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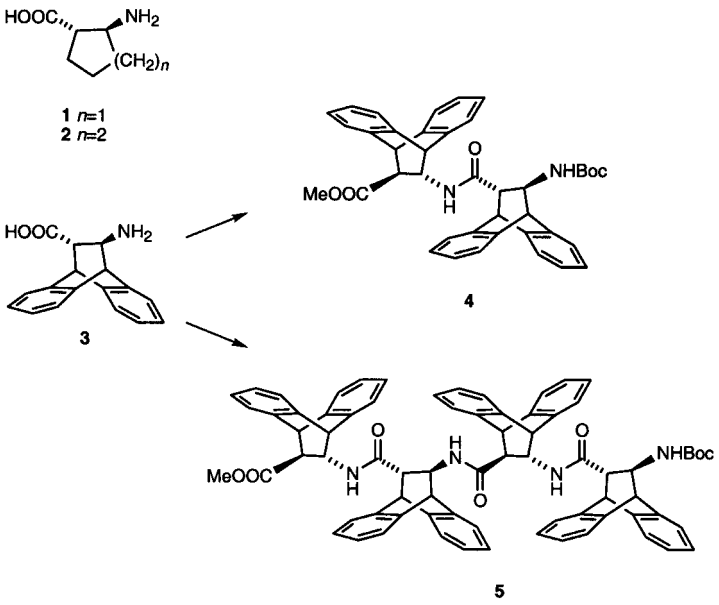
[18] The values for the activities are the averages of the results from different experiments. The deviation of each set of results from the average lies in a range between 0 and 10% of the average value. To test the robustness of our equipment, our results were also compared to the results from similar experiments performed at Shell Research Laboratories Amsterdam; the results were in good agreement.

important goal.[1] β-peptides are resistant to cleavage by most proteases and are therefore of considerable interest as building blocks in drug design.[2] The groups of Seebach, Gellman, and DeGrado have demonstrated that oligomers derived from β-amino acids such as **1** and **2** can adopt predictable conformations that are a direct consequence of the nature of the monomeric building blocks **1** and **2** (Scheme 1).[3] We reasoned that incorporation of two aromatic rings into **2** would constrain the amino acid backbone of oligomeric derivatives, creating foldamers with novel and well-defined hydrogen-bonding patterns.



Scheme 1.

Design and Synthesis of Foldamers Based on an Anthracene Diels–Alder Adduct**

Jeffrey D. Winkler,* Evgueni L. Piatnitski, John Mehlmann, Jiri Kasparec, and Paul H. Axelsen*

Dedicated to Professor Ronald Breslow on the occasion of his 70th birthday

The design and synthesis of peptides and peptide analogues with predictable and reproducible folding patterns is an important goal.[1] β-peptides are resistant to cleavage by most proteases and are therefore of considerable interest as building blocks in drug design.[2] The groups of Seebach, Gellman, and DeGrado have demonstrated that oligomers derived from β-amino acids such as **1** and **2** can adopt predictable conformations that are a direct consequence of the nature of the monomeric building blocks **1** and **2** (Scheme 1).[3] We reasoned that incorporation of two aromatic rings into **2** would constrain the amino acid backbone of oligomeric derivatives, creating foldamers with novel and well-defined hydrogen-bonding patterns.

We describe herein the preparation of the protected β-amino acid **9** from **6** (Scheme 2), the Diels–Alder adduct of anthracene and dimenthyl fumarate, and the synthesis and study of both the dipeptide **4** and the tetrapeptide **5**. The presence of the dihydroanthracene moieties leads to a high level of structural definition in both **4** and **5**. The structure of **4** exhibits a unique level of organization. The NMR-derived solution structure of **5** reveals a twelve-membered ring helical conformation with a molecular volume of about 1200 Å.

The synthesis of the tetracyclic β-amino acid monomer is outlined in Scheme 2. Reaction of anthracene with dimenthyl fumarate under Lewis acid catalysis leads to the formation of **6** in 88% yield and 99% *ee*.[4] Conversion of **6** to the corresponding dimethyl ester **7**[5] in acidic methanol[6] followed by saponification of **7** under mild basic conditions produces a statistical mixture of the desired monoacid **8**, along with the starting diester **7** and the corresponding diacid (not shown) which can be efficiently recycled. Curtius reaction of the acyl azide derived from **8** gave the *N*-Boc amino ester **9** in 34% yield over three steps. Reaction of **9** with NaOH gave the corresponding acid **10**, whereas exposure of **9** to trifluoroacetic acid led to the formation of the deprotected amino ester **11**. Condensation of **12**, the acid chloride derived from **10**, with **11** gave dipeptide **4** in 79% overall yield from **9**.

