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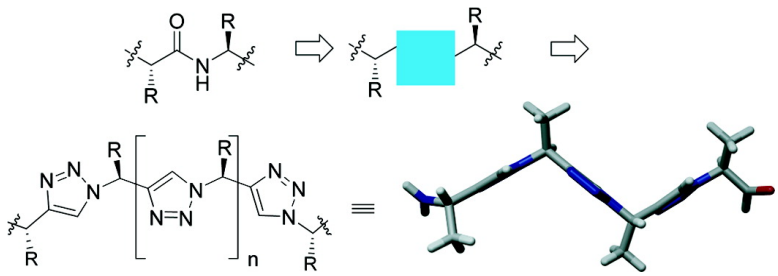

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Nonpeptidic Foldamers from Amino Acids: Synthesis and Characterization of 1,3-Substituted Triazole Oligomers

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The intrinsic instability of peptides limits their potential as reagents in molecular biology and drug discovery. Nonpeptidic scaffolds that adopt well-defined conformations and display protein-like side chains would be invaluable alternatives to peptides.[1,2] Biomimetic oligomers,[2,3] such as β-peptides,[4] have been intensively studied because they possess a high propensity to adopt defined secondary structures and resist degradation by proteolytic enzymes. These oligomers also retain perhaps the most important asset offered by peptides, namely, access to a diverse set of side chain functional groups needed for molecular recognition and catalysis. We conjectured that it may be possible to increase the number of defined backbone conformations possible from α- and β-amino acids *and* introduce "drug-like" character into these oligomers by swapping the amide bond with aromatic rings and by projecting the attached main chains at different angles from a given ring (Figure 1).[5,6] Several nonpeptidic oligomers composed of carbamates, sulfonamides, ureas, hydrazino acids, aminoxy acids, anthranilamides, oligophenylacetylenes, and pyrrolinones, among others, have been described.[2,3] Here we report a new class of distinctly folded nonpeptidic oligomers in which the amide bond is replaced by aromatic rings yet the chiral main chain and amino acid side chains are maintained (Figure 1). These molecules potentially afford specific conformations featuring a diverse set of side chains without the limitations imposed by the secondary amide bond.[5]

We were inspired in this endeavor by previous efforts,[6,7] in which the amide bond is substituted with heteroaromatic rings to generate peptidomimetics, and sought to extend these methodologies to the synthesis of nonpeptidic oligomers directly from amino acids. Although several ring systems are synthetically accessible, we began by swapping the amide bonds with triazole rings for two reasons: (1) dipeptides bearing both 1,2,3-triazole[8] and 1,2,4-triazole[9] rings (Figure 1a) have been described in the literature, and (2) we were intrigued by the large dipole moment (~5 D)[10] in these rings and wondered whether defined conformations could be obtained through forces, such as dipole−dipole interactions and torsional effects.

This report presents the design, synthesis, and initial structural studies on the 1,3-substituted oligomers derived from the 1,2,3-triazoles (Figure 1b).[11] Solution NMR studies on trimers and tetramers suggest that these oligomers adopt zigzag conformations reminiscent of peptide β-strands. Dipole−dipole interactions between neighboring triazole rings appear to play a critical role in stabilizing the observed conformations in polar solvents, such as DMSO and acetone.

The 1,3-substituted oligomers were prepared from amino acid methyl esters through an iterative reaction sequence consisting of conversion of the amine to the corresponding azide,[12] copper(I)-catalyzed azide−alkyne [3+2] cycloaddition[13] with the suitable amino alkyne **1** followed by removal of the protecting group (Figure 1c). To examine the solution conformations of short 1,3-substituted triazole oligomers, we prepared and studied two trimers **3a**,**b** and two tetramers **4a**,**b**.

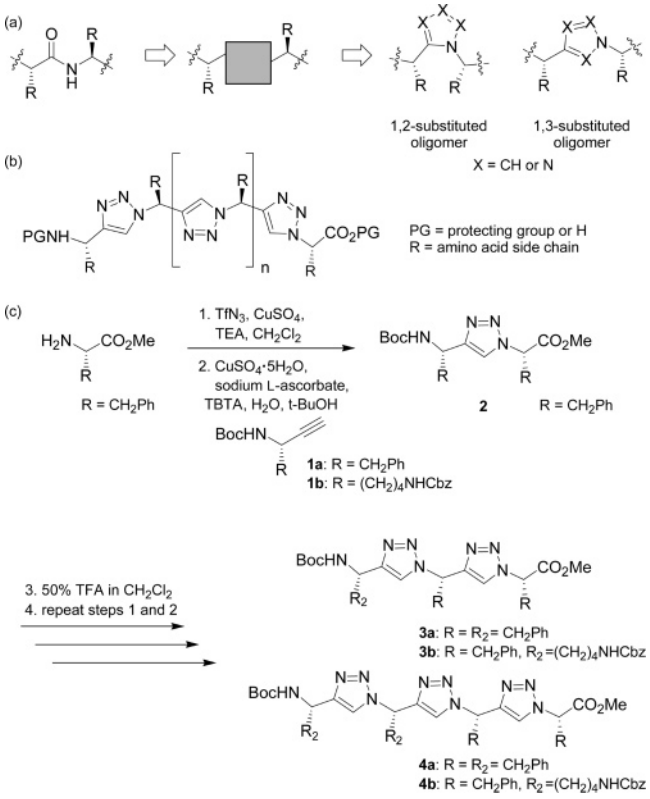

Figure 1. (a) Development of nonpeptidic foldamers by replacement of the amide bond with triazole rings. (b) A 1,3-substituted *triazolamer*. (c) Synthesis of the triazole oligomers from amino acids.

