Helix Formation and Folding in γ-Peptides and Their Vinylogues

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Dedicated to Professor Dr. *Dieter Seebach* on the occasion of his 65th birthday

A complete overview of all possible periodic structures with characteristic H-bonding patterns is provided for oligomers composed of γ-amino acids (γ-peptides) and their vinylogues by a systematic conformational search on hexamer model compounds employing *ab initio* MO theory at various levels of approximation (HF/6-31G*, DFT/B3LYP/6-31G*, SCRF/HF/6-31G*, PCM//HF/6-31G*). A wide variety of structures with definite backbone conformations and H-bonds formed in forward and backward directions along the sequence was found in this class of foldamers. All formally conceivable H-bonded pseudocycles between 7- and 24-membered rings are predicted in the periodic hexamer structures, which are mostly helices. The backbone elongation in comparison to α- and β-peptides allows several possibilities to realize identical H-bonding patterns. In good agreement with experimental data, helical structures with 14- and 9-membered pseudocycles are most stable. It is shown that the introduction of an (E)-double bond into the backbone of the γ-amino acid constituents, which leads to vinylogous γ-amino acids, supports the folding into helices with larger H-bonded pseudocycles in the resulting vinylogous γ-peptides. Due to the considerable potential for secondary-structure formation, γ-peptides and their vinylogues might be useful tools in peptide and protein design and even in material sciences.

1. Introduction. – The imitation and the improvement of structural features of peptides and proteins are great challenges for chemists and biochemists. The application of native peptides for pharmacological and pharmaceutical purposes often suffers from their insufficient resistance to proteases and their unfavorable transport properties. Besides, better selectivity for different receptor subtypes is desired [1] [2]. It is an old idea to solve these problems by substitution of non-proteinogenic amino acids for one or several natural amino acids in the sequence. In the last years, the consistent extension of this idea led to the search for oligomers that are composed only of non-proteinogenic amino acids [3–11]. Since protein and peptide structures are essentially determined by characteristic secondary-structure elements such as helices, sheets, and turns, the modified compounds still have to reflect the steric and electronic properties of their native counterparts to keep or even to improve the biological activity. Consequently, such oligomers should be able to form definite backbone conformations.

All these efforts to develop efficient peptidomimetics could be considered part of a general search for oligomers built from 'any' chemical monomer unit that folds into definite conformational states. The term foldamer was suggested for such structures [4]. It is obvious that this concept goes far beyond the structural imitation of peptides or the other two major backbones of biopolymers, ribonucleic acids, and polysaccharides, even if peptidomimetics remain a topic of outstanding interest [4–11]. Due to the wide variety of chemical monomer units, foldamers with specific properties could be expected, which might be interesting in other fields as, for instance, in material sciences.

Very interesting and surprising results were obtained for oligomers composed of β-amino acids (β-peptides). In comparison to α-amino acids, each β-amino acid constituent contributes an additional CH_2 group to the backbone. Contrary to original assumptions of higher conformational flexibility in the backbone that could prevent the formation of ordered structures, several elements of secondary structure have been found [4][9–11]. Most impressive were diverse helix types with H-bonded pseudocycles of different sizes. One of these helices, a *2.5*$_1$ helix with 12-membered pseudocycles (C_{12}) [12–14], corresponds to the familiar α-helix in the α-peptides by the backward direction of the H-bonds between the peptidic NH group of amino acid *i* and the peptidic CO group of amino acid $(i-3)$ along the sequence ($1 \leftarrow 4$ interaction). But, different from native peptides and proteins, there are also β-peptide helices forming the H-bonds in the forward direction, such as a *3*$_1$ helix with H-bonds arranged in 14-membered pseudocycles (C_{14}) between the NH group of amino acid *i* and the CO group of amino acid $(i+2)$ ($1 \rightarrow 3$ interaction) [14–16]. Even periodically alternating helices, sometimes called 'mixed' helices, were found, where two different pseudocycles, *e.g.*, 10- and 12-membered, are alternating with their H-bonds in the forward and backward directions along the sequence [17–19]. Apart from the various helix types, β-peptides are also able to realize sheet- and turn-like structures [20–24]. Thus, it is not surprising that foldamer characteristics could be predicted and experimentally confirmed in β-peptide derivatives such as hydrazino [25][26] and aminooxy peptides [27–30]. Moreover, it can be expected that further homolongation of the monomer unit leading to γ-amino acids makes well-defined backbone conformations in the corresponding γ-peptides also possible.