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Supporting information for this article (synthetic procedures and spectroscopic data for dipeptide **4**, tetrapeptide **5**, and all synthetic intermediates) is available on the WWW under http://www.angewandte.com or from the author.

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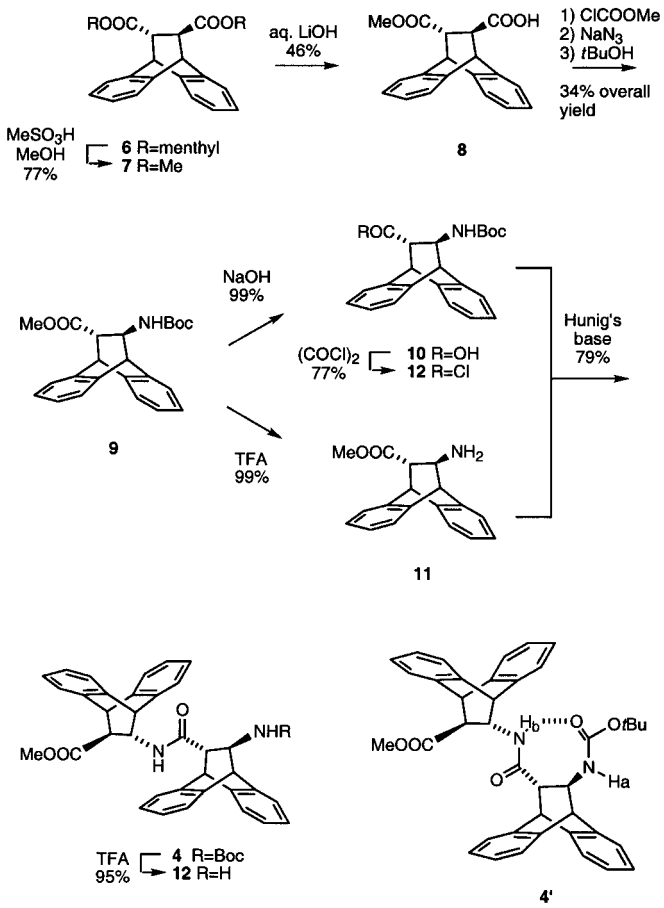

Scheme 2.

The consequences of the introduction of the aromatic rings are exemplified by the unique structure of the resulting dipeptide **4**. Energy minimization of **4** leads to the eight-membered hydrogen-bonded ring structure **4′**, which can also be clearly identified in solution by ^{1}H NMR spectroscopy. The chemical shift of one of the N–H protons (H_a; $\delta = 4.4$) in the ^{1}H NMR spectrum of dipeptide **4** is similar to the N–H resonance in the monomer **9** ($\delta = 4.5$). However, the other N–H proton (H_b; $\delta = 7.5$) in **4** is shifted downfield by 2 ppm relative to the chemical shift for H_b ($\delta = 5.5$) that is observed for the amide proton in the free amine **12**. Deuterium-exchange experiments with **4** revealed that the upfield carbamate proton (H_a) undergoes rapid exchange ($t_{1/2} =$ 20 min) in deuterated methanol, while the downfield amide N–H resonance (H_b) disappears slowly ($t_{1/2} > 5$ h; Figure 1). In contrast, rapid exchange of H_b is observed on exposure of free amine **12** to the same experimental conditions. These data support a pronounced difference in conformation between **4** and **12** which is consistent with the eight-membered ring hydrogen bonding shown in **4′**. This structural feature has been described by Yang and co-workers in α-aminoxy acids but is without precedent in β-amino acids.[7] Well-defined secondary structure was observed in the systems derived from **1** and **2** only with tetra-β-peptide and larger systems.[3a] A unique feature of this work and an important consequence of the presence of the dihydroanthracene moieties is that the secondary structure of dipeptide **4** is well-defined.

