Herein, we describe the preparation of oligopiperidines as a new family of water-soluble, rigid oligomers. The design of molecules with nanometer dimensions, defined shapes, and physical properties (solubility, conductivity, etc.) is a matter of considerable interest in macromolecular chemistry.[1,2] “Molecular rods” are rigid, linear macromolecules that constitute promising materials for applications in nanotechnology, such as spacers, wires, and construction elements.[3] The poor water solubility of many current examples of molecular rods[1,4] limit their applications, particularly in biology. Only a few bio-oligomers exhibit a rigid-rod structure[5] of which oligoprolines, which have been considered the most rigid,[3] have been used as spacers in biochemistry.[6] The structure of these compounds is, however, still a subject of discussion. Levins and Schafmeister reported the synthesis of a water-soluble molecular rod based on fused diketopiperazine oligomers starting from a complex building block.[7]

We hypothesized that an oligomeric backbone of piperidine rings would be a rigid rod, with the piperidine moieties adopting chair conformations in aqueous solution.[8] We have developed a synthesis of representative members of this class of molecules and investigated their conformations in polar solvents, including deuterated water. We are particularly interested in the possibility that they might serve as extended,

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.
water-soluble linkers or scaffolds for the oligovalent display of ligands. 

Scheme 1 outlines the strategy used to synthesize the oligopiperidines in solution. In this strategy, elongation is based on iterative reductive amination. We protected the commercially available 4,4-piperidinediol hydrochloride (1) with a benzyloxycarbonyl (Cbz) group to obtain 2. This compound was allowed to react with 1,4-dioxa-8-aza-spiro[4.5]decane (3) in the presence of triacetoxyborohydride to afford piperidinopiperidin-4-one 4 diprotected with a cyclic ketal and a Cbz group. [9] Compound 4 led to two further intermediates. Its catalytic hydrogenation yielded compound 5, and treatment of which with a concentrated aqueous HCl solution afforded compound 6. Reductive amination of 5 and 6 yielded the tetramer derivative 7.

We used solid-phase techniques to synthesize oligopiperidines up to ten units in length (Scheme 2). Solid-phase synthesis of oligopiperidine was performed on preloaded Fmoc-β-Ala Wang resin 8 (Fmoc = 9-fluorenylmethoxycarbonyl) on a 50-μmol scale. After deprotection with 20% piperidine in dimethylformamide (DMF), the resin was allowed to react with the N-Fmoc-protected isonipeptic acid in the presence of benzotriazolyl-N-oxo-tris(dimethylamino)phosphonium (BOP reagent) and the Hunig base to afford 9. We assembled building blocks to form the molecular rod by using a sequential procedure: deprotection, reductive amination with Fmoc-4-piperidone, and capping with acetic anhydride. The resin was then washed and dried prior to treatment with trifluoroacetic acid (TFA)/H2O (95:5) for 2 h. HPLC purification on a C18 column and lyophilization afforded pure oligopiperidines 10 and 11.

The structure of 7 was investigated by 1D and 2D NMR spectroscopy in CD3OD. This solvent was used because it produced a larger dispersion of chemical shifts than solvents such as CDCl3 or D2O. The spin systems of all four piperidine residues were unambiguously identified from COSY experiments. The sequence was assigned on the basis of NOESY experiments (mixing time = 400 ms) and was deduced from the strong NOE interaction connectivities between piperidine rings. Analysis of 1D spectra recorded between 273 and 323 K at 10 K increments revealed that the coupling values are only weakly affected by temperature changes; we infer that a single conformation dominates over this range of temperature. In the 1H NMR spectrum recorded at room temperature, in CD3OD, at 500 MHz (Figure 1), the axial and equatorial protons of the piperidine rings B, C, and D (H5, H6, H8, H9, H11, and H12) are discernible. The eight ring protons (H2 and H3) of the piperidine ring A appear as two triplets at δ = 2.66 and 1.71 ppm; this observation indicates that the axial and equatorial positions in this ring exchange rapidly on the NMR time scale through combined nitrogen inversion and chair–chair inversion. Rings B–D all display approximately the same series of signals with 1) a triplet of triplets for H4, H7, and H10, all in axial positions and 2) significant chemical-shift differences (∆δ<sub>ae</sub> < 1.4 ppm) between the axial and the equatorial sites of each methylene group with the axial proton at higher field. These characteristics provide strong evidence that all of these rings have the same chair conformation.[10] The chemical-shift difference between H12a and H12e in ring D is accentuated by the location of H12e in the shielding zone of the Cbz group.

NOESY experiments at 298 K with a mixing time of 400 ms yielded additional information about the three-dimensional structure of the tetrapiperidine 7. Several inter- and intraresidue

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**Scheme 1.** Solution-phase synthesis of tetrapiperidine 7. a) Na2CO3, CbzCl; b) 1,4-dioxa-8-aza-spiro[4.5]decane (3), NaBH(OAc)3, 1,2-dichloroethane; c) Pd/C, H2, EtOH; d) concentrated HCl, 0°C to room temperature, 20 min; e) NaBH(OAc)3, 1,2-dichloroethane.