Formal possibilities for H-bonding in γ-peptides are illustrated in *Fig. 1,a*. Obviously, competition between periodic structure alternatives with nearest-neighbor H-bonds (C_7 and C_9 pseudocycles) and non-nearest-neighbor H-bonds with larger H-bonded pseudocycles (C_{12}, C_{14}, and higher) could be expected. Some of these structures were confirmed in experimental studies. Thus, early investigations on polymers of γ-linked D-glutamic acid, which is the main constituent of the capsule of *Bacillus anthracis*, indicated helical structures with 17- or 19-membered H-bonded pseudocycles [31]. Recently, it has been reported that unsubstituted γ-amino acids adopt C_9 conformations [32]. Other studies show that substituents at the γ-peptide backbone favor the formation of helices with 14-membered pseudocycles [33–39].

C_7 Pseudocycles are defined by an interaction between the peptidic NH and CO groups within the same monomer constituent ($1 \rightarrow 1$ interaction), whereas the C_9 pseudocycles are formed between the two amino acids adjacent to a monomer unit ($1 \leftarrow 3$ interaction). Oligomeric structures of α- and β-peptides with closer H-bonded pseudocycles tend more to the formation of sheet- or ribbon-like structures, whereas helices are more probable in structures with larger pseudocycles. In γ-peptides, structures with nearest-neighbor H-bonds could possibly be more favored relative to their non-nearest-neighbor H-bonded counterparts than in α- and β-peptides. The backbone elongation improves the possibilities for effective orientation of the H-bond donor and acceptor parts in the closer pseudocycles [32]. An interesting idea to avoid the formation of smaller pseudocycles and to favor *a priori* helices with larger

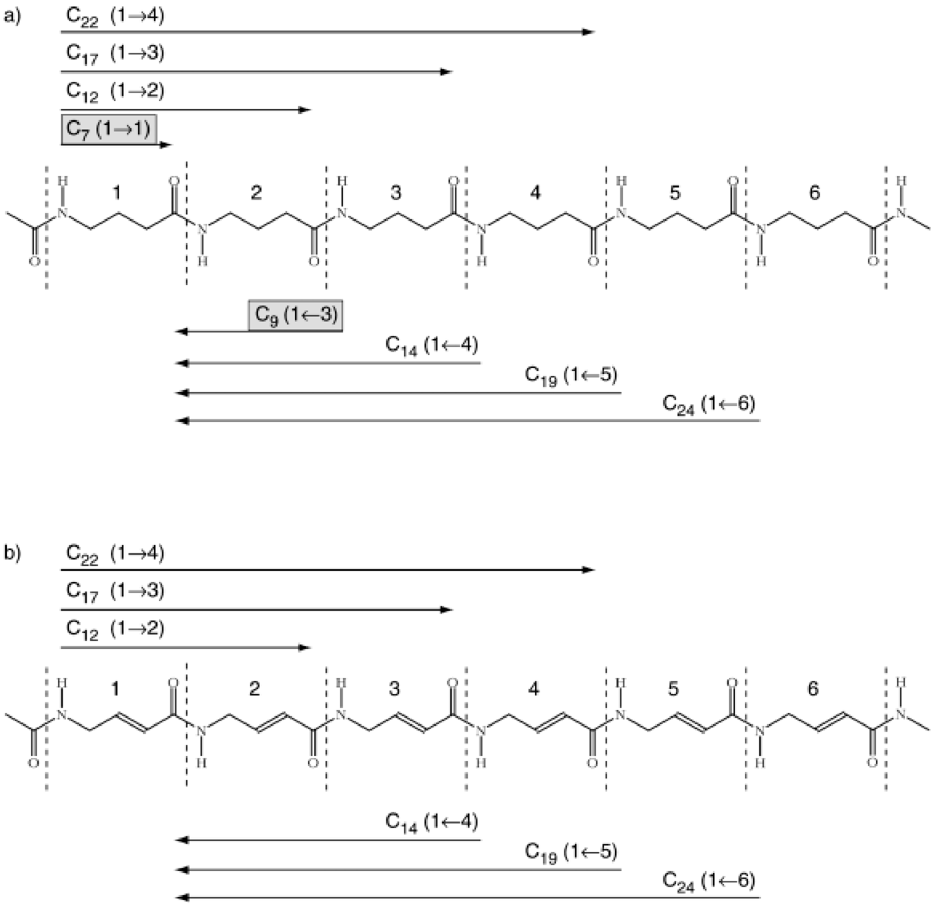
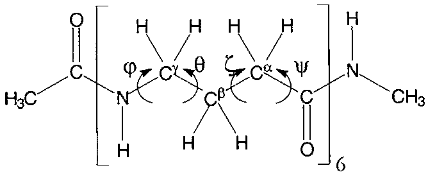


Fig. 1. *Possible H-bonding patterns in γ-peptides* (a) *and their vinylogues* (b). Nearest-neighbor H-bonded pseudocycles C_7 and C_9 are highlighted.

pseudocycles could be the introduction of an (*E*)-double bond between the C(α) and C(β) atoms of the γ-amino acid constituents, which rigidifies the backbone and restricts the conformational possibilities [40]. The scheme of the possible H-bonding patterns in the corresponding vinylogous γ-peptides (*Fig. 1,b*) shows that the formation of the smaller H-bonded pseudocycles becomes impossible by this type of modification. Vinylogous γ-amino acids are synthetically accessible [41][42]. Their introduction into α-peptide sequences as monomer constituents was successfully performed, and some oligomers were also synthesized [43][44], but structural data for the oligomers have not been available until now.

