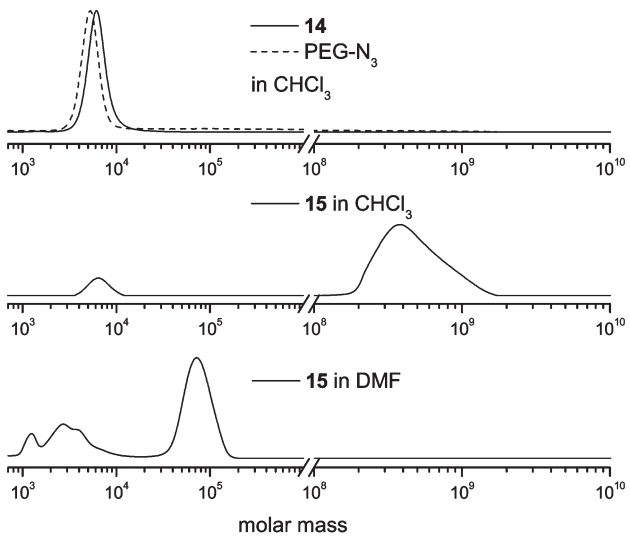


Fig. 2 GPC traces. Top: PEG–N_3 (dashed line) and **14** (full line) in $CHCl_3$; middle: **15** in $CHCl_3$; bottom: **15** in DMF.

The GPC elugram of the same sample of **15** in DMF (Fig. 2, bottom) also showed the presence of aggregates as well as molecularly dissolved polymer. The aggregates of **15** in DMF appear as a multi modal mass distribution, which was unexpected and had not been observed by us previously. However, the previously reported rod–coil copolymers differed from the ones shown here.[6,7,9] Detailed investigations had previously been carried out on a hepta(*p*-benzamide) carrying six amide groups. The octamer shown here carries eight amide groups and it is likely that this causes the increased aggregation strength. By comparing the very different aggregate masses and mass distributions in the elugrams of **15** in $CHCl_3$ and DMF it could safely be concluded that all aggregation phenomena were due to non-covalent interactions rather than covalent cross-linking.

The non-aggregating *N*-DMB-protected copolymer **14** could be analysed by ^{1}H-NMR spectroscopy in DMSO-d_6 and all peaks of the spectrum could be assigned. A ^{1}H-NMR spectrum of **15** was recorded in DMSO-d_6. The polymer appeared to aggregate in this solvent, as the aromatic signals of the OPBA block integrated to only 15% of the expected value when compared to the integral of the PEG methylene protons. This can be explained, considering the observed aggregation of **15** in DMF (see GPC results above). The solvent (DMSO-d_6) was then removed under vacuum and the residue dissolved in deuterated sulfuric acid, which is known to be a strong hydrogen bond disrupting solvent.[18] The ^{1}H-NMR spectrum of **15** in D_2SO_4 shows a significant increase in intensity of the aromatic protons in the range δ = 7.0–8.5 compared to the spectrum recorded in DMSO-d_6. This marked difference in intensity is further evidence for the strong aggregation of **15** in DMSO (NMR data is available in the ESI‡).

In order to further study the aggregation phenomena, chloroform solutions of **15** were investigated by transmission electron microscopy (TEM). Fig. 3 shows a representative TEM image of aggregates of **15**. Elongated, rod-like micelles can be observed similar to those reported previously.[7] The

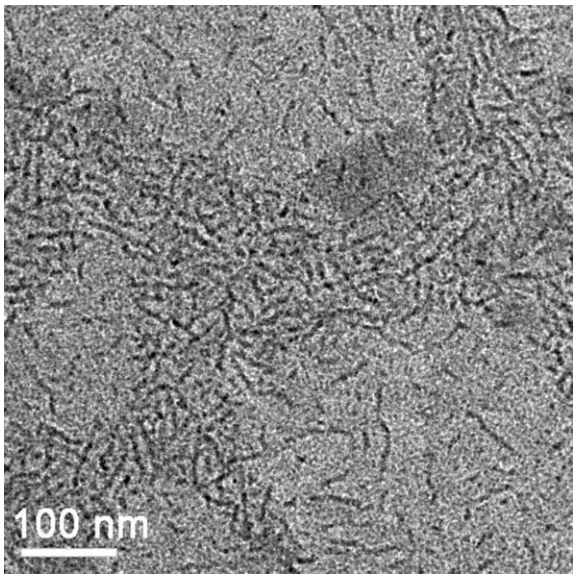


Fig. 3 TEM image of aggregates of **15** drop cast (3 times) from chloroform solution (0.5 mg mL^{-1}) onto carbon coated copper grids. The sample was stained with OsO_4.

anisotropic aggregation is most likely driven by highly directional intermolecular hydrogen bonds.

In conclusion, we have successfully employed the 2,4-dimethoxybenzyl protective group for the protection of oligo(*p*-benzamide)s up to the octamer. Protection of every second amide group was sufficient to suppress aggregation during synthesis. The more acid labile DMB-protective group was cleaved faster than the previously employed 4-methoxybenzyl group, yet tolerates the activation of the amino acid as an acid chloride without any detectable cleavage. An alkyne derivatized octa(*p*-benzamide) could be linked to a polymer chain *via* Cu(I)-catalyzed [2 + 3]-cycloaddition. The *N*-DMB-protected amphiphilic block copolymer showed no aggregation in non-polar solvents while the deprotected polymer aggregated strongly in chloroform. Both polymers could be analysed by MALDI-TOF mass spectroscopy. TEM imaging showed rod-like micelles for the DMB-deprotected polymer in chloroform solution. Further investigations will focus on the variation of the polymer block and investigate the effect on superstructure formation in solution.

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