Control of Helix Formation in Vinylogous γ-Peptides by (E)- and (Z)-Double Bonds: A Way to Ion Channels and Monomolecular Nanotubes

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A complete overview on the alternative and competitive helices in vinylogous γ-peptides is given, which was obtained on the basis of a systematic conformational analysis at various levels of ab initio MO theory (HF/6-31G*, DFT/B3LYP/6-31G*, PCM/HF/6-31G*). Contrary to the parent γ-peptides, there is a strict control of helix formation by the configuration of the double bond between the C(α) and C(β) atoms of the monomer constituents. (E)-Double bonds favor helices with larger pseudocycles beginning with 14- up to 27-membered hydrogen-bonded rings, whereas the (Z)-configuration of the double bonds supports a distinct preference of helices with smaller seven- and nine-membered pseudocycles showing interactions between nearest-neighbor peptide bonds. The rather stable helices of the (E)-vinylogous peptides with 22-, 24-, and 27-membered hydrogen-bonded pseudocycles have inner diameters large enough to let molecules or ions pass. Thus, they could be interesting model compounds for the design of membrane channels and monomolecular nanotubes. Since (E)- and (Z)-vinylogous γ-amino acids and their oligomers are synthetically accessible, our study may stimulate structure research in this novel field of foldamers.

Introduction

The design of oligomers that fold into definite secondary structures is a very actual and interesting field for synthetic chemists.1 The monomers of these oligomers come from a wide variety of different structure classes. A particularly important group among them results from the homologation of the native α-amino acids to β-, γ-, and δ-amino acids, respectively. Obviously, studies on the oligomers of these amino acids aim at the mimicking of native peptide structures. They provide deeper insight into basic principles of folding and structure formation and contribute to a better understanding of the structure

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and function of biopolymers. Considering also more abiotic oligomers, we enter a realm of novel molecular scaffolds with functional properties, which could be also be of importance for material sciences and even information storage.

For oligomers with secondary structures formed by noncovalent interactions between nonadjacent monomers in solution the term foldamers was introduced.1a,b Foldamer research was essentially stimulated by the investigation of peptidic foldamers, in particular oligomers of β-amino acids (β-peptides).2 Numerous ordered secondary structures, as for instance various helices, strands, and turns, were found. Thus, the most prominent secondary structure types of β-peptides are helices with 12- and 14-membered hydrogen-bonded pseudocycles (H₁₂, H₁₄), respectively.2a,b,c,d Definite secondary structures can also be expected in oligomers of γ- and δ-amino acids. Thus, studies on γ-linked d-glutamates provided hints on helical structures with 17- or 19-membered rings,2a,b whereas unsubstituted γ-peptides adopt a poly-Cα-conformation.2b,c Substituents at the γ-positions of the γ-peptide constituents enforce a helix with 14-membered pseudocycles.2a,b,c,d Secondary structure formation in δ-peptides has a special note, since a δ-amino acid constituent corresponds approximately to a dipeptide unit in the native α-peptides. Thus, it can be supposed that δ-peptides are able to mimic the secondary structure elements of the native peptides and proteins better than the other peptic foldamers.4

Numerous theoretical studies employing ab initio MO theory and molecular dynamics techniques confirmed the experimental data and predicted further folding alternatives in sequences of homologous amino acids.5 It was an interesting result that all important folding patterns in oligomers of β-peptides can be derived from the conformational properties of the blocked monomer units (monomer approach), even in the case of the helices H₁₄ and H₁₂ with hydrogen-bonded turns for which the structural requirements are not yet given in the monomers.5a,b,c,d Contrary to this, the experimentally indicated H₁₄ helix of the γ-peptides with the larger hydrogen-bonded cycles can only be obtained by conformational analyses on larger oligomers (oligomer approach).5b Studies on blocked monomers provide only secondary structures with interactions between neighboring peptide bonds, which are competitive to the aforementioned structures with the non-neighboring peptide bond interactions. Obviously, a critical sequence length is required for the formation of the latter ones.

It would be an advantage to find possibilities for a selective influencing of the secondary structure formation in peptides. This could be realized for instance by introduction of special side chains at the various backbone positions that can influence the secondary structure formation simply by their size or by specific interactions such as hydrogen bonds, salt bridges or π-stacking. In fact, systematic theoretical studies on the substituent influence on β-peptide structures5b provide useful hints for the support of special secondary structure types. Introduction of steric restrictions into the backbone could

![Figure 1](image_url)

**FIGURE 1.** HF/6-31G* (▲) and B3LYP/6-31G* (○) potential curves for (E)-(- - -) and (Z)-(- - -) 2-butenoic acid N-methylamide.
be another possibility to control secondary structure formation. Experimental studies on β-peptides show impressively that the H12 helix is favored when the C(α) and C(β) backbone atoms are part of a cyclopentane ring,6a whereas the H14 helix is obtained when the C(α) and C(β) atoms are part of a cyclohexane ring.6b In the same way, sugar amino acids of γ- and δ-amino acid type support selectively special secondary structure elements.4a

Now, we want to turn the attention to the simple case of the introduction of (E)- and (Z)-double bonds into the peptide backbone. Whereas a double bond between the C(α) and C(β) atoms of a β-amino acid constituent is less attractive for helix formation due to the resulting conjugated system, γ-amino acids having a double bond between the C(α) and C(β) atoms (vinyllogous γ-amino acids) might represent a good compromise between backbone rigidification and a sufficient conformational flexibility for secondary structure formation.5i Several methods were suggested for the synthesis of both (E)- and (Z)-vinyllogous γ-amino acids and their oligomers.7 Despite their accessibility, structure information of vinyllogous γ-peptides is not available until now. Therefore, we want to provide a complete overview on the possibilities of helix formation in vinyllogous γ-peptides and its influencing by (E)- and (Z)-double bonds to stimulate synthetic work and structure research. Besides, we compare the monomer and the oligomer approach in order to see which secondary structures are already preformed in the blocked monomeric units and which are only available at a critical sequence length by taking profit from cooperative effects.