In the last years, numerous quantum-chemical conformational analyses of non-proteinogenic amino acids and their oligomers were reported [26][28][45–59]. The *ab initio* MO methods employed proved to be reliable tools to obtain a rather complete overview of the possibilities of secondary-structure formation in these classes of compounds. In this study, we extend our investigations to γ-peptides and their vinylogues, and focus especially on ordered periodic structures with characteristic H-bonding patterns.

2. Methods. – Numerous studies show that the major types of secondary-structure elements in α- and β-peptides, and their derivatives can be deduced from the conformer pool of the blocked monomer constituents, even when H-bonding is still impossible in the monomer unit [26][28][45–68]. Nonetheless, it cannot be excluded that higher-ordered structures exist, but become possible only in longer sequences by cooperativity effects. Therefore, such a monomer approach has to be complemented by conformational searches on oligomer structures, as it was shown in some molecular-dynamics studies on various peptidomimetics [30][69–74]. Here, we employ another strategy to find all periodic structures with specific H-bond patterns. Periodic conformations of the blocked γ-peptide hexamer **1** were generated by a systematic variation of the backbone torsion angles φ, θ, ζ, and ψ in each monomer constituent between $-150°$ and $180°$ in steps of $30°$. The torsion angles ω of the peptide bonds were set to values of $-165°$, $180°$, and $165°$, respectively. From the resulting pool of *ca.* 36,000 conformations, we selected those fitting into possible periodic H-bonding patterns up to 24-membered H-bonded pseudocycles according to general geometry criteria of H-bonds. These structures were starting points for geometry optimizations at the HF/6-31G* level of *ab initio* MO theory [75].



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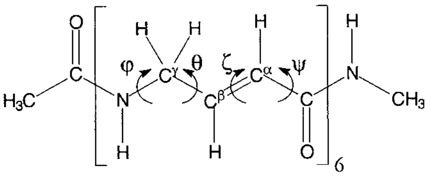

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All conformers that retained the periodic H-bonding patterns were re-optimized at the B3LYP/6-31G* approximation level of density functional theory (DFT) to estimate the influence of electron-correlation energy [76][77]. The same procedure was employed for the corresponding vinylogous γ-peptide hexamer **2** with the exception that the torsion angles ζ were assigned the same values as the angles ω because of the approximately planar arrangement at the (*E*)-double bond. Thus, the pool of starting conformations is reduced to *ca.* 9,000 conformations in this case.

Since some solvation influence could be expected on peptide structures, an estimation of medium effects was performed employing the *Onsager* self-consistent-reaction-field (SCRF) model and the polarizable-continuum model (PCM) [78–80]. The geometries of the HF/6-31G* minima were the starting points in both cases. Whereas the starting structures in the SCRF/HF/6-31G* calculations were subject to complete geometry optimization, the PCM energies arise from single-point calculations (PCM//HF/6-31G*). The PCM energies were not available for all conformers, probably because of inconsistencies of the formalism resulting from delicate surface-area problems in some cases. To simulate an aqueous environment, the dielectric constant was set to $\varepsilon = 78.4$. The radii of the solute molecules necessary within the SCRF model were estimated from the *Conolly* surface areas of the gas-phase monomers. Even though both models neglect specific solute–solvent interactions, the results might be considered as a first estimation of the general trend of solvation influence.

All quantum-chemical calculations were performed employing the GAUSSIAN98 [81] and GAMESS-US [82] program packages.

3. Results and Discussion. – The *Tables 1* and *2* provide information on the backbone torsion angles φ, θ, ζ, and ψ of all periodic minimum conformations of the blocked γ-peptide hexamer **1** with H-bonding patterns in the forward and backward directions obtained at the HF/6-31G* level of *ab initio* MO theory. The corresponding data at further levels of approximation (B3LYP/6-31G*, SCRF/HF/6-31G*) are part of the *Supplementary Material*. In the following paragraphs, the symbol H_x denotes the general helix type with the index x giving the size of the H-bonded pseudocycles C_x. The bold face notation $\mathbf{H}_x$ ($\mathbf{vH}_x$ in the case of vinylogous γ-peptides) stands for an actual conformer of this type. Regarding the torsion-angle values in all conformers in detail, φ corresponds to *anti-clinal* (*ac*) [83] and *syn-clinal* (*sc*), and, in a few cases, also to *anti-periplanar* (*ap*) orientations. The two central torsion angles θ and ζ correspond only to *sc* and *ap* arrangements. The torsion angle ψ exhibits values for all three mentioned conformation types (*ac*, *ap*, *sc*).