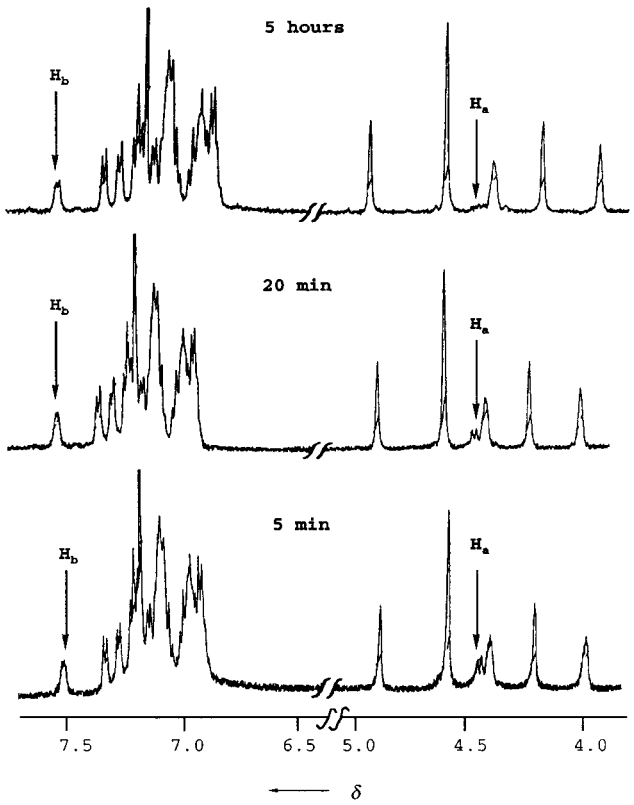

Figure 1. Deuterium (CD_3OD) exchange experiment with dipeptide **4** in $CDCl_3$.

We next examined the structure of the tetrameric product **5**, which was prepared by the same methodology used for the preparation of **4**. Reaction of the acid chloride derived from **4** with Hunig's base and the free amine derived from **4** gave the tetrameric product **5** in 66% overall yield from **4**. Careful examination of the ^{1}H NMR spectrum of **5** indicated the significant downfield shift of two of the four N–H resonance siganls. Removal of the Boc group from tetrapeptide **5** led to a single downfield shift in the ^{1}H NMR spectrum of the derived amine, indicating that the Boc moiety is involved in hydrogen bonding in **5**. While peak overlap in the ^{1}H NMR spectrum of **5** did not allow deuterium-exchange experiments, the same information could be obtained from FT-IR spectra. As indicated in Figure 2, both hydrogen-bonded and non-hydrogen bonded amide N–H bonds can be detected in the dipeptide **4** and the tetrapeptide **5**, but not in the monomeric protected aminoester **9**.

Complete assignment of the ^{1}H NMR spectrum of the peptide backbone of **5** could be achieved by a combination of double quantum-filtered COSY[8] and rotating-frame nuclear Overhauser effect spectroscopy (ROESY)[9] and the identification of a series of long-range NOEs (see Supporting Information). The structure of **5** was then examined in energy-minimized structures sampled from an NOE-restrained molecular dynamics simulation performed at 300 K using CHARMM.[10] These structures consistently exhibited a full 12-helical turn of the type illustrated in Figure 3. Both the eight- and twelve-membered hydrogen-bonded rings of **5** are shown explicitly in Figure 3a, and the peptide backbone of **5** is highlighted in Figure 3b.