Methodology

The monomer approach is based on a complete scan of the conformational space of the blocked unsubstituted (U) and γ-methyl-substituted (G) vinyllogous γ-amino acid monomers 1 and 2 (n = 1) with (E)- and (Z)-double bonds, respectively. The considerable dimension of the conformation problem with the three backbone torsion angles ψ, θ, and ψ prevents the calculation of a grid with relatively small torsion angle intervals at higher levels of ab initio MO theory. Thus, we applied the following strategy. The torsion angle ψ was set at 0° and 180°, respectively. This is confirmed by conformational analyses on (E)- and (Z)-2-butenic acid N-methylamide at the HF/6-31G* and DFT/B3LYP/6-31G* levels of ab initio MO theory (Figure 1, cf. also ref 8). All combinations of the

\[
\begin{align*}
\text{C}_{11} & (1 \rightarrow 8) \\
\text{C}_{22} & (1 \rightarrow 4) \\
\text{C}_{13} & (1 \rightarrow 3) \\
\text{C}_{12} & (1 \rightarrow 2) \\
\text{C}_{11} & (1 \rightarrow 1) \\
\text{C}_{19} & (1 \rightarrow 3) \\
\text{C}_{14} & (1 \rightarrow 4) \\
\text{C}_{15} & (1 \rightarrow 5) \\
\text{C}_{16} & (1 \rightarrow 6) \\
\text{C}_{21} & (1 \rightarrow 7) \\
\end{align*}
\]

**Figure 2.** Possible hydrogen bonding patterns for helices of (E)- (ζ = 180°) and (Z)- (ζ = 0°) vinyllogous γ-peptides with the hydrogen bonds formed in forward and backward direction along the sequence.

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values of $-120^\circ$, $-60^\circ$, $0^\circ$, $60^\circ$, $120^\circ$ and $180^\circ$ were assigned to the torsion angles $\varphi$ and $\theta$. The resulting structures were the starting points for complete geometry optimizations at the HF/6-31G* level of ab initio MO theory. The optimized structures obtained were characterized as minimum conformations by the determination of the vibration frequencies. Because of symmetry, there are always pairs of energetically equivalent conformers in the U series, where the torsion angles differ only by sign. This does not longer hold for the G derivatives, where only approximate backbone mirror image conformers can be expected. In all cases of G, where the pairs of the approximate backbone mirror images did not result from the grid search, the signs of the torsion angles of an obtained conformer were reversed and the corresponding conformation reoptimized to test for the possibility of the alternative backbone handedness. Such conformer alternatives were denoted by the same symbol, but adding a prime. For the minimum conformations the influence of correlation energy was estimated by optimization at the B3LYP/6-31G* level of density functional theory (DFT). The solvent influence was described on the basis of a polarizable continuum model (PCM) by geometry optimization of the gas phase conformers at the PCM/HF/6-31G* level of ab initio MO theory for the solvent water ($\varepsilon = 78.4$).

The conformational analysis within the oligomer approach was performed at the level of the blocked hexamers 1 and 2 ($n = 6$) in two ways. At first, all periodic hexamers resulting from the conformers of the monomer approach were generated and optimized at the HF/6-31G* level. Since there was a considerable lack of helical structures with non-neighboring peptide bond interactions in the case of the (E)- and (Z)-vinylogous peptides, we complemented this procedure by another strategy, which was already applied in our searches for the hydrogen-bonded helices of $\gamma$- and $\delta$-peptides and of mixed helices with an alternating hydrogen bonding pattern.5i,k,l Periodic structures of hexamers were sys-
The values of B3LYP/6-31G* level were complemented to estimate the properties of Figure 2, geometry optimizations at the minimum conformations, which still fulfill the helix entropies of the various helices were calculated. For the enthalpies, the thermal energy corrections, and the constants. On the basis of the vibration frequencies, the structures by the determination of the matrix of the force constants. The optimized structures were characterized as minimum conformations, which resulted for the (E)-hexamers derived from the monomers. The double bond torsion angles were set at −150°, 180°, and 165° for the (E)-hexamers and −15°, 0°, and 15° for the (Z)-hexamers, respectively, while values of −165°, 180°, and 165° were allowed for the ω torsion angles. This procedure leads to 9,072 conformations. All structures out of these conformations, which fit into the possible periodic hydrogen bonding patterns in Figure 2 according to general geometry criteria for hydrogen bonds, were starting points for geometry optimizations at the HF/6-31G* level of ab initio MO theory. The criteria for the acceptance of a conformation as a potential candidate for a helix with the periodic hydrogen-bonded pseudocycles of Figure 2 were the H⋯O distances between the hydrogen atoms of the peptidic NH bonds and the oxygen atoms of the corresponding peptidic CO bonds, which should be in the range of 1.8−2.4 Å. Besides, the values of the angles ∠NH⋯O and ∠H⋯OC should be between 100° and 180°. In this way, 147 and 61 starting conformations for hydrogen-bonded helices resulted for the (E)- and (Z)-hexamers, respectively, in addition to the hexamers derived from the monomers. The optimized structures were characterized as minimum structures by the determination of the matrix of the force constants. On the basis of the vibration frequencies, the enthalpies, the thermal energy corrections, and the entropies of the various helices were calculated. For the minimum conformations, which still fulfill the helix properties of Figure 2, geometry optimizations at the B3LYP/6-31G* level were complemented to estimate the

