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Toward Folding Control in Oligomers and Polymers

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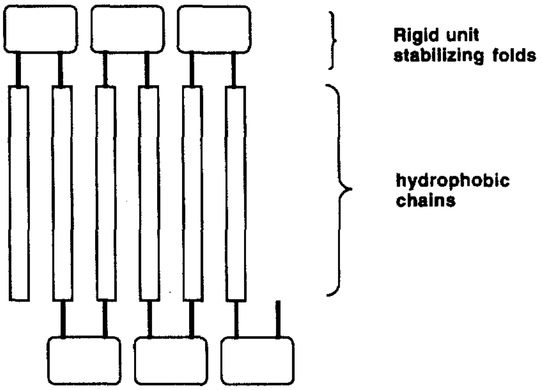
Abstract: A facile synthetic route affording polycondensable monomers containing alkyl chains connected to a rigid aromatic core allowing chain folding was developed. The stepwise condensation of the monomer was shown to afford dimer, tetramer and was further proved to be applicable to higher oligomers. Such oligomers composed of "tinker toy" building blocks may be of interest for inducing controlled conformations in nanostructured materials.

The conformational control of polymers through an appropriate design of folding regions is a topic of current interest. Many synthetic polymers exist under more or less regularly folded conformations in the solid state. These folds occur in polyethyleneoxyde[1], polyamides or polyethylene[2-4] and their stabilization arises from packing energies in crystals. Even if the folds can be distributed evenly along the chain, one cannot chose their precise location. Furthermore, in terms of programmed properties, the control of chain folding in solution is another aspects of interest. Since polymers with tailored conformation may be used to engineer materials with new physical properties, recently progress has been made for the design of polymers which fold into a predetermined pattern. For this purpose, different strategies have been addressed, using mesogeneous interactions between chains[5], steric hindrance to induce folds[6] or bioengineered production of β-sheets enriched peptides[7].



Scheme 1

The strategy we currently develop is based on an alternate sequence of rigid units and linear alkyl chains (scheme 1). The rigid units feature tailored distances and angles between connecting bonds and are expected to promote back folding of the main chain. The hydrocarbon chains should provide hydrophobic interactions in adequate solvents. To test our approach we synthesized model oligomers with a benzoic acid based connector as rigid unit

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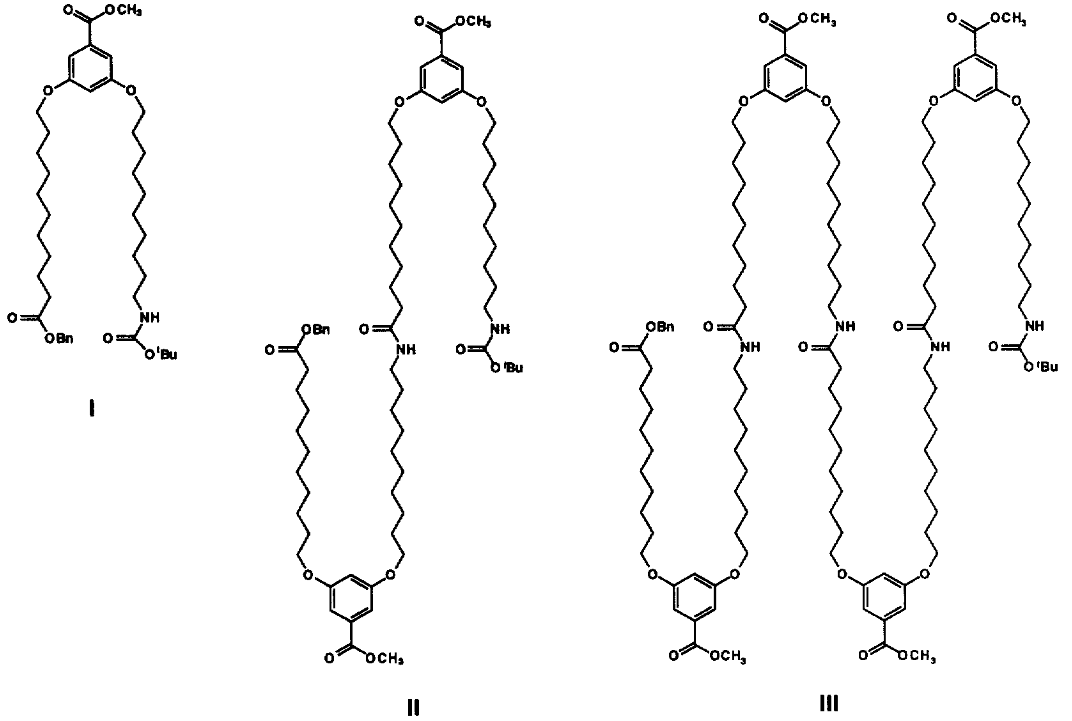
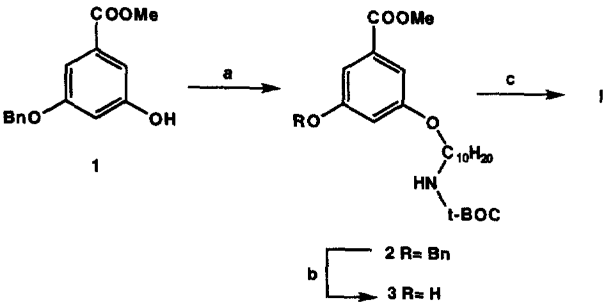
(scheme 2). The alkyl chains (10 and 11 carbon atoms) are bound to the connector via ether junction. The distance of ca 4.9 Å between both ether oxygen atoms, although slightly larger than the required distance for the close packing[8-10] , is imposed by the rigidity of the aromatic moiety, remains constant for all stable conformations . Recently, rather similar molecules have been synthesized by Wegner *et al*[11]. The reported molecules ,when spread at the air-water interface, have been shown to spontaneously adopt a zig-zag conformation.