Table 1. *Backbone Torsion Angles of Conformers of the Blocked γ-Peptide Hexamer* **1** *with H-Bonds Formed in the Forward Direction Obtained at the HF/6-31G* Level of* ab initio *MO Theory*[a])

Conformer	φ	θ	ζ	ψ	Conformer	φ	θ	ζ	ψ
$\mathbf{H}_{7}^{\mathrm{I}}$	178.2	– 64.1	91.4	158.4	$\mathbf{H}_{17}^{\mathrm{I}}$	77.4	70.9	– 76.8	152.2
	179.5	– 65.1	91.0	155.9		81.7	67.5	– 79.8	145.5
	– 179.7	– 65.2	91.0	154.6		84.7	64.3	– 167.0	– 175.9
	– 179.9	– 65.3	90.8	155.0		75.8	65.8	– 80.6	149.2
	– 179.8	– 65.4	90.7	155.5		78.5	60.4	– 171.2	– 168.6
	177.9	– 65.4	88.8	163.2		75.4	66.4	– 72.9	137.4
$\mathbf{H}_{7}^{\mathrm{II}}$	– 89.1	– 48.8	– 50.9	– 101.6	$\mathbf{H}_{17}^{\mathrm{II}}$	120.1	– 56.2	73.0	58.9
	– 93.6	– 48.6	– 50.4	– 103.6		– 168.3	178.6	63.2	60.0
	– 94.4	– 48.4	– 50.1	– 103.6		155.0	– 69.9	75.5	58.0
	– 94.6	– 48.3	– 50.1	– 103.9		170.7	– 169.5	74.3	90.7
	– 94.7	– 48.3	– 50.2	– 104.3		140.0	– 71.8	73.5	63.5
	– 92.9	– 48.7	– 50.4	– 102.1		119.1	– 179.6	69.1	– 168.4
$\mathbf{H}_{12}^{\mathrm{I}}$	78.9	68.5	– 77.1	147.0	$\mathbf{H}_{22}^{\mathrm{I}}$	146.5	177.3	179.7	98.7
	85.7	70.2	– 76.8	144.8		85.3	177.0	178.6	89.8
	87.0	70.1	– 76.9	145.6		78.6	178.9	180.0	90.6
	86.3	69.9	– 77.1	147.5		82.9	178.9	– 177.1	97.7
	85.9	69.3	– 78.6	151.4		79.4	177.5	173.8	96.2
	84.1	66.3	– 73.9	135.3		78.8	– 176.2	173.8	157.0
$\mathbf{H}_{12}^{\mathrm{II}}$	123.1	– 59.9	76.3	58.9	$\mathbf{H}_{22}^{\mathrm{II}}$	91.8	66.4	– 176.6	– 157.5
	155.4	– 67.2	77.3	63.2		81.6	65.1	– 170.8	– 174.3
	156.6	– 69.2	75.5	67.4		77.3	64.4	– 165.1	– 168.3
	154.2	– 69.0	75.9	68.4		78.7	63.8	– 169.2	– 166.3
	151.9	– 68.0	77.2	67.1		75.1	62.7	– 167.6	– 163.2
	150.6	– 66.1	76.3	63.8		74.8	65.1	– 167.8	– 107.3

[a]) Torsion angles in degrees.

Table 2. *Backbone Torsion Angles of Conformers of the Blocked γ-Peptide Hexamer* **1** *with H-Bonds Formed in Backward Direction Obtained at the HF/6-31G* Level of* ab initio *MO Theory*[a])