tematically generated assigning all values from −150° to 180° in steps of 30° to the backbone torsion angles ϕ, θ, and ψ. The double bond torsion angles ζ were set at −165°, 180°, and 165° for the (E)-hexamers and −15°, 0°, and 15° for the (Z)-hexamers, respectively, while values of −165°, 180°, and 165° were allowed for the ω torsion angles. This procedure leads to 9,072 conformations. All structures out of these conformations, which fit into the possible periodic hydrogen bonding patterns in Figure 2 according to general geometry criteria for hydrogen bonds, were starting points for geometry optimizations at the HF/6-31G* level of ab initio MO theory. The criteria for the acceptance of a conformation as a potential candidate for a helix with the periodic hydrogen-bonded pseudocycles of Figure 2 were the H⋯O distances between the hydrogen atoms of the peptidic NH bonds and the oxygen atoms of the corresponding peptidic CO bonds, which should be in the range of 1.8−2.4 Å. Besides, the values of the angles ∠NH⋯O and ∠H⋯OC should be between 100° and 180°. In this way, 147 and 61 starting conformations for hydrogen-bonded helices resulted for the (E)- and (Z)-hexamers, respectively, in addition to the hexamers derived from the monomers. The optimized structures were characterized as minimum structures by the determination of the matrix of the force constants. On the basis of the vibration frequencies, the enthalpies, the thermal energy corrections, and the entropies of the various helices were calculated. For the minimum conformations, which still fulfill the helix properties of Figure 2, geometry optimizations at the B3LYP/6-31G* level were complemented to estimate the

![FIGURE 3](image-url). Sketch of the most stable conformers of 1 (n = 1) at the HF/6-31G* level of ab initio MO theory.

Influence of correlation effects. All helical HF/6-31G* conformers were also subjected to PCM/HF/6-31G* single-point calculations to examine the solvent influence. The quantum chemical calculations were performed employing the Gaussian98, Gaussian03, and the Gamess-US program packages.9

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**TABLE 3.** HF/6-31G* Backbone Torsion Angles* of All Periodic Hexamer Structures 1 (n = 6) Derived from the Conformers U in Table 1

<table>
<thead>
<tr>
<th>Conf.</th>
<th>ϕ</th>
<th>θ</th>
<th>ζ</th>
<th>ψ</th>
<th>Conf.</th>
<th>ϕ</th>
<th>θ</th>
<th>ζ</th>
<th>ψ</th>
</tr>
</thead>
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<tr>
<td>(U1)b</td>
<td>−133.7</td>
<td>−125.7</td>
<td>−179.4</td>
<td>176.8</td>
<td>(U3)b</td>
<td>−110.8</td>
<td>6.1</td>
<td>177.4</td>
<td>26.6</td>
</tr>
<tr>
<td>(U2a)b</td>
<td>−131.6</td>
<td>−125.5</td>
<td>−179.4</td>
<td>176.9</td>
<td>(U4)b</td>
<td>−100.0</td>
<td>5.0</td>
<td>177.8</td>
<td>26.0</td>
</tr>
<tr>
<td>(U3a)b</td>
<td>−130.2</td>
<td>−125.4</td>
<td>−179.4</td>
<td>177.0</td>
<td></td>
<td>−98.9</td>
<td>4.9</td>
<td>177.7</td>
<td>26.3</td>
</tr>
<tr>
<td>(U2b)b</td>
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<td>−125.4</td>
<td>−179.4</td>
<td>176.9</td>
<td></td>
<td>−98.6</td>
<td>4.9</td>
<td>177.7</td>
<td>26.2</td>
</tr>
<tr>
<td>(U2c)(H2):b</td>
<td>−131.2</td>
<td>−125.4</td>
<td>−179.5</td>
<td>176.7</td>
<td>(U3c)b</td>
<td>−98.8</td>
<td>4.7</td>
<td>177.8</td>
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<td>177.4</td>
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<td>(U4a)b</td>
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<td>0.4</td>
<td>176.5</td>
<td>32.6</td>
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<td>(U2c):b</td>
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<td>−179.9</td>
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<td>(U3c):b</td>
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<td>0.8</td>
<td>176.7</td>
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<tr>
<td>(U4a):b</td>
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<td>−179.8</td>
<td>176.3</td>
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<td>−102.1</td>
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<td>(U3a):b</td>
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<td>115.3</td>
<td>−179.8</td>
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<tr>
<td>(U2c):b</td>
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<td>−179.9</td>
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<td>−179.6</td>
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<td>(U2c):b(H2):b</td>
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<td>(U4b):b</td>
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<td>−123.9</td>
<td>177.9</td>
<td>25.9</td>
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<td>(U3b):b(H2):b</td>
<td>−94.2</td>
<td>121.9</td>
<td>−179.0</td>
<td>−26.3</td>
<td>(U4b):b</td>
<td>−78.9</td>
<td>−123.8</td>
<td>178.0</td>
<td>26.1</td>
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<tr>
<td>(U3b):b(H2):b</td>
<td>−104.3</td>
<td>123.7</td>
<td>−177.9</td>
<td>−29.7</td>
<td>(U4b):b</td>
<td>−78.9</td>
<td>−123.8</td>
<td>178.0</td>
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<tr>
<td>(U3b):b(H2):b</td>
<td>−78.8</td>
<td>122.5</td>
<td>175.6</td>
<td>35.9</td>
<td>(U4b):b</td>
<td>−78.7</td>
<td>−124.0</td>
<td>178.1</td>
<td>25.9</td>
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<tr>
<td>(U3b):b(H2):b</td>
<td>−123.6</td>
<td>122.4</td>
<td>175.5</td>
<td>28.8</td>
<td>(U4b):b</td>
<td>−78.8</td>
<td>−124.5</td>
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<td>(U3b):b(H2):b</td>
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<td>−174.8</td>
<td>−37.4</td>
<td>(U4b):b</td>
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<td>−124.7</td>
<td>176.1</td>
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<td>111.6</td>
<td>−176.7</td>
<td>−37.4</td>
<td>(U4b):b</td>
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<td>−123.0</td>
<td>176.6</td>
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<td>7.0</td>
<td>179.6</td>
<td>−175.4</td>
<td></td>
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* Angles in degrees.
Results and Discussion