Scheme 2

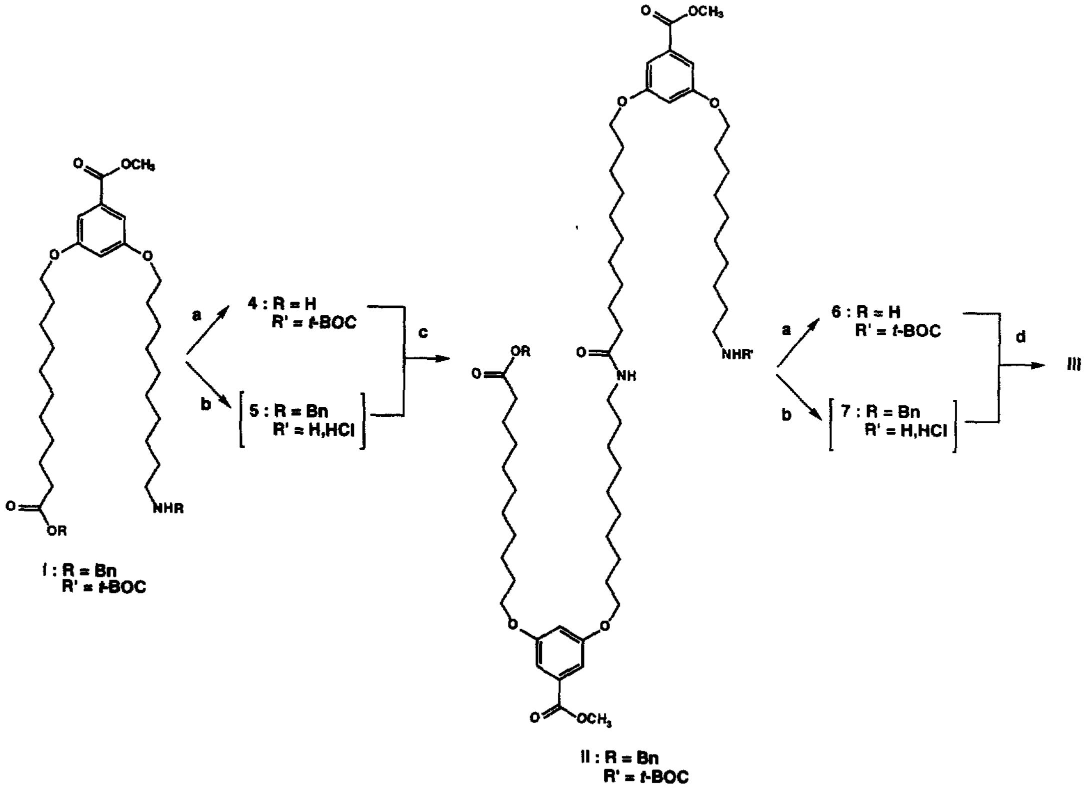
A recurrent issue associated with any strategy is the interplay between intramolecular and intermolecular interactions: the intramolecular interactions promote the target conformation while intermolecular interactions lead to aggregations. As far as energy is concerned, none of them can be ruled out. However, in order to determine if above a certain degree of oligomerization one type would prevail over the other one we have designed and synthesized dimers and tetramers.