Conformer	φ	θ	ζ	ψ	Conformer	φ	θ	ζ	ψ
$\mathbf{H_9^{I}}$	98.7	−69.5	−75.5	99.3	$\mathbf{H_{19}^{I}}$	118.4	−65.5	−71.1	179.1
	97.4	−69.7	−75.2	97.0		168.1	−64.6	−69.1	164.0
	97.4	−69.6	−75.1	97.0		148.1	−64.7	−68.7	160.1
	97.5	−69.6	−75.2	97.0		172.3	−67.5	−70.2	159.9
	97.5	−69.8	−75.3	97.1		154.1	−63.5	−69.8	160.1
	98.4	−70.5	−74.5	100.1		170.2	−64.7	−71.4	161.8
$\mathbf{H_9^{II}}$	75.1	−161.2	72.9	4.5	$\mathbf{H_{19}^{II}}$	72.7	64.2	−170.9	148.4
	75.0	−161.3	73.5	3.1		70.9	61.8	−165.3	148.9
	74.8	−161.1	73.4	3.3		73.1	64.9	−169.2	150.6
	74.9	−161.2	73.5	3.1		75.5	63.8	171.8	139.3
	74.8	−161.6	73.2	3.9		78.1	62.8	−172.8	153.3
	74.9	−162.9	72.5	5.4		83.0	59.1	171.7	147.5
$\mathbf{H_9^{III}}$	44.8	52.2	−157.9	65.3	$\mathbf{H_{19}^{III}}$	123.1	179.5	64.2	87.8
	43.6	52.3	−156.2	64.1		139.1	−173.5	64.4	80.7
	43.9	52.1	−155.6	64.1		125.9	−174.7	63.1	78.1
	44.4	51.9	−155.4	63.8		146.3	−176.4	62.2	76.4
	44.5	51.9	−155.9	64.3		134.0	−172.0	62.6	70.8
	46.9	51.7	−156.6	70.6		151.5	−175.8	64.3	70.6
$\mathbf{H_{14}^{I}}$	106.1	−62.6	−67.5	165.6	$\mathbf{H_{24}^{I}}$	−133.3	−176.5	−65.8	−93.8
	136.5	−63.2	−68.2	138.3		−137.9	−174.8	−66.9	−103.0
	138.0	−60.1	−65.1	141.4		−154.8	176.4	−69.0	−103.5
	132.9	−61.0	−66.0	144.4		−105.2	−177.4	−64.9	−90.6
	135.3	−63.4	−66.7	143.0		−174.6	−178.8	−63.0	−68.5
	138.3	−61.0	−64.1	139.7		−166.4	178.9	−61.8	−66.4
$\mathbf{H_{14}^{II}}$	−64.5	−60.1	154.9	−118.2	$\mathbf{H_{24}^{II}}$	75.4	175.9	165.9	81.4
	−64.4	−59.3	156.1	−118.5		72.8	177.9	167.7	83.2
	−64.2	−59.1	153.3	−117.2		75.6	174.8	166.9	53.3
	−62.8	−58.6	155.1	−120.7		82.4	173.8	175.4	85.5
	−68.5	−61.2	159.9	−108.3		78.7	175.5	171.6	65.6
	−73.8	−58.9	175.1	−126.3		81.1	175.3	172.0	66.0
$\mathbf{H_{14}^{III}}$	95.2	−169.4	64.9	81.8					
	98.9	−165.4	61.1	70.4					
	108.8	−163.7	62.2	68.7					
	104.6	−163.2	62.7	70.3					
	104.4	−164.5	59.8	67.0					
	122.3	−169.5	65.0	45.6					

[a]) Torsion angles in degrees.

Referring to the scheme of H-bond possibilities in *Fig. 1,a*, it is striking that all pseudocycles between C_7 and C_{24} can be realized in ordered periodic structures. *Fig. 2* shows the most-stable hexamer structure for each pseudocycle type. In the majority of cases, several alternatives exist for the same pseudocycle, which is demonstrated for the H_7, H_{12}, and H_{14} helices in *Fig. 3*. This is not surprising for the structures with the nearest-neighbor H-bonded pseudocycles C_7 and C_9. When there are several minimum-energy conformations with these pseudocycle types in the monomer constituents, the same or different of them may be arranged in periodic and aperiodic oligomers. This is already known from the β-peptides, where several oligomeric structures with nearest-neighbor H-bonded pseudocycles could be localized [23][24][53][69], whereas the larger pseudocycles are present only in singular periodic oligomers [12–16]. Obviously, the homolongation in the monomer constituents opens up the possibility for conformational alternatives in the larger pseudocycles, too. In numerous cases, structure alternatives with identical H-bonding patterns exhibit the values for the torsion angles φ, θ, ζ and θ in reversed order, *e.g.*, $\mathbf{H^{I}_{12}/H^{II}_{12}}$, $\mathbf{H^{II}_{14}/H^{III}_{14}}$, and others (*Tables 1* and *2*). A comparison of the torsion angles of some representatives with the same H-bond orientations shows strong interrelationships, *e.g.*, $\mathbf{H^{I}_{9}/H^{I}_{14}/H^{I}_{19}}$, $\mathbf{H^{II}_{14}/H^{II}_{19}}$, and $\mathbf{H^{III}_{14}/H^{III}_{19}}$, respectively. This is similar to the situation in α-peptides concerning the relation between the α- and 3_{10}-helices there. Thus, the possibility of interconversion between such structures has to be considered, in particular in the case of small energy differences. A special comment is deserved for the two helices with the 17-membered pseudocycles $\mathbf{H^{I}_{17}}$ and $\mathbf{H_{17}}$. The values of the two central torsion angles θ and ζ are not the same in all monomer constituents, as it is required for periodic structures, but are alternating. Interestingly, these alternating values correspond to those in the periodic H_{12} and H_{22} hexamers with the smaller and larger pseudocycles, respectively, which have the same direction of H-bond formation. Nonetheless, the C_{17} pseudocycle is maintained. All attempts to localize a completely periodic H_{17} structure failed. Obviously, the C_{17} H-bond pattern cannot periodically be kept in γ-peptides. This could be a hint that the possibility to keep special H-bonding patterns with alternative backbone conformations in the monomer constituents increases with proceeding homolongation. Thus, completely aperiodic or alternating structures for the same H-bonding patterns become stronger competitive to periodic secondary structures.

