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Solid-Phase Synthesis of Oligo(*p*-benzamide) Foldamers

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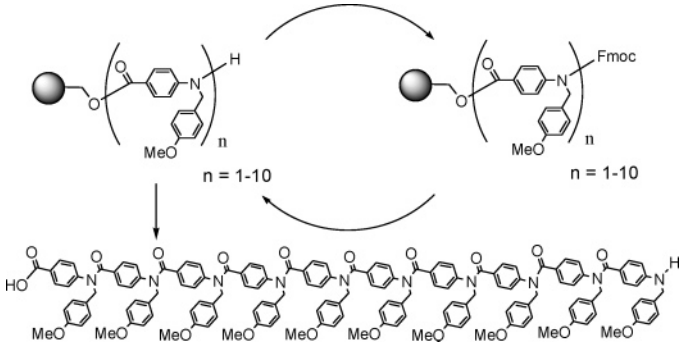
ABSTRACT



A coupling protocol has been developed which allows the synthesis of oligo(*p*-benzamide)s on solid support. Aromatic carboxylic acids are activated in situ with thionyl chloride and used to acylate secondary aromatic amines. *N*-*p*-Methoxy benzyl (PMB) as well as *N*-hexyl protected monomers were investigated. Heterosequences of both monomers were synthesized. Such nanoscale objects are important building blocks for supramolecular chemistry.

Shape-persistent rigid rodlike molecules with dimensions on the nanometer scale are important building blocks for supramolecular architectures such as rod−coil block-copolymers and have recently received increased attention.[1] As most of these rodlike molecules are oligomers, solid-supported synthesis is an ideal tool for their preparation via repetitive coupling protocols. However, few examples describing the synthesis of rigid rodlike molecules on solid support have been reported to date. Nelson[2] as well as Huang[3] et al. described a solid-supported synthesis of linear oligo(phenylene ethynylene)s, and Wang and co-workers synthesized phenylacetylene dendrons on solid support.[4] The Fréchet group successfully prepared oligothiophenes up to the pentamer on the solid phase.[5] Nanometer-sized molecular rods of uniform length based on oligoamides were prepared by Levins et al.[6] Aromatic oligoamides have been synthesized on soluble[7,8] as well as solid support.[9,10] Most recently, the Whitesides group described the solid-supported synthesis of rodlike oligopiperidines up to the decamer.[11]

Most rigid rods employed in supramolecular chemistry are based on extended π-systems and aggregate via relatively weak $\pi-\pi$ interactions. Extended rigid rods that are capable

(1) Schwab, P. F. H.; Levin, M. D.; Michl, J. *Chem. Rev.* **1999**, *99*, 1863−1933. Schwab, P. F. H.; Smith, J. R.; Michl, J. *Chem. Rev.* **2005**, *105*, 1197−1279.
(2) Nelson, J. C.; Young, J. K.; Moore, J. S. *J. Org. Chem.* **1996**, *61*, 8160−8168. Young, J. K.; Nelson, J. C.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 10841−10842.
(3) Huang, S.; Tour, J. M. *J. Org. Chem.* **1999**, *64*, 8898−8906. Huang, S.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 4908−4909. Jones, L.; Schumm, J. S.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1388−1410.
(4) Chi, C.; Wu, J.; Wang, X.; Zhao, X.; Li, J.; Wang, F. *Macromolecules* **2001**, *34*, 3812−3814.
(5) Malenfant, P. R. L.; Fréchet, J. M. J. *Chem. Commun.* **1998**, 2657−2658.
(6) Levins, C. G.; Schafmeister, C. E. *J. Am. Chem. Soc.* **2003**, *125*, 4702−4703.
(7) König, B.; Papke, U.; Rödel, M. *New J. Chem.* **2000**, *24*, 39−45.
(8) König, B.; Rödel, M. *Chem. Commun.* **1998**, 605−606.
(9) Baird, E. E.; Dervan, P. B. *J. Am. Chemn. Soc.* **1996**, *118*, 6141−6146.
(10) Wurtz, N.; Turner, J. M.; Baird, E. E.; Dervan, P. B. *Org. Lett.* **2001**, *3*, 1201−1203.
(11) Semetey, V.; Moustakas, D.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 588−591.

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of strong directional intermolecular noncovalent interactions such as hydrogen bonds are scarce.

We have recently described the synthesis[12] and solution organization[13] of block-copolymers in which hepta(*p*-benzamide) rods are responsible for solution structure formation via strong intermolecular hydrogen bonds between the rigid rodlike molecules.