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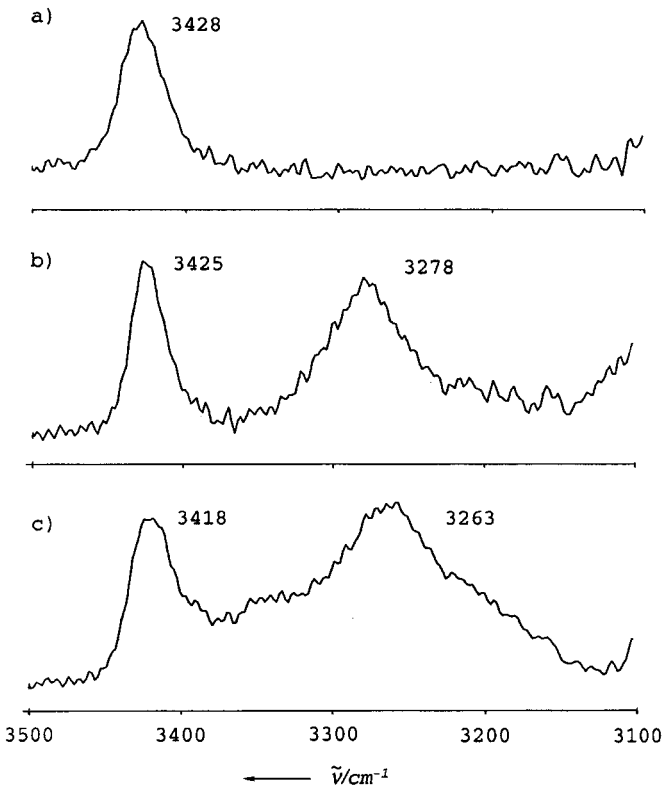

Figure 2. Amide N–H regions of IR spectra for *N*-Boc amino ester **9** (monomer), dipeptide **4**, and tetrapeptide **5**.

These results establish that high levels of conformational definition are observed in foldamers **4** and **5** derived from the anthracene Diels–Alder adduct **3**. The eight-membered hydrogen-bonded ring observed with **4** and the twelve-membered hydrogen-bonded ring and resulting helical structure in **5** illustrate the structural consequences of the incorporation of the novel β-amino acid **3**. Further studies on the effects of aryl substitution on these novel structures as well as the development of water-soluble systems are currently underway and our results will be reported in due course.

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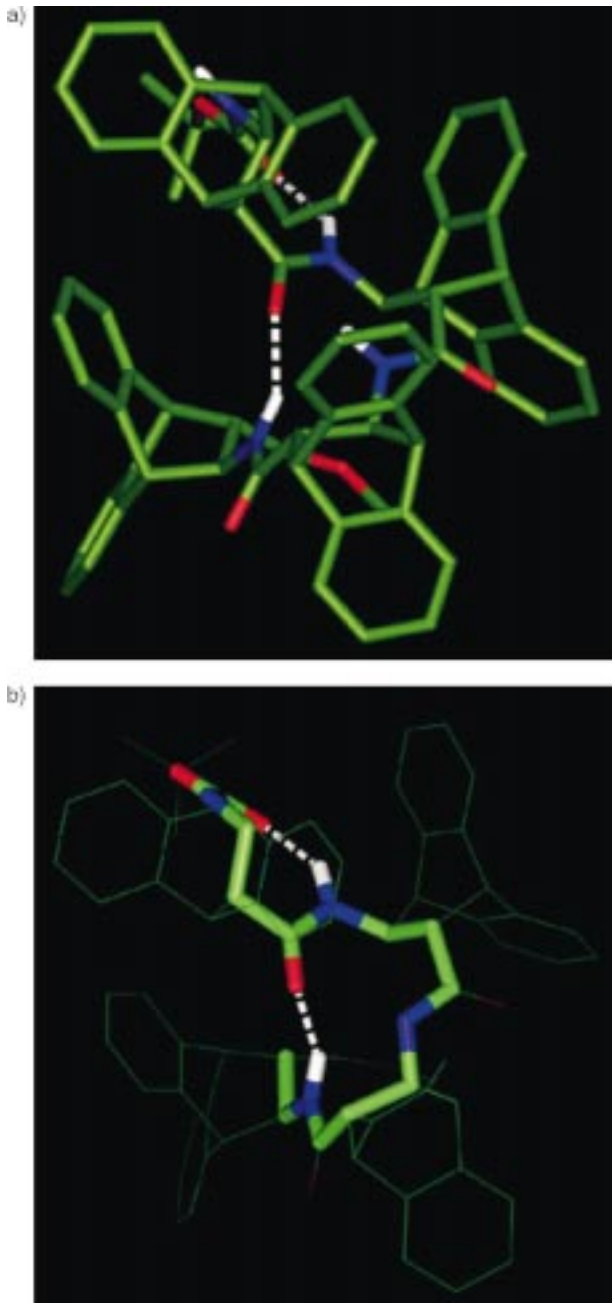

Figure 3. Solution structure of tetrapeptide **5**: a) full structure; b) peptide backbone.

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