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Tuning the solubility of hepta(*p*-benzamide)s via the monomer sequence

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The automated synthesis of hepta(p-benzamide) hetero sequences on solid support using a modified peptide synthesizer is reported. The oligomers are synthesized from 4-aminobenzoic acid and 4-amino-2-(hexyloxy)benzoic acid, the latter carrying a solubilizing hexyl side chain. It is known from previous studies that both the unsubstituted hepta(p-benzamide) and the fully hexyloxy-substituted hepta(p-benzamide) are insoluble in all common organic solvents. Heterosequences in which both types of monomers alternate are, however, soluble in polar organic solvents such as DMSO. The heterosequence heptamers behave as strong organogelators when DMSO solutions are left at room temperature for several hours. Transmission electron microscopic (TEM) investigations revealed that the gelation was due to the oligomers forming long entangled fibers via a non-covalent aggregation mechanism. We explain these phenomena by a heterosequence triggered switch of aggregation mechanism. The unsubstituted oligomers strongly aggregate via a directional hydrogen-bond driven mechanism which changes to a less directional □-interaction driven aggregation mechanism for the substituted oligomers.
We thereby demonstrate that designed hetero sequences in non-natural oligoamides can lead to materials with distinctly different conformations which directly affects the intermolecular interactions and their supramolecular organization.

Molecular rods built from lower molecular weight building blocks allow precise length control have been attracting interest over the last two decades.[1,2] Synthetic approaches that allow the precise control over the building block sequence are of particular interest. Solid supported syntheses allow facile sequence control while offering the possibility of automation. Molecular rods have been employed as beam-like building blocks in supramolecular assemblies[3] or as molecular spacers that place two active residues at precise distances from each other.[4,5] Molecular rods have also been used in protein binding to α-amino acid residue arrangements in peptide helices[7] or to prevent protein binding by inhibiting a substrate as shown in the case of rigid arylamide oligomers binding to low-molecular-weight heparin.[8] They have also been extensively used in the shape of conjugated electro- and photoactive materials.[9,10]

We recently reported several synthetic routes to rigid rod-like oligo(*p*-benzamide)s employing modified peptide coupling protocols on commercially available peptide synthesizers[11,12] and using solution chemistry.[13] Oligo(*p*-benzamide)s (OPBA) are particularly rigid aromatic amides which suffer from poor solubility due to their linearly aligned hydrogen bond donors and acceptors.[14,15] In order to solubilize these oligomers, we previously conjugated them with polyethylene glycol chains, resulting in supramolecular rod-coil block copolymers, which self-assemble into rod-like micelles in non-polar solvents.[15,16,17,18]

The most common strategy to improve solubility in rigid rod-like molecules is the attachment of flexible side chains to the stiff oligomer/polymer backbone. It is believed that such side chains act like a covalently attached solvent, allowing for a gain in entropy upon dissolution of the oligomer or polymer.[19-23]

The fine structural balance between solubility and aggregation has been exploited in the field of organogelators.[24] For gelation to be oberseved an aggregation or supramolecular polymerization needs to occur in order to achieve the required high connectivity of the individual gelator molecules. In many examples the ability of secondary amides to form hydrogen bonded structures is used as the non-covalent polymerization mechanism.[25-27]

Here we report the synthesis of hepta(*p*-benzamide) hetero sequences, varying in the number and pattern of hexyloxy substituents. Using automated solid supported synthesis allowed for facile and rapid access to precisely defined hetero sequences. We present evidence that the number and position of hexyloxy substituents strongly affects oligomer solubility and

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aggregation/gelation behavior.

We previously reported that the heptamer of 4-amino-2-(hexyloxy)benzoic acid (Fig. 1 bottom) is insoluble in most common organic polar and non-polar solvents.[28] However, covalently attached side chains typically increase solubility of otherwise insoluble oligomers and polymers.[19-23] We rationalized that in the case of hexyloxy-substituted oligo(*p*-benzamide)s, the side chain not only acted as a covalently attached solvent but also as an intramolecular hydrogen bond acceptor, thereby rendering two neighboring phenyl rings perfectly coplanar. In the case of the hepta(2-hexyloxy-*p*-benzamide) all amide *N-H* groups can form hydrogen bonds to neighboring hexyloxyethers and thus render all phenyl rings in the heptamer perfectly coplanar (Figure 1, bottom). We believe that aggregation of this heptamer occurs via π-interactions and that hexyl side chains are insufficient to solubilize the aggregates.