According to the energy data in *Table 3*, the most-stable hexamer is $\mathbf{H^{I}_{14}}$, followed by $\mathbf{H^{I}_{9}}$, which is only by 5.8 kJ/mol less stable, and $\mathbf{H^{I}_{12}}$ with 21.8 kJ/mol above $\mathbf{H^{I}_{14}}$ at the HF/6-31G* level of *ab initio* MO theory. The other alternatives are distinctly more unstable, but one has to keep in mind that only three pseudocycles can be formed in H_{22} and H_{24} helices in comparison to five H-bonds in H_{12} and H_{14} helices. The $\mathbf{H^{I}_{14}}$ helix corresponds to the *2.6*$_1$-helix suggested by the groups of *Seebach* and co-workers [35–37] and *Hanessian et al.* [38][39]. It differs from the *3*$_1$-helix with 14-membered pseudocycles in the β-peptides above all by the opposite direction of H-bond formation, which is the same as in α-peptides. There is rather perfect agreement between the calculated torsion angles and those from the crystal-structure analysis of a substituted γ-peptide tetramer [36][37]. Considering the small energy difference between $\mathbf{H^{I}_{14}}$ and $\mathbf{H^{I}_{9}}$ and remembering the strong geometric relatedness of these two conformers (*Tables 2* and *3*, *Fig. 2*), rapid interconversion of these helices may occur. It was already mentioned that the closer pseudocycles are the basis for sheet- or ribbon-like structures in β-peptides, whereas helix formation is observed only with larger pseudocycles. However, the backbone elongation in the γ-amino acid constituents supports helix formation also with the closer pseudocycles C_7 and C_9. In the case of the H_7 conformers, the $\mathbf{H^{II}_{7}}$ helix is still less stable than the sheet-like conformer $\mathbf{H^{I}_{7}}$, whereas the $\mathbf{H^{I}_{9}}$ helix is not only the most-stable structure of all H_9 conformers, but belongs to the most-stable hexamer structures at all (*Table 3*, and *Figs. 2* and *3*).

The stability order at the *Hartree–Fock* level is not essentially changed at the B3LYP/6-31G* level of DFT (*Table 3*). The $\mathbf{H^{I}_{14}}$ and $\mathbf{H^{I}_{9}}$ hexamers remain closely