**Scheme 2.** General procedure for the solid-phase synthesis of oligopiperidine. a) Fmoc-isonipeptic acid, BOP, NEt(iPr)2 in DMF; b) 20% piperidine in DMF, 20 min; c) Fmoc-4-piperidone, NaBH(OAc)3 in 1,2-dichloroethane, 2×60 min; d) acetic anhydride, NEt(iPr)2, CH2Cl2; e) TFA/H2O (95:5).
NOE interactions were extracted and are consistent with the presence of a rodlike conformation (Figure 2). Intraresidue NOE interactions confirmed the existence of a chair geometry in piperidine rings. Interresidue NOE interactions revealed: 1) a linear structure with each piperidine unit in an equatorial position and 2) the existence of several conformations of the N–C bond between each piperidine unit that are probably the three minimum-energy staggered conformations of this bond.[11] The same characteristic NOE interactions were found with a small model molecule, methylpiperidinopiperidine (see the Supporting Information). The $^1$H NMR spectra of 7 and methylpiperidinopiperidine (see the Supporting Information) in deuterated water exhibit approximately the same characteristic pattern of signals as that in CD$_3$OD, with significant chemical-shift differences between axial and equatorial protons from the same methylene group; these characteristics indicate the presence of a unique structure in methanol and water. IR analysis of the oligopiperidine 7 in CDCl$_3$ and the Bohlmann band at 2814 cm$^{-1}$ (see the Supporting Information) provide further evidence in favor of an extended structure in which the piperidine rings are in equatorial positions.[10a] Collectively, these data strongly suggest that 7 adopts a well-defined rodlike structure in solution.

The slow evaporation of a solution of 7 in deuterated methanol yielded crystals of the unprotected base suitable for X-ray structural determination.[12] The unit cell contains two tetrapiperidine 7 molecules. The conformations of these two molecules differ in the arrangement of their Cbz groups. Their ORTEP representations clearly reveal linear rodlike structures (Figure 3). The molecules each consist of four piperidine rings in chair conformations. All piperidine segments occupy the equatorial position on each connected ring and are separated by approximately 4.3 Å.

Molecular dynamics (MD) simulations on the oligomer 7 were performed at 300, 350, and 400 K to characterize the conformational ensemble of the oligopiperidine as a function of increasing temperature. For each temperature, the system was equilibrated for 10 ps using a 2-fs time step, during which time the temperature was ramped from 0 K to the final system temperature (300, 350, or 400 K). Production simulations were run for 1 ns using a 2-fs time step. Snapshots of the system were written out every ten steps to insure that fine details of the system were observed. To determine how linear the geometry of the molecule remained during each simulation, two metrics were used. The first is the length of the major axis, defined as the distance between two carbon atoms at the opposite ends of the molecule (Table 1), which was measured for each snapshot in each MD trajectory. The second is the major axis angle, formed by the previously defined major-axis carbon atoms and a central nitrogen atom in the molecule (see the Supporting Information). These two values characterize the overall geometry of the molecule during the simulations, thus describing its tolerance for stretching, compressing, and bending. The distributions of the oligopiperidine lengths remain fairly invariant across all three temperatures simulated (Table 1), thus indicating that the linear geometry of this molecule, and its corresponding ability to resist stretching and compressing, is stable across a large range of temperatures.

Furthermore, the values of the major-axis angles indicate that the molecule remains very extended through simulations.

Table 1: Statistics of the major-axis length (measured from the carbon atoms labeled A and B) distributions of 7 observed in three MD simulations.

<table>
<thead>
<tr>
<th>Temperature [K]</th>
<th>Mean length [Å]</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>15.0</td>
<td>0.4</td>
</tr>
<tr>
<td>350</td>
<td>14.9</td>
<td>0.7</td>
</tr>
<tr>
<td>400</td>
<td>14.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>
at all three temperatures. At higher temperature simulations, the distribution of the major axis angle values has an increased mean and a decreased variance. This implies that as the temperature increases, the oligopiperidine structure tends to bend less and remain slightly more fully extended. Altogether, these data demonstrate that these oligopiperidine molecules adopt a stable linear conformation. Visual inspection of the simulation trajectories confirms that the molecule retains an extended structure throughout the entire simulation.

This report describes a simple, inexpensive, and widely accessible method for the preparation of rigid, rodlike oligopiperidines with a defined length of up to ten units (4.3 nm length). This oligomeric system does not require oligopiperidines with a defined length of up to ten units. Although rotations about the C–N bonds occur, these rotations result in only small deviations around the linear geometry of the molecule.

Key points:
- A simple, inexpensive, and widely accessible method for the preparation of rigid, rodlike oligopiperidines with a defined length of up to ten units (4.3 nm length).
- This oligomeric system does not require oligopiperidines with a defined length of up to ten units.
- At higher temperature simulations, the distribution of the major axis angle values has an increased mean and a decreased variance. This implies that as the temperature increases, the oligopiperidine structure tends to bend less and remain slightly more fully extended.
- These data demonstrate that these oligopiperidine molecules adopt a stable linear conformation.

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