Herein, we describe the first solid-phase synthesis of oligo(*p*-benzamide)s (OPBA) up to the decamer via acylation of secondary aromatic amines on a Wang resin support.

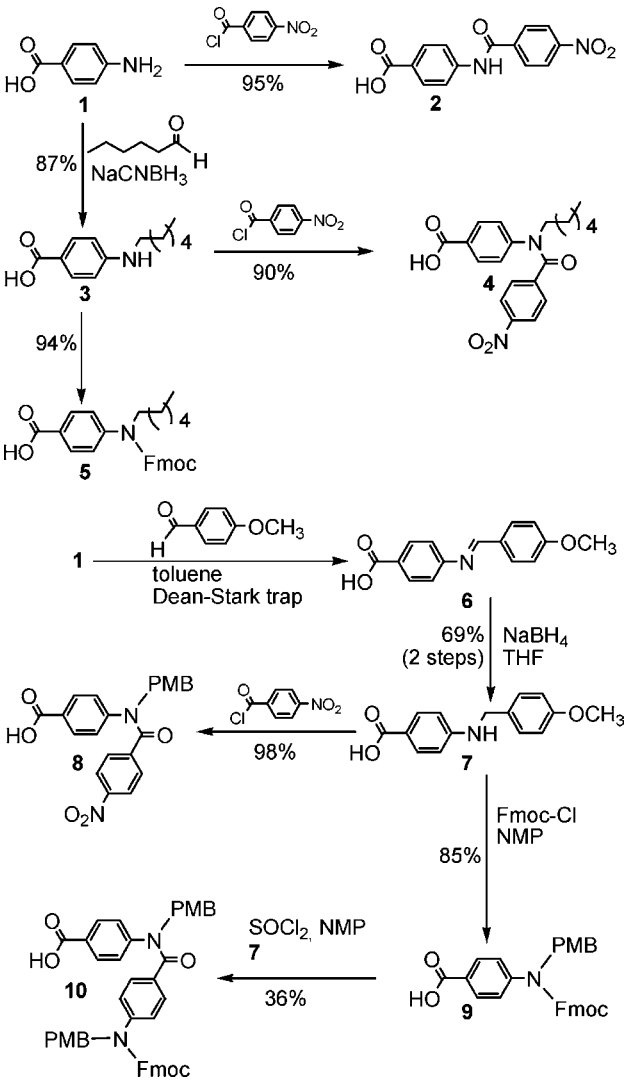
Our initial investigations explored the direct synthesis of amide N-unprotected OPBA using a repetitive coupling cycle in which we (1) acylated with *p*-nitrobenzoyl chloride followed by (2) reduction of the nitro group with $SnCl_2$, etc. However, because of increasing intermolecular hydrogen bond formation among the growing oligomers, the trimer was the largest oligomer that could successfully be prepared and isolated via this strategy.

To avoid hydrogen bonding among the immobilized oligomers, the amide groups had to be protected. We chose the *p*-methoxy benzyl (PMB) protective group, which is well established for amide protection.[14] We also prepared oligomers with amide *N*-hexyl substitution for reasons discussed below.

As outlined in Scheme 1, *p*-amino benzoic acid was reductively alkylated with hexanal or anisaldehyde to give secondary aromatic amine **3** (87%) and **7** (69%), respectively. These were either directly Fmoc protected using Fmoc−Cl to give compounds **5** (94%) and **9** (85%) or reacted with *p*-nitrobenzoyl chloride to give the amides **4** (90%) and **8** (98%).

For our initial attempts to build OPBAs on Wang resin (1.2 mmol OH g^{-1}), we chose Fmoc- and PMB-protected *p*-amino benzoic acid **9**. First residue attachment was easily achieved using standard DCC coupling. Fmoc deprotection with piperidine in DMF was also successful as determined by UV spectroscopy and RP-HPLC analysis of an analytical sample cleaved from the resin (TFA/DCM = 1:1). The attachment of the next residue, i.e., coupling of **9** with the secondary aromatic amine immobilized on solid support, was, however, unsuccessful with the standard coupling protocols typically employed in α-peptide synthesis.[15] Neither the symmetrical anhydride method (with DIC) nor DIC/HOBt, HBTU,[10] or HATU activation of **9** gave the desired coupling product. Coupling reagents typically used for the synthesis of aromatic amides and polyamides such as DBOP[16] and TPP[17] were also evaluated, but no product formation was observed.