(E)-Vinylogous \(\gamma\)-Peptides. Table 1 contains the geometry data for the conformers of the unsubsti-
tuted (U) and \(\gamma\)-methyl-substituted (G) model compounds 1 \((n = 1)\) with an (E)-double bond obtained at
the HF/6-31G* level of ab initio MO theory. The corre-
sponding geometry information at the DFT/B3LYP/
6-31G* and PCM/HF/6-31G* levels is given as Supporting
Information. It is possible to collect the conformers in
various families denoted by Arabic numerals with ap-
proximately the same values of \(\varphi\) and \(\theta\). The relative
energies of the conformers are given in Table 2. There
are only a few changes of the stability order at the various
approximation levels. Some gas phase conformers disap-
pear in the water continuum. The most stable conformers
are visualized in Figure 3.

In the next step, periodic secondary structures were
derived from the conformer pool of the unsubstituted
monomer unit. Contrary to the blocked \(\beta\)- and \(\gamma\)-amino
acids, there is no structure with a stabilizing hydrogen
bond among the monomer conformers. Obviously, the (E)-
double bond prevents the formation of hydrogen bonds
between neighboring peptide bonds. Thus, helices with
larger hydrogen-bonded pseudocycles could only be ex-
pected in longer sequences of (E)-vinylogous amino acids.

Table 4. Relative Energies of Selected Periodic Hexamers 1 \((n = 6)\) at Various Approximation Levels of
ab Initio MO Theory

<table>
<thead>
<tr>
<th>conformation</th>
<th>(\Delta E) (HF)</th>
<th>(\Delta E) (B3LYP)</th>
<th>(\Delta E) (PCM)</th>
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<tr>
<td>(U1) (_6)</td>
<td>36.9</td>
<td>46.2</td>
<td>0.0</td>
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<td>(U2a) (_6)</td>
<td>46.5</td>
<td>68.4</td>
<td>14.3</td>
</tr>
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<td>(U2b) (_6)</td>
<td>107.6</td>
<td>133.4</td>
<td>73.9</td>
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<td>(U2c) (_6)</td>
<td>64.3</td>
<td>75.7</td>
<td>89.8</td>
</tr>
<tr>
<td>(U3a) (_6)</td>
<td>33.3</td>
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<td>(U4a) (_6)</td>
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<td>55.4</td>
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<td>(U4b) (_6)</td>
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<td>63.4</td>
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<td>(H2) (_9)</td>
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<td>(H27)</td>
<td>17.2</td>
<td>33.7</td>
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\(a\) Energies in kJ/mol. \(b\) Monomers U from Table 3; helices H, resulting from the oligomer approach in Table 5; H denotes a helix
with \(n\)-membered hydrogen-bonded pseudocycles. \(c\) \(E_T = -1949.239855\) au. \(d\) \(E_T = -1960.996152\) au. \(e\) \(E_T = -1949.211533\) au.

(Z)-Vinylogous \(\gamma\)-Amino Acids. The geometry data at the HF/6-31G* level of ab initio MO theory for the var-
ious conformers of the unsubstituted (U) and \(\gamma\)-meth-
yl-substituted (G) vinylogous \(\gamma\)-amino acid derivatives 2 
\((n = 1)\) are given in Table 6. The data at the other
approximation levels are again part of Supporting Infor-
mation. Contrary to the monomers with (E)-double bonds,
there are several conformers with seven- and nine-
membered hydrogen-bonded pseudocycles (C7, C9). The
most stable conformers U1, U2, G1, G2, and G3 are 
among them (Table 7). They are visualized in Figure 5.