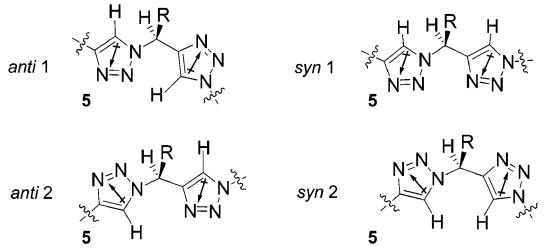

Figure 2. Conformations adopted by the triazole dimer (**5**). The *syn* and *anti* conformations are defined by the dipole−dipole interactions between adjacent triazole rings. The *anti* conformations are calculated to be roughly 4 kcal/mol lower in energy than the *syn* conformations.[14]

Molecular mechanics and ab initio calculations were used to predict the conformations of these oligomers,[14] and the predictions were confirmed by 2D NMR analysis. We began our studies by calculating the conformational preferences of the triazole dimer (**5**), which can adopt two *anti* and two *syn* conformations (Figure 2). The *syn* and *anti* conformations are defined based on the relative direction of the dipoles in adjacent rings. Both molecular mechanics and ab initio studies predict that the *anti* conformations are ~4

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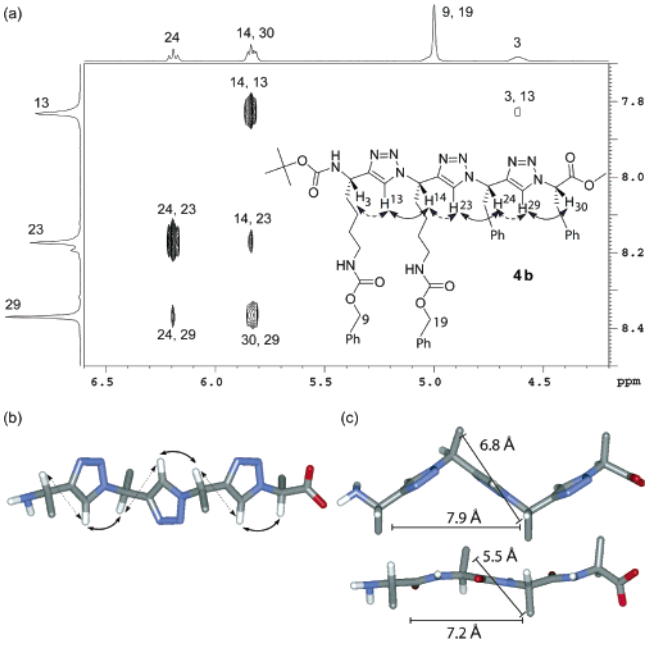

Figure 3. (a) A cross-section of the ROESY spectra of **4b** (in DMSO-d_6) displaying cross-peaks between the aromatic and the C_α protons. (b) Predominant triazolamer conformation revealed by ROESY experiments. Solid and dashed lines indicate observed strong and weak NOE cross-peaks, respectively. (c) Comparison of triazolamer **4b** in a zigzag conformation (top) to a peptide β-strand (tetraalanine) (bottom). The triazolamer mimics a peptide β-strand with similar axial distances between the i and $i + 2$ side chains. For clarity, side chains are depicted as methyl groups.

kcal/mol more stable than the *syn* conformations. We anticipated that the restriction imposed by the *anti* conformation on the possible number of rotamers may lead to a specific set of defined backbone structures.

Examination of the 2D NMR spectra reveals that the backbones of *triazolamers* **3** and **4** predominantly adopt zigzag structures arising from the *anti* conformation (Figure 3). NMR studies were performed in acetone-d_6 or DMSO-d_6 solutions;[15] a combination of TOCSY, DFQ-COSY, and ROESY experiments was used to assign ^{1}H NMR resonances. The *anti* conformation can also lead to a *turn* backbone structure, which was ruled out through NMR studies (see Supporting Information for details). It remains to be determined what specific backbone structure will predominate in longer oligomers or in compounds with different side chain groups.

The zigzag triazolamer structure is reminiscent of peptide β-strand conformation (Figure 3c) and oligopyrrolinones described by Smith and Hirschmann.[6] The axial distance between i and $i +$ 2 residues in β-strands is 7.2 Å; this distance is roughly 7.9 Å in the zigzag triazolamer. The C_β to C_β distances in adjacent residues are 5.5 Å in β-strands and a little longer (6.8 Å) in the triazolamer. Thus, one surface of the zigzag triazolamer may effectively mimic a β-strand and prove useful for targeting protein pockets and surfaces involved in β-strand recognition.[16] Although the triazolamer backbone does not offer a β-strand's hydrogen bond functionality, the N-2 and N-3 electron pairs may serve as hydrogen bond acceptors.[8a]

In summary, we have reported an approach for the synthesis of nonpeptidic scaffolds capable of displaying protein-like side chains by swapping amide bonds with 1,2,3-triazole rings. The overall conformation of these triazole oligomers appears to be dictated by dipole−dipole interactions between adjacent rings. Solution NMR studies suggest that a zigzag conformation, which closely mimics the β-strand structure, predominates in two different tetramers.

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Supporting Information Available: Detailed conformational analyses, synthetic procedures, and characterization of monomers and oligomers (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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