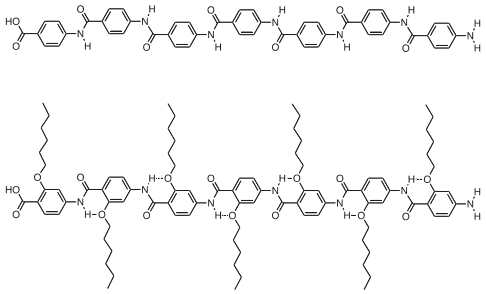
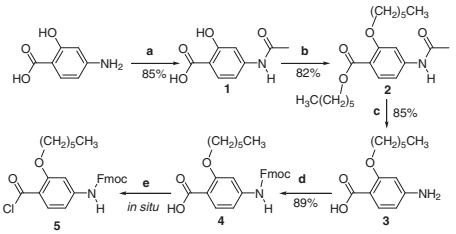


Figure 1. Hepta(*p*-benzamide) (*top*) and hepta(2-hexyloxy-*p*-benzamide) (*bottom*) are both insoluble in common polar and nonpolar organic solvent. Hepta(*p*-benzamide) aggregates via directional hydrogen bond formation whereas hepta(2-hexyloxy-*p*-benzamide) forms aggregates via π-interactions.

The parent structure that lacks all flexible side chains, hepta(*p*-benzamide) (Figure 1, top), is also insoluble in all common organic polar and non-polar solvents. In this case, insolubility is a result of directional hydrogen bond formation between the individual amide groups, as has been shown for smaller oligomers via x-ray crystal structure analysis.[14,15] We were interested in exploring the aggregation behavior of heterosequences situated structurally in between the two insoluble extremes described above.

4-Amino-2-(hexyloxy)benzoic acid (**3**) was prepared as shown in Scheme 1. 4-Aminosalicylic acid was *N*-acetylated using one equivalent of acetyl chloride to give **1** in 85% yield. The subsequent reaction with hexyl bromide produced the corresponding hexyl ether and ester **2** in 82% yield. Alkaline hydrolysis with KOH resulted in ester as well as amide cleavage to give 4-amino-2-(hexyloxy)benzoic acid (**3**) in 85% yield. *N*-Fluorenylmethyloxycarbonyl (Fmoc) protection was achieved using 9-fluorenylmethylchloroformate (Fmoc-Cl) to give **4** in 89% yield. Activation of **4** as an acid chloride was carried out in situ without further work-up of the activated species **5** using $SOCl_2$ and *N*-methylpyrrolidone (NMP).[29]

We synthesized two heterosequence heptamers **6** and **7** (Figure 2 top) on solid support according to reported procedures.[11,12] 4-Amino-2-(hexyloxy)benzoic acid and 4-amino-benzoic acid alternate in both structures with one heptamer carrying three and the other four hexyloxy side chains.

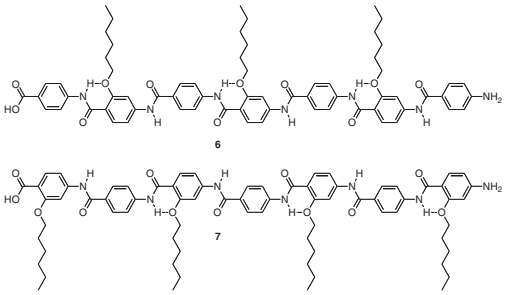


Scheme 1. Synthesis and activation of 4-amino-2-(hexyloxy)benzoic acid. a) acetyl chloride b) hexyl bromide c) KOH d) Fmoc-Cl e) $SOCl_2$ and NMP

The oligomers **6** and **7** are insoluble in chloroform, THF or dichloromethane but show good solubility in DMSO (or DMSO-d_6) as evidenced by the ^{1}H-NMR solution spectra shown in Figure 2 (bottom). In contrast, hepta(*p*-benzamide)s carrying no alkyloxy side chains or carrying seven alkyloxy side chains are both completely insoluble in virtually all organic solvents. The increased solubility for **6** and **7** in DMSO is therefore a direct result of the monomer sequence. However, the DMSO solutions of **6** and **7** slowly turn into gels when left at room temperature for ca. 12h. Oligomer **6** forms a clear gel, while oligomer **7**, just carrying one hexyloxy side chain more than **6**, forms an opaque gel (see graphical abstract).