Some of the lesser stable conformers are stabilized by
N...HN hydrogen bonds. Their C\(_7\) pseudocycles are
denoted by an asterisk. There are only a few inversions in
the stability order of the most stable conformers at the
other levels of ab initio MO theory. The hydrogen
bonds of U1 and U4 are open when considering the


\(\varphi\) and \(\theta\) denote the preferred values of dihedral angles. For the hydrogen bonding
direction along the sequence, the helices H\(_{14}\), H\(_{19}\), and
H\(_{24}\) in backward direction. For the hydrogen bonding patterns in
H\(_{22}\) and H\(_{27}\), there are even two representatives denoted by upper-script Roman numbers in the
order of decreasing stability. The H\(_{22}\) and H\(_{19}\) helices are
the most stable helices among the hydrogen-bonded helix

types (Table 4). They are also distinctly more stable than
the helices without hydrogen bonds derived from the
monomers U1, U2a, and U3a, respectively (Tables 3 and
4). This is particularly valid for apolar media, whereas
the most stable helices without hydrogen bonds gain
considerable stability in a polar environment because of
their better interaction possibilities with the solvent due
to the missing intramolecular peptide hydrogen bonds.

The stability order of the helix hexamers within the two
groups of helices with and without hydrogen bonds
obtained on the basis of the energy data is essentially
confirmed by the free enthalpy data resulting from the
calculation of the vibration frequencies (see Table S5 of
the Supporting Information). However, it has to be
mentioned that the helices without hydrogen bonds get
some stability at the free energy level in comparison to
their hydrogen-bonded counterparts resulting from the
entropy contributions. Due to the missing hydrogen
bonds, the entropy values of these helices are distinctly
higher than those of the hydrogen-bonded helices. Figure
4 visualizes the most stable helices of (E)-vinylogous
\(\gamma\)-peptides.

The Supporting Information). However, it has to be
mentioned that the helices without hydrogen bonds get
some stability at the free energy level in comparison to
their hydrogen-bonded counterparts resulting from the
entropy contributions. Due to the missing hydrogen
bonds, the entropy values of these helices are distinctly
higher than those of the hydrogen-bonded helices. Figure
4 visualizes the most stable helices of (E)-vinylogous
\(\gamma\)-peptides.
solvent within the polarizable continuum model. The situation for the helix formation in oligomers of (Z)-vinylogous \( \gamma \)-amino acids is rather different from that for the (E)-oligomers. The most stable helix conformers H\(_{2}\) and H\(_{3}\) are characterized by nearest-neighbor peptidic hydrogen bonds (Figure 6). They can immediately be derived from the monomer conformers U1 and U2 by oligomerization (Tables 6 and 8). Both helices are of comparable stability at the HF/6-31G* level of ab initio MO theory and also in a polar environment, but H\(_{2}\) is preferred at the DFT/B3LYP/6-31G* level (Table 9). A rather unstable helix (U3)\(_{b}\) without hydrogen bonds results from the extension of the monomer U3. The oligomerization of the other U conformers in Table 6 does not provide stable helices. It can be supposed that there are further helices in (Z)-vinylogous \( \gamma \)-peptides with larger hydrogen-bonded pseudocycles than in the helices H\(_{2}\) and H\(_{3}\). Searching for such helices in hexamers in the same way as it was performed for the (E)-vinylogous \( \gamma \)-peptides provides in fact the helices H\(_{12}\), H\(_{14}\), and H\(_{17}\), but no helices with still larger pseudocycles (Table 8, Figure 6). However, these helices are distinctly less stable than the H\(_{2}\) and H\(_{3}\) conformers with the nearest-neighbor peptidic hydrogen bond interactions (Table 9).

\textbf{(E)- vs (Z)-Double Bonds. Nanotubes and Channels.} Comparing the formation of hydrogen-bonded helices in (E)- and (Z)-vinylogous \( \gamma \)-peptides, it is most striking that the (E)-double bonds prevent the formation of helices with nearest-neighbor peptide bond interactions. Most stable are helices with 22- and 19-membered hydrogen-bonded rings, whereas the (Z)-double bonds favor peptidic nearest-neighbor interactions leading to helices with seven- and nine-membered pseudocycles. The other helix types are distinctly less stable in both cases. In the parent \( \gamma \)-peptides, the preferred helices span a much wider range of hydrogen-bonded ring sizes with the most stable H\(_{14}\) and H\(_{3}\) helices and the also relatively stable H\(_{12}\) and H\(_{17}\) helices. Obviously, the double bond configuration is able to direct the helix formation in a special direction. A detailed look at the helices of the (E)-vinylogous \( \gamma \)-peptides, as for instance the helices with 22-, 24-, and 27-membered rings, reveals that these structures have rather large inner diameters, which are comparable with the diameter of 3.5 Å of the well-known trans-membrane channel in gramicidin A.\(^{10}\) Table 10 lists the relative energies and diameters for the three helix undercamers H\(_{19}\), H\(_{22I}\), and H\(_{27I}\). The relatively stable periodic H\(_{19}\) structure (Table 10) cannot form channel-like structures and is only given for comparison. The diameters of H\(_{22I}\) and H\(_{27I}\) are large enough for ions and water molecules to pass. Therefore, (E)-vinylogous \( \gamma \)-peptides might become interesting for the design of ions channels or monomolecular nanotubes\(^{11}\) as it is shown for the H\(_{22I}\) and H\(_{27I}\) undercamers of the (E)-vinylogous peptides in Figure 7. The high stability of the channel-like conformers of the (E)-vinylogous peptides in an apolar environment could support such a process. The formation of monomolecular nanotubes has some general advantages over that by self-assembly of cyclopeptides, because it is induced within the same molecule. Besides, it is possible to design channels and nanotubes with definite length and composition.