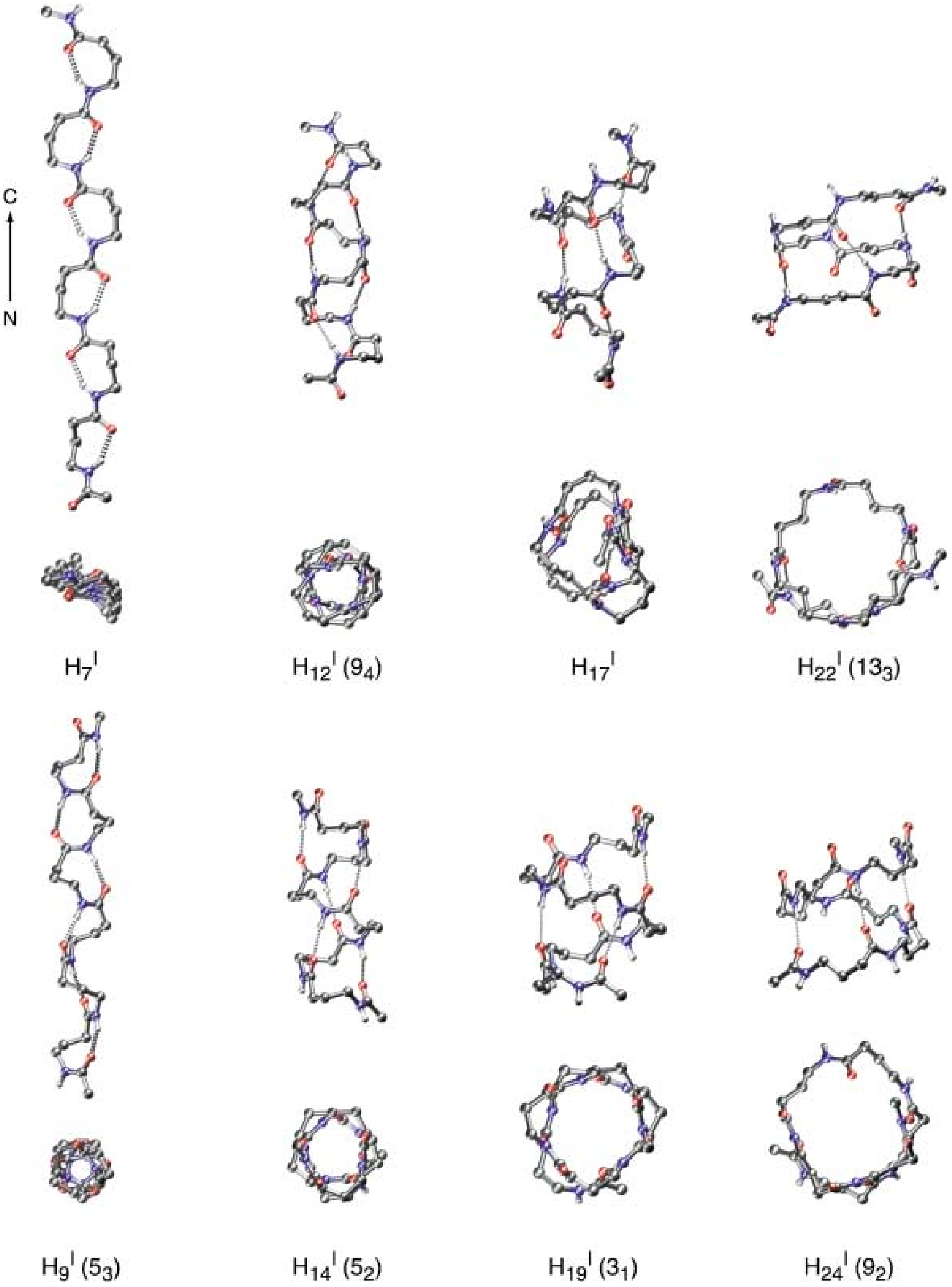


Fig. 2. *Most-stable periodic structures of hexamer* **1** *for each type of H-bonded pseudocycle obtained at the HF/6-31G* level of* ab initio *MO theory* (helix nomenclature in parentheses)