Scheme 1. Synthesis of Monomers **5**, **9**, and **10** as Well as Model Compounds **4** and **8**



This was not unexpected, considering that even secondary aliphatic amines pose considerable challenges in peptide synthesis.[18] Successful, however, was an activation method described by Ueda et al. using 1 equiv of thionyl chloride in NMP in which the carboxylic acid is turned into an acid chloride under otherwise mild conditions.[19] Activated **9** was used to prepare a deca(*p*-benzamide) in 10 coupling steps on solid support (Wang resin, 1.2 mmol OH g^{-1}) as shown in Scheme 2.

Encouraged by this success, we decided to prepare **10**, an Fmoc-protected dimer of **9**, which would allow the synthesis of larger oligomers in fewer coupling steps on the solid phase. **9** was therefore activated using Ueda's protocol and reacted with **7** to give dimer **10** (36% after chromatographic purification). The potential advantage of coupling a dimer

(12) Abbel, R.; Frey, H.; Schollmeyer, D.; Kilbinger, A. F. M. *Chem.−Eur. J.* **2005**, *11*, 2170−2176.

(13) Abbel, R.; Schleuss, T. W.; Frey, H.; Kilbinger, A. F. M. *Macromol. Chem. Phys.* **2005**, *206*, 2067−2074. Schleuss, T. W.; Abbel, R.; Gross, M.; Schollmeyer, D.; Frey, H.; Maskos, M.; Berger, R.; Kilbinger, A. F. M. *Angew. Chem., Int. Ed.* **2006** in press.

(14) Brooke, G. M.; Mohammes, S.; Whiting, M. C. *Chem. Commun.* **1997**, 1511−1512. Yokozawa, T.; Ogawa, M.; Sekino, A.; Sugi, R.; Yokoyama, A. *J. Am. Chem. Soc.* **2002**, *124*, 15158−15159.

(15) Chan, W. C.; White, P. D. In *Fmoc Solid-Phase Peptide Synthesis, A Practical Approach*; Chan, W. C., White, P. D., Eds.; Oxford University Press: Oxford, Great Britain, 2000.

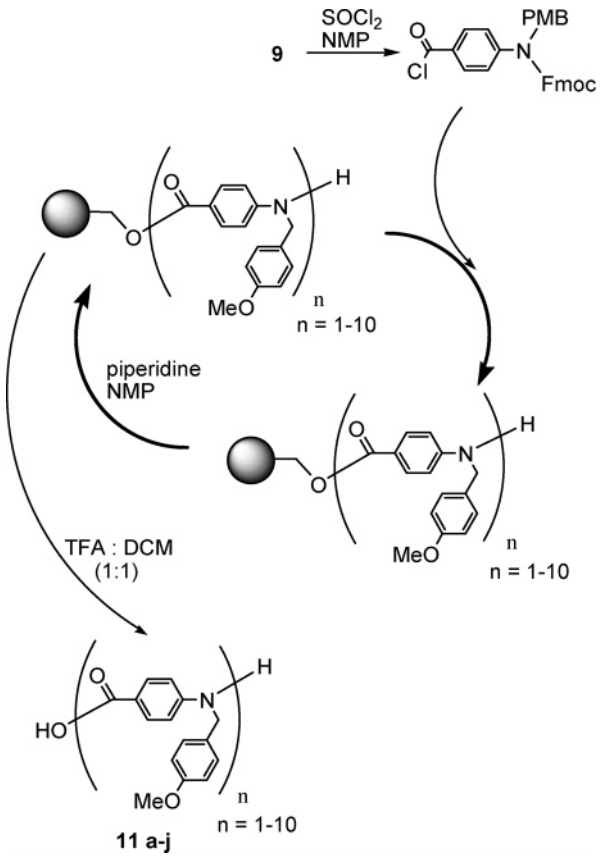
(16) Ueda, M.; Kameyama, A.; Hashimoto, K. *Macromolecules* **1988**, *21*, 19−24.

(17) Yamazaki, N.; Matsumoto, M.; Higashi, F. *J. Polym. Sci. Polym. Chem. Ed.* **1975**, *13*, 1373−1380.

(18) See, for example: Seewald, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4661−4663.

(19) Washio, I.; Shibasaki, Y.; Ueda, M. *Org. Lett.* **2003**, *5*, 4159−4161.

Scheme 2. Coupling Cycle for the Solid-Phase Synthesis of Oligo(*p*-benzamide)s **11a**−**j**



instead of a monomer was lost, as the dimer **10** exhibited a remarkably lower reactivity compared to the monomer **9**. RP-HPLC monitoring of the solid-supported oligomerization of **9** and **10** (Scheme 2) revealed that a typical reaction cycle using dimer **10** took at least 20 h, whereas activated monomer **9** could be coupled within 1 h. Such short coupling cycles are on the same time scale as those for α-amino acid couplings using standard Fmoc chemistry on a peptide synthesizer.