\textbf{Monomer versus Oligomer Approach.} For a better understanding of structure formation in oligomers and polymers, it is very tempting to refer the periodic secondary structure elements to special conformers of blocked monomer units. In fact, the \( \beta \)-strand conformations, the 3\( \beta \)-helices, and the \( \gamma \)-turns in \( \alpha \)-peptides and the H\(_{10}\), H\(_{12}\), and H\(_{14}\) helices in \( \beta \)-peptides can be derived in this way. This is in some way surprising since the structural presuppositions for hydrogen bond linking in the aforementioned helices are not yet given in the blocked

\begin{table}[h!]
\centering
\caption{HF/6-31G* Backbone Torsion Angles\(^{a}\) for the Hydrogen-Bonded Helical Structures of the Hexamer 1 (\( n = 6 \)) Found in the Oligomer Approach}
\begin{tabular}{cccccccc}
\hline
conf\(^b\) & \( \varphi \) & \( \theta \) & \( \zeta \) & \( \psi \) & \( \varphi \) & \( \theta \) & \( \zeta \) & \( \psi \) \\
\hline
H\(_{1}\) & 71.4 & 18.2 & -166.2 & 164.2 & 103.6 & -123.5 & 176.3 & 31.6 \\
65.1 & 15.4 & -164.6 & 163.7 & 100.3 & -116.7 & 173.7 & 35.8 \\
65.6 & 16.9 & -164.6 & 160.5 & 96.1 & -110.4 & 173.1 & 37.3 \\
66.0 & 16.8 & -165.6 & 161.4 & 90.4 & -107.9 & 172.5 & 38.8 \\
67.6 & 15.1 & -165.1 & 155.1 & 85.9 & -106.4 & 170.9 & 41.6 \\
81.6 & -3.8 & -179.4 & 177.3 & 81.7 & -116.2 & 177.1 & 33.1 \\
H\(_{17}\) & -166.6 & -132.5 & 176.6 & 24.2 & H\(_{24}\) & 77.2 & -125.9 & 175.8 & 32.9 \\
84.7 & -107.1 & 166.6 & 38.7 & 76.3 & -127.1 & 173.8 & 39.2 \\
93.6 & -100.6 & 166.6 & 41.0 & 81.7 & -116.2 & 177.1 & 33.1 \\
83.5 & -101.1 & 164.6 & 49.2 & 98.4 & -117.3 & 172.7 & 30.5 \\
84.2 & -99.0 & 163.7 & 44.8 & 94.2 & -117.3 & 177.2 & 4.8 \\
82.3 & -93.9 & 169.5 & 45.6 & 103.4 & -131.5 & 174.1 & 20.6 \\
H\(_{19}\) & 79.3 & 10.9 & -173.3 & 175.8 & H\(_{25}\) & 105.3 & 112.9 & 179.5 & 165.7 \\
70.1 & 33.1 & -172.9 & 174.2 & 73.8 & 114.5 & 178.6 & 164.1 \\
80.0 & 16.6 & -173.2 & 172.6 & 73.3 & 110.5 & 179.6 & 160.1 \\
83.4 & 16.1 & -172.3 & 179.8 & 70.0 & 110.3 & 179.5 & 161.6 \\
87.8 & 14.3 & -175.8 & 175.7 & 71.4 & 118.5 & 178.4 & 169.0 \\
114.5 & -2.9 & 180.0 & 176.0 & 77.4 & 129.8 & 177.2 & 178.1 \\
H\(_{22I}\) & 118.5 & 117.6 & -178.4 & 165.3 & H\(_{27I}\) & -94.2 & 121.9 & -179.0 & -26.3 \\
74.1 & 107.3 & -175.2 & 157.3 & -104.3 & 123.7 & -179.9 & -29.7 \\
66.6 & 109.0 & -174.0 & 158.4 & -78.8 & 142.2 & 175.6 & 38.9 \\
72.1 & 108.0 & -172.7 & 158.1 & 125.6 & 122.4 & -175.5 & -28.8 \\
70.3 & 108.5 & -175.6 & 159 & -83.7 & 108.5 & -174.8 & -37.4 \\
73.3 & 130.5 & -178.8 & -174.9 & -88.8 & 111.6 & -176.7 & -37.4 \\
\hline
\end{tabular}
\begin{flushright}
\textsuperscript{a} Angles in degrees. \textsuperscript{b} \( H \) denotes a helix with \( x \)-membered hydrogen-bonded pseudocycles.
\end{flushright}
\end{table}
TABLE 6. HF/6-31G* Backbone Torsion Angles* for the Unsubstituted (U) and γ-Methyl-Substituted (G) Conformers of 2 (n = 1)