The DMSO gels of **6** and **7** were investigated by transmission electron microscopy (TEM). As can be seen in Figure 3, both oligomers form multi-micrometer long fibers in DMSO, which entangle to give a gel-like macroscopic behavior. The TEM image of oligomer **7,** carrying four hexyloxy side chains, shows a denser, more entangled fiber network than oligomer **6**, carrying three hexyloxy side chains. The bundles of fibers observed in the TEM images are typically around 4-5□m long for oligomer **7** while oligomer **6** shows bundles of 1-2□m size on average.

This data suggests that the number of hexyloxy side chains in the substituted hepta(*p*-benzamide)s **6** and **7** also plays an important role in their supramolecular aggregation, i.e. fiber and gel formation. Both gels of **6** and **7** formed in DMSO are thermo reversible and were investigated with regard to their sol-gel transition temperatures using the dropping ball method.[30] The gel formed from **6** in DMSO shows a sol-gel transition at 70°C, that from **7** in DMSO a sol-gel transition at 84°C. This is in agreement with our previous assumption that the number of side chains is important for supramolecular aggregation. Oligomer **6**, carrying three hexyloxy side chains forms a weaker aggregate than oligomer **7** carrying four hexyloxy side chains. It could be shown in the solid state that the carbonyl groups of such oligoaramides strictly alternate their orientation along the oligomer strand, most likely in order to minimize the net dipole moment of the individual oligomers. [14,15]



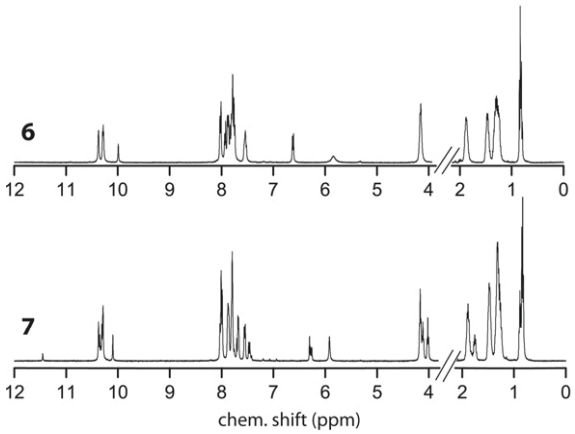


Figure 2. *Top*: Molecular structures of hepta(*p*-benzamide) heterosequences **6** and **7**. *Bottom*: Corresponding ^{1}H-NMR (DMSO-d_6, 300 MHz) spectra.

We assume that this alternation of the carbonyl dipole along the oligomer chain is preserved in solution for hexyloxy substituted oligomers. The formation of intramolecular hydrogen bonds between the amide *N-H* and the alkyloxy-ethers would then lead to a molecular structure in which all alkyloxy side chains are attached to the same edge of the oligomer (always trans to the carbonyl group, see Fig.2 top).

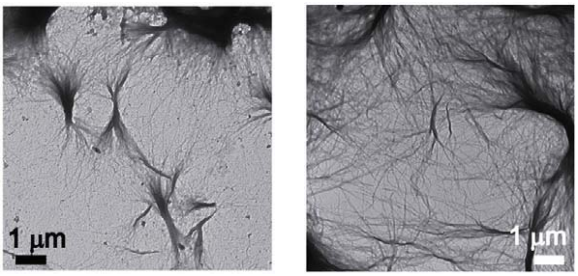


Figure 3. *Left*: TEM image of a gel of oligomer **6** in DMSO (c = 7.6 mM). *Right* TEM image of a gel of oligomer **7** in DMSO (c = 7.6 mM).