As could be shown by RP-HPLC and ^{1}H NMR spectroscopy, the $SOCl_2$ activation of **9** or **10** did not result in any loss of the acid-labile PMB-protective groups.

Cleavage of the decamer **11j** from the Wang resin was achieved using TFA in DCM (1:1). **11j** could be purified by preparative RP-HPLC. The RP-HPLC elugram of purified **11j** is shown in Figure 1. The ESI mass spectrum shows the product peak as well as the product that has lost PMB protective groups. The loss of PMB groups most likely occurs in the mass spectrometer.

To the best of our knowledge, no unsubstituted OPBAs larger than the tetramer have been reported.[20] This is most likely due to the very low solubility of these compounds as a result of their rigid rodlike geometry combined with perfectly aligned hydrogen-bond donors and acceptors.

(20) For the synthesis of the tetramer, see: Bredereck, H.; von Schuh, H. *Chem. Ber*. **1948**, *81*, 215−221.

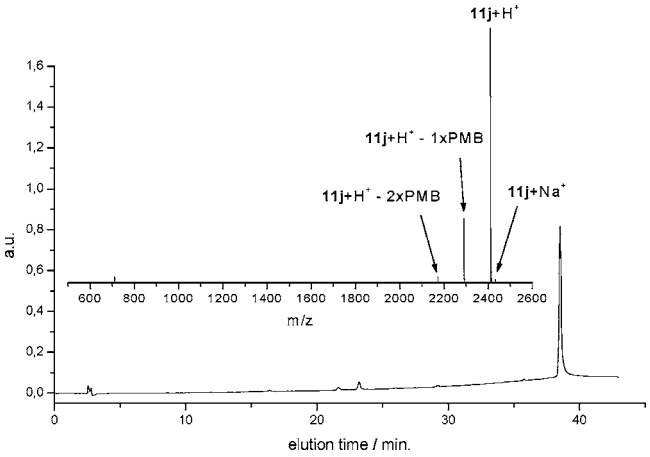


Figure 1. RP−HPLC elugrams of **11j** after preparative HPLC purification. The inset shows the ESI−MS spectrum of purified **11j**.

On the other hand, the decamer **11j** exhibits very good solubility in solvents such as acetonitrile or chloroform, a fact that cannot merely be due to the lack of hydrogen bonds if the rigid rodlike shape persists. The improved solubility is due to the preference of N-alkylated aromatic amides to adopt a cis transformation and the preference of N-unsubstituted aromatic amides to adopt a trans conformation,[21,22] allowing the oligomer **11j** to explore more geometrically diverse conformers which greatly reduce its tendency to aggregate.

To test this hypothesis, dimeric model compounds **4** and **8** were prepared and revealed the expected cis conformation in the solid state as well as in solution (see Supporting Information).

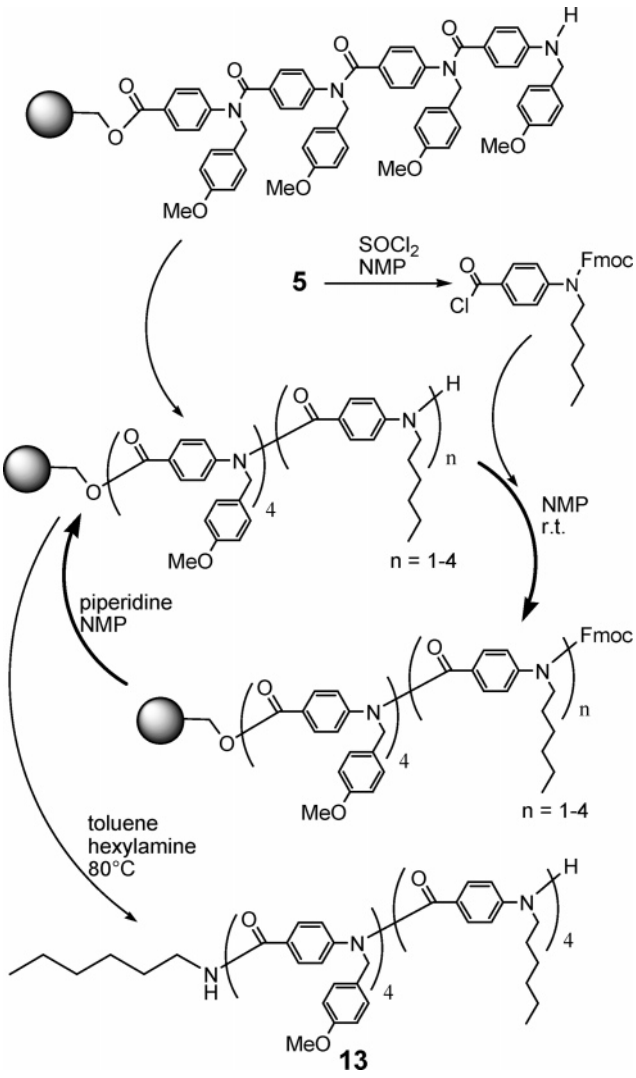
The two monomers **5** and **9** can therefore be used to build soluble OPBA precursors. Upon deprotection of the PMB groups, linear *trans*-amide bonds (vide supra) are expected to form whereas the hexyl-substituted amides should remain in the cis conformation under these conditions. Designed heterosequences of monomers **5** and **9** should therefore, after deprotection of the PMB groups, allow the synthesis of nanoscale shape-persistent objects with predefined geometry composed of linear and "bent" segments.