<table>
<thead>
<tr>
<th>conf</th>
<th>φ</th>
<th>θ</th>
<th>α</th>
<th>γ</th>
<th>type</th>
</tr>
</thead>
<tbody>
<tr>
<td>U1</td>
<td>80.9</td>
<td>74.8</td>
<td>-0.8</td>
<td>166.7</td>
<td>C7</td>
</tr>
<tr>
<td>U2</td>
<td>80.5</td>
<td>-123.7</td>
<td>-0.1</td>
<td>45.7</td>
<td>C9</td>
</tr>
<tr>
<td>U3</td>
<td>84.9</td>
<td>126.2</td>
<td>0.2</td>
<td>50.4</td>
<td>G6</td>
</tr>
<tr>
<td>U4</td>
<td>179.3</td>
<td>-91.6</td>
<td>-1.3</td>
<td>35.5</td>
<td>C7*</td>
</tr>
<tr>
<td>U5</td>
<td>-79.6</td>
<td>-122.6</td>
<td>1.7</td>
<td>54.7</td>
<td>G8</td>
</tr>
<tr>
<td>U6</td>
<td>78.5</td>
<td>34.7</td>
<td>1.2</td>
<td>60.1</td>
<td>G9</td>
</tr>
<tr>
<td>U7</td>
<td>106.2</td>
<td>-138.1</td>
<td>1.5</td>
<td>41.7</td>
<td>G10</td>
</tr>
<tr>
<td>G1</td>
<td>-79.8</td>
<td>122.8</td>
<td>0.1</td>
<td>-46.5</td>
<td>C7*</td>
</tr>
<tr>
<td>G2</td>
<td>-101.8</td>
<td>-47.5</td>
<td>-0.5</td>
<td>177.3</td>
<td>C7*</td>
</tr>
<tr>
<td>G3</td>
<td>58.7</td>
<td>77.2</td>
<td>-1.4</td>
<td>168.0</td>
<td>C7*</td>
</tr>
</tbody>
</table>

* Torsion angles in degrees. C7 denotes a hydrogen-bonded pseudocycle with x atoms; eq. ax: pseudoequatorial or pseudoaxial orientation of the C(γ) substituents; an asterisk denotes NH–N hydrogen bonding.

TABLE 7. Relative Energies* of the Unsubstituted (U) and γ-Methyl-Substituted (G) Conformers of 2 (n = 1) at the HF/6-31G*, DFT/B3LYP/6-31G* and PCM/HF/6-31G* Levels of ab Initio MO Theory

<table>
<thead>
<tr>
<th>conf</th>
<th>ΔE(HF)</th>
<th>ΔE(B3LYP)</th>
<th>ΔE(PCM)</th>
<th>type</th>
</tr>
</thead>
<tbody>
<tr>
<td>U1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>C7</td>
</tr>
<tr>
<td>U2</td>
<td>3.5</td>
<td>3.8</td>
<td>3.8</td>
<td>C9</td>
</tr>
<tr>
<td>U3</td>
<td>20.6</td>
<td>9.7</td>
<td>9.7</td>
<td>C7*</td>
</tr>
<tr>
<td>U4</td>
<td>25.6</td>
<td>11.4</td>
<td>11.4</td>
<td>C7</td>
</tr>
<tr>
<td>U5</td>
<td>26.4</td>
<td>11.1</td>
<td>11.1</td>
<td>C7*</td>
</tr>
<tr>
<td>U6</td>
<td>30.0</td>
<td>15.8</td>
<td>15.8</td>
<td>C7*</td>
</tr>
<tr>
<td>U7</td>
<td>31.7</td>
<td>12.2</td>
<td>12.2</td>
<td>C7*</td>
</tr>
<tr>
<td>G1</td>
<td>0.0</td>
<td>5.4</td>
<td>5.4</td>
<td>C7*</td>
</tr>
<tr>
<td>G2</td>
<td>4.0</td>
<td>10.6</td>
<td>10.6</td>
<td>C7*</td>
</tr>
<tr>
<td>G3</td>
<td>5.6</td>
<td>9.5</td>
<td>9.5</td>
<td>C7*</td>
</tr>
<tr>
<td>G4</td>
<td>9.4</td>
<td>4.1</td>
<td>4.1</td>
<td>C7*</td>
</tr>
<tr>
<td>G5</td>
<td>10.1</td>
<td>4.1</td>
<td>4.1</td>
<td>C7*</td>
</tr>
<tr>
<td>G6</td>
<td>17.8</td>
<td>21.5</td>
<td>21.5</td>
<td>C7*</td>
</tr>
<tr>
<td>G7</td>
<td>25.9</td>
<td>17.6</td>
<td>17.6</td>
<td>C7*</td>
</tr>
<tr>
<td>G8</td>
<td>26.9</td>
<td>21.5</td>
<td>21.5</td>
<td>C7*</td>
</tr>
<tr>
<td>G9</td>
<td>27.3</td>
<td>24.4</td>
<td>24.4</td>
<td>C7*</td>
</tr>
<tr>
<td>G10</td>
<td>27.8</td>
<td>21.0</td>
<td>21.0</td>
<td>C7*</td>
</tr>
<tr>
<td>G11</td>
<td>28.7</td>
<td>17.9</td>
<td>17.9</td>
<td>C7*</td>
</tr>
<tr>
<td>G12</td>
<td>38.4</td>
<td>36.3</td>
<td>36.3</td>
<td>C7*</td>
</tr>
<tr>
<td>G13</td>
<td>41.0</td>
<td>41.5</td>
<td>41.5</td>
<td>C7*</td>
</tr>
</tbody>
</table>

* ΔE energy differences in au.; angles in degrees; C7 denotes a hydrogen-bonded pseudocycle with x members; eq. ax: pseudoequatorial or pseudoaxial orientation of the C(γ) substituents; an asterisk denotes NH–N hydrogen bonding.