In other words, placement of such alkyloxy groups on only the "even phenyl rings" (**6**, Figure 2 top; phenyl rings counted from *C*-terminus to *N*-terminus) would selectively prevent one edge of the oligomer from further intermolecular stacking via hydrogen bonds, as all hydrogen bond donors would be intramolecularly saturated. Placement of alkyloxy groups on all "odd phenyl rings" (**7**, Figure 2 top; phenyl rings counted from *C*-terminus to *N*-terminus) would selectively prevent further intermolecular hydrogen bonds on the opposite edge of the oligomer. Hence, in both oligomeric heterosequences **6** and **7** one edge would be sterically blocked by hexyloxy groups and intramolecular hydrogen bonds while the other edge would be available for hydrogen bond interactions with the solvent DMSO. Therefore, the amide bonds present in compounds 6 and 7 have a solubilizing effect in the polar solvent DMSO and are not driving the aggregation as in many other amide organogelators.
Figure 4 shows a dimeric model with and without the hexyloxy substituent. In the non-substituted dimer the planes of the phenyl rings twist out of coplanarity by ca. 60° due to steric interactions of the N-H and ortho C-H groups as was observed by x-ray crystallography for similar unsubstituted compounds previously.[15,31] The hexyloxy substituted dimer forms an intramolecular (*N-H···O*) hydrogen bond that allows the phenyl rings to be coplanar.

As the *C*-terminal hexyloxy side chain in heptamer **7** can not form a hydrogen bond to an amide *N-H* donor, the number of pairwise coplanarized phenyl rings is identical in oligomers **6** and **7** (3 pairs). Nonetheless, heptamer **7** forms a macroscopically stronger gel (s. above). This is a good indication that the stronger aggregation tendency is directly related to the number of hexyl chains present.

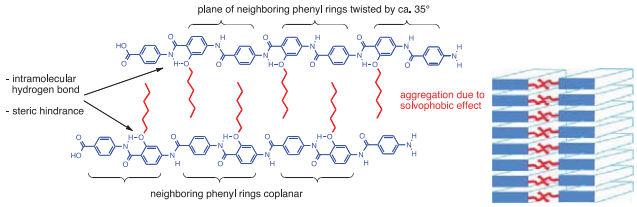


Figure 4. *Left*: Proposed aggregation model shown for oligomer **6**. *Right*: Side-on view of the proposed stacking of the dimers.

Figure 4 shows a model for the aggregation of oligomer **6** in DMSO. We believe that both oligomers aggregate via the hexyl side chains due to poor solvent interaction (solvophobic effect) in the self-associating solvent DMSO.[32] Micellation of alkyl group bearing amphiphiles in DMSO has been reported previously.[33,34,35]
In **6** the edge opposite the hexyloxy side chains consists of carbonyl and *N-H* hydrogen bond acceptors and donors and can therefore interact strongly with the solvent DMSO. **7** forms aggregates via the same mechanism. The higher number of hexyloxy side chains in **7** compared to **6** leads to a stronger solvophobic effect in DMSO and hence a macroscopically stronger gel.
In conclusion, we could show that the number of hexyloxy side chains attached to two hepta(*p*-benzamide) heterosequences strongly (and counter intuitively) affects the solubility and aggregation behavior of these oligomers. The hexyloxy side chains form intermolecular hydrogen bonds to the nearby amide *N-H* donor thus coplanarizing neighboring phenyl rings. This has two effects: the hexyl substituted edge of the oligomers becomes sterically less accessible and additionally all amide *N-H* hydrogen bond donors on that particular edge of the oligomer are intramolecularly saturated. Further aggregation / non-covalent polymerization via this edge of the oligomer is therefore impossible. On the other hand, the pairwise coplanarization of neighboring phenyl rings leads to a more rigid and flattened oligomer structure rendering less directional π-interactions more important for the observed aggregation. We believe that two non-covalent aggregation mechanisms are in play: aggregation via the hexyl side chains and π-interactions of the planarized oligomers. Exploring non-natural oligoaramide heterosequences will lead to a more detailed understanding of aggregation processes in general and potentially the development of new functional polymeric materials.

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Supplementary Material

Electronic Supplementary Information (ESI) available: Sol-gel transition temperature measurements (dropping ball) of the gels **6** and **7**, Fmoc UV-absorption cleavage elugrams for the automated synthesis of **6** and **7**, MALDI ToF MS data for **6** and **7** and a full experimental section