To prove that heterosequences of **5** and **9** or **10** can be prepared, the octamer **13** was synthesized on solid support from two monomer units of **10** and four monomer units of **5** as shown in Scheme 3. To demonstrate that PMB-protected

(21) Tanatani, A.; Yokoyama, A.; Azumaya, I.; Takakura, Y.; Mitsui, C.; Shiro, M.; Uchiyama, M.; Muranaka, A.; Kobayashi, N.; Yokozawa, T. *J. Am. Chem. Soc.* **2005**, *127*, 8553−8561. Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649−10650. Masu, H.; Sakai, M.; Kishikawa, K.; Yamamoto, M.; Yamaguchi, K.; Kohmoto, S. *J. Org. Chem.* **2005**, *70*, 1423−1431. Nishimura, T.; Maeda, K.; Yashima, E. *Chirality* **2004**, *16*, S12−S22. Tanatani, A.; Kagechika, H.; Azumaya, I.; Fukutomi, R.; Ito, Y.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 4425−4428. Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277−5290.

(22) Arylamides with a solvent-dependent cis−trans ratio have also been observed: Forbes, C. C.; Beatty, A. M.; Smith, B. D. *Org. Lett.* **2001**, *3*, 3595−3598.

Scheme 3. Coupling Cycle for the Solid-Phase Synthesis of Octa(*p*-benzamide) **13**



OPBA can be cleaved from Wang resin without loss of PMB groups, nucleophilic cleavage with hexylamine in toluene at 80 °C was carried out. Figure 2 shows the ESI mass spectrum of **13**.

In summary, a solid-phase coupling protocol has been developed that allows the synthesis of oligomers of N-substituted *p*-amino benzoic acids. Such oligomers show a dramatic increase in solubility in organic solvents compared to the unsubstituted case. We explain this fact on the basis of X-ray crystallographic and NOESY−NMR experiments of model compounds: the N-unsubstituted oligomers exist in a linear all-trans form, whereas the N-substituted oligomers seem to adopt a more compact form due to the presence of *cis*-amides thereby gaining solubility. Heterosequences of differently N-substituted monomers can be synthesized as was demonstrated by an octa(*p*-benzamide) carrying two types of N-substituents. Designed heterosequences will allow the synthesis of objects with different geometries consisting of linear (trans) segments and bent (cis) segments. We are currently investigating the synthesis of object-coil block-copolymers with varying object geometries prepared by solid-phase synthesis.

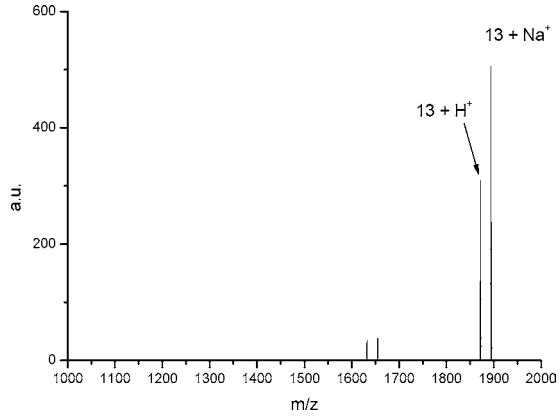


Figure 2. ESI mass spectrum of **13**.

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Supporting Information Available: Crystallographic data in CIF format, synthesis, and characterization of **2**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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