TABLE 8. HF/6-31G* Backbone Torsion Angles* of All Periodic Hexamer Structures Either Derived from the Monomers U in Table 6 or Obtained in the Oligomer Approach on Hexamers of 2 (n = 6)

<table>
<thead>
<tr>
<th>conf</th>
<th>φ</th>
<th>θ</th>
<th>α</th>
<th>γ</th>
<th>type</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(U1)h</td>
<td>83.7</td>
<td>73.6</td>
<td>-0.7</td>
<td>166.7</td>
<td>H14</td>
</tr>
<tr>
<td>H(U2)h</td>
<td>81.0</td>
<td>-122.6</td>
<td>0.5</td>
<td>47.7</td>
<td>H17</td>
</tr>
<tr>
<td>H(U3)h</td>
<td>72.0</td>
<td>71.9</td>
<td>-3.5</td>
<td>41.3</td>
<td>(U3)h</td>
</tr>
</tbody>
</table>

* Angles in degrees. Hh denotes a helix with x-membered hydrogen-bonded pseudocycles.
monomer units. However, this study on vinylogous γ-peptides and our preceding study on γ-peptides demonstrate that the monomer approach is only partially able to provide information on the characteristic periodic secondary structures in these classes of compounds. In particular, the helices with the larger hydrogen-bonded pseudocycles between non-nearest-neighbor peptide bonds are missing now. This tendency is obviously increasing with lengthening of the monomer backbone. Within the monomer approach, it is always possible to predict those periodic structures of the oligomers which result from the oligomerization of the monomeric conformers without steric restrictions. This is independent of the possibility of additional hydrogen bonds or not. If there are hydrogen bonds between nearest-neighbor peptide bonds in the blocked monomer, such conformers are anyway favored. The hydrogen-bonded helices with the larger non-nearest neighbor pseudocycles can only be found by a systematic conformational analysis of oligomers. Thus, it is obvious that the oligomer approach, which principally allows the finding of all periodic structures, is superior over the monomer approach. However, the realization of a complete oligomer approach, as for instance for a hexamer,
with relatively small grid intervals for the numerous torsion angles at a higher level of ab initio MO theory is rather tedious. Therefore, the combination of the monomer and a limited oligomer approach could be a good alternative to get a complete overview on all periodic secondary structures. Based on the monomer approach it is possible to find practically all periodic structures without hydrogen bonds and the structures with peptidic nearest-neighbor hydrogen bonds. A limited oligomer approach based on general criteria for hydrogen bonds predicts additionally the periodic structures with the non-nearest neighbor hydrogen bonds, which cannot be found within the monomer approach for larger backbones of the amino acid constituents.

Conclusions

Our systematic theoretical investigation of helical structures in vinylogous \( \gamma \)-peptides provides a wide variety of alternative and competitive helices with and without hydrogen-bonded pseudocycles of different size. Contrary to the parent \( \gamma \)-peptides, there is a strict control of helix formation by the configuration of the double bond between the \( C(\alpha) \) and \( C(\beta) \) atoms of the monomer constituents. (E)-Double bonds favor helices with larger pseudocycles beginning with 14- up to 27-membered rings. Contrary to this, the (Z)-configuration supports a distinct preference of helices with interactions between nearest neighbor peptide bonds. Therefore, helices with 22- and 19-membered rings are most stable in (E)-vinylogous \( \gamma \)-peptides, and those with seven- and nine-membered rings are the preferred ones in (Z)-vinylogous \( \gamma \)-peptides. In the case of the (E)-vinylogs, some helices without hydrogen bonds might become competitive to the hydrogen-bonded helices in polar environments. The rather stable helices \( H_{22}^1, H_{34}^1, \) and \( H_{27}^1 \) of the (E)-hexamers have inner diameters large enough to let molecules or ions pass. Thus, they could be interesting model compounds for the design of membrane channels and monomolecular nanotubes. Our study shows that a combination of the monomer approach and a limited

FIGURE 6. Most stable helices with and without hydrogen bonds of (Z)-vinylogous \( \gamma \)-peptide hexamers 2.

FIGURE 7. Helical undecamers \( H_{22}^1 \) and \( H_{27}^1 \) of the (E)-vinylogous \( \gamma \)-peptides as models for membrane channels and nanotubes.
oligomer approach is able to provide a complete overview on all helical structures. Contrary to this, a complete oligomer approach search at a higher level of ab initio MO theory is too time-consuming, and the monomer approach is not able find all possible helical structures.

**Acknowledgment.** We thank Deutsche Forschungsgemeinschaft (Project HO 2346/1 “Sekundärstrukturbildung in Peptiden mit nicht-proteinogenen Aminosäuren” and SFB 610 "Proteinzustände mit zellbiologischer und medizinischer Relevanz") for support of this work.

**Supporting Information Available:** Tables with the backbone torsion angles of the monomers 1 and 2 at the B3LYP/6-31G* and PCM/HF/6-31G* levels, with the backbone torsion angles of the hexamers 1 and 2 at the B3LYP/6-31G level and with the backbone torsion angles of selected undecamers 1 at the HF/6-31G* level of ab initio MO theory, with the enthalpies, free enthalpies, and entropies of all helix hexamers, coordinates of all helix hexamers and undecamers as pdb files. This material is available free of charge via the Internet at http://pubs.acs.org.