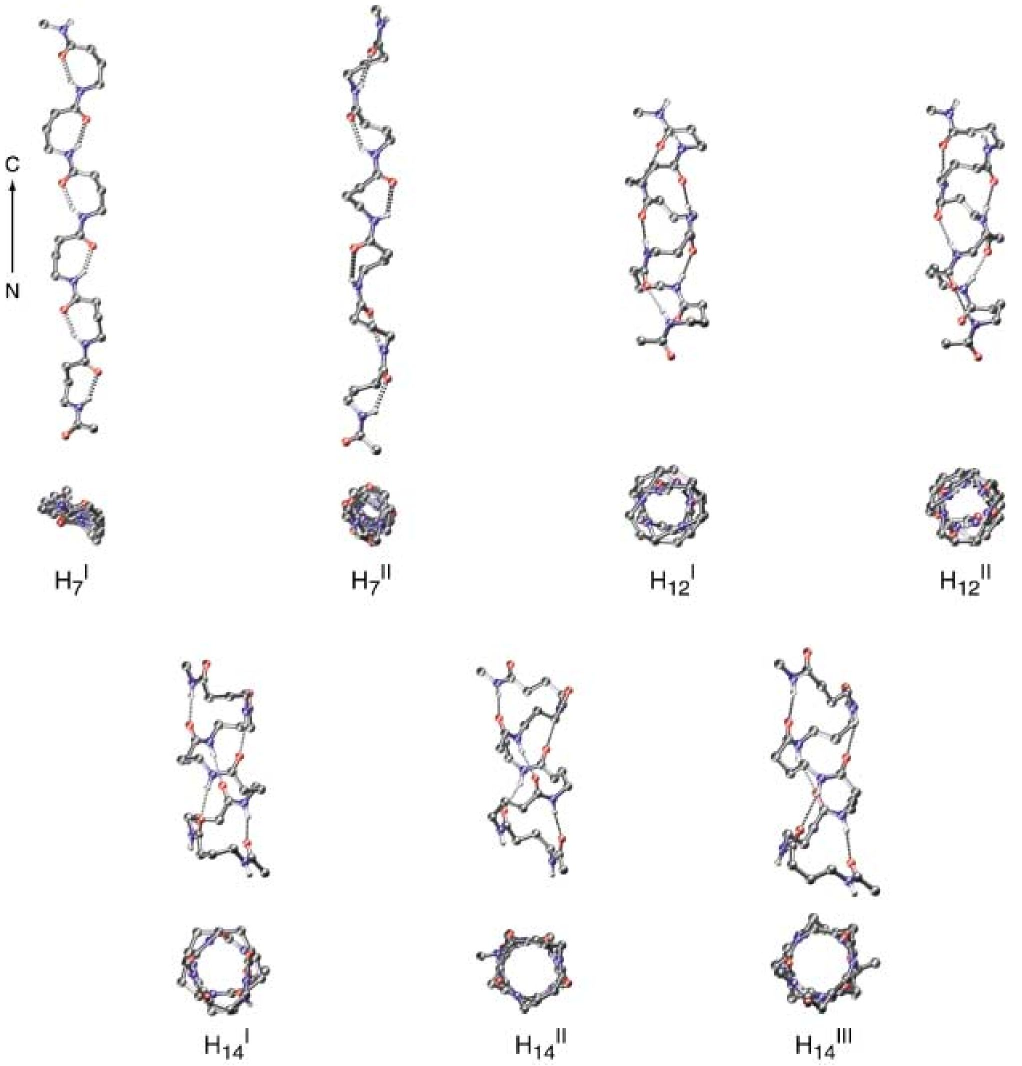


Fig. 3. *All periodic conformers in the γ-peptide hexamer* **1** *with 7-, 12-, and 14-membered H-bonded pseudocycles obtained at the HF/6-31G* level of* ab initio *MO theory*

together, but with a small preference of $\mathbf{H}_{9}^{\mathbf{I}}$ by 3.4 kJ/mol now, which might be caused by overestimation of H-bonding effects in DFT calculations. This would favor $\mathbf{H}_{9}^{\mathbf{I}}$ with one H-bond more than in $\mathbf{H}_{14}^{\mathbf{I}}$. The $\mathbf{H}_{12}^{\mathbf{I}}$ helix is with 30.6 kJ/mol somewhat destabilized.

The estimation of the solvent influence on the conformer stability shows contradictory results (*Table 3*). Remarkable changes in the stability order are predicted by the *Onsager* SCRF model. Now, the $\mathbf{H}_{12}^{\mathbf{I}}$ hexamer is distinctly more stable than the competitive structures $\mathbf{H}_{14}^{\mathbf{I}}$ and $\mathbf{H}_{9}^{\mathbf{I}}$. Even $\mathbf{H}_{12}^{\mathbf{II}}$ experiences significant stabilization by the solvent continuum. This effect is unequivocally related to the distinctly higher dipole

Table 3. *Relative Energies of the Conformers of the Blocked γ-Peptide Hexamer* **1** *Obtained at Various Levels of* ab initio *MO Theory*a)

Conformer	ΔE			
	HF/-31G*	B3LYP/6-31G*	SCRF/HF/6-31G*b)	PCM//HF/6-31G*b)
$\mathbf{H}^{\mathbf{I}}_{7}$	34.6	31.4	42.1	n.a.c)
$\mathbf{H}^{\mathbf{II}}_{7}$	48.4	57.3	107.0	n.a.
$\mathbf{H}^{\mathbf{I}}_{9}$	5.8	*0.0*d)	33.8	13.3
$\mathbf{H}^{\mathbf{II}}_{9}$	50.7	46.0	48.8	47.3
$\mathbf{H}^{\mathbf{III}}_{9}$	125.1	129.6	158.7	126.2
$\mathbf{H}^{\mathbf{I}}_{12}$	21.8	30.6	*0.0*e)	1.8
$\mathbf{H}^{\mathbf{II}}_{12}$	66.0	75.0	26.4	44.5
$\mathbf{H}^{\mathbf{I}}_{14}$	*0.0*f)	3.4	24.6	*0.0*g)
$\mathbf{H}^{\mathbf{II}}_{14}$	73.5	81.4	84.6	n.a.
$\mathbf{H}^{\mathbf{III}}_{14}$	83.6	82.9	91.0	n.a.
$\mathbf{H}^{\mathbf{I}}_{17}$	34.1	73.0	44.9	22.3
$\mathbf{H}^{\mathbf{II}}_{17}$	96.1	107.9	95.9	n.a.
$\mathbf{H}^{\mathbf{I}}_{19}$	43.4	58.0	84.8	15.6
$\mathbf{H}^{\mathbf{II}}_{19}$	60.8	78.2	83.1	n.a.
$\mathbf{H}^{\mathbf{III}}_{19}$	81.8	85.9	88.0	n.a.
$\mathbf{H}^{\mathbf{I}}_{22}$	78.2	101.2	125.2	n.a.
$\mathbf{H}^{\mathbf{II}}_{22}$	82.0	103.5	124.6	n.a.
$\mathbf{H}^{\mathbf{I}}_{24}$	99.5	110.8	140.9	n.a.
$\mathbf{H}^{\mathbf{II}}_{24}$	101.8	97.1	133.5	n.a.

a) Relative energies in kJ/mol. b) $\varepsilon = 78.4$. c) Not available; *cf.* Text. d) $E_T = -1968.409228$ a.u. e) $E_T = -