The synthesis we developed relies on the use of orthogonal benzyl ester/^{t}BOC protective groups allowing selective and quantitative deprotection steps. For the synthesis of the monomer I (scheme 3) the starting material was 3-benzyloxy-5-hydroxybenzoate methyl ester **1** which was alkylated by the N-tertbutyloxycarbonyl)-10 aminodecyl methanesulfonate under phase transfer catalysis affording the compound **2**. The benzyl ether was deprotected quantitatively by hydrogenolysis on Pd/C at r.t. and the resulting phenol **3** was alkylated by bromoundecanoate benzyl ester (1.1 equiv., K_2CO_3, Bu_4NBr) to produce I in excellent yield (90 %). The synthesis of II and III (scheme 4) was achieved using suitably deprotected precursors. Deprotection of the benzyl ester under hydrogenation conditions (1 atm. of H_2 Pd/C) afforded the free acid **4** in a quantitative yield.



Scheme 3: a) 1.1 equiv. $MsOC_{10}H_{20}NHBOC$, 0.05 Bu_4NBr, K_2CO_3, DMF, 91 %; b) H_2, Pd/C, 97 %; c) 1.1 equiv. $BrC_{11}H_{22}Br$, K_2CO_3, DMF, 95 %.

In order to synthesize the dimer, the amino group of the monomer was deprotected under acidic conditions (4M HCl in dioxane). The resulting solution was evaporated to yield the crude hydrochloride salt 5 that was not purified, but subsequently condensed with the free acid (3 equiv. of EDCI, 2 equiv. of $NaHCO_3$, 0.1 equiv. of DMAP, DMF) to yield the dimer II (95 %). When no DMAP was used, formation of the N-acyl urea byproduct was observed to an extent of 5 %.



Scheme 4: a) 1 atm of H_2, Pd/C, 25 °C, 4 h, 90%; b) 4 M HCl in dioxane; c) 1 equiv. of $NaHCO_3$, 0.1 equiv. of DMAP, 3 equiv. of EDCI, DMF, 12 h, 25 °C, 95 %; d) 2 equiv. of NEt_3, 0.1 equiv. of DMAP, 2 equiv. of DPPA, 12 h, 25 °C, 57 %.

The product II was subjected to a similar deprotection-coupling sequence to produce the tetramer III: catalytic hydrogenation (1 atm of H_2, Pd/C) lead to the free acid dimer **6** (89%). Acid catalyzed deprotection of the monomer (4 M HCl in dioxane) afforded the amine-free dimer **7** and was followed by immediate coupling with the free acid (2 equiv. of DPPA, 2 equiv. NEt_3, 0.1 equiv. of DMAP, DMF) providing the tetramer III (57 %). The use of EDCI for the tetramer formation would only provide poor yields (25 %).

It is worth noting that the versatile synthetic strategy developed for the monomer based on sequential introduction of both chains, in principle should allow the introduction of chains of different chemical nature or different lengths leading thus to a large variety of molecules from the same pool of intermediates. Furthermore, the reported synthetic strategy may also be applied to other aromatic rings such as naphthalene, anthracene allowing the control of both the width of the rigid moiety and the angles between ether linkages.

In conclusion, gram scale synthesis of dimers, tetramers featuring alternate sequences of rigid units and flexible linear alkyl chains was achieved in high yields. The study of molecular areas as well as layer thickness is under current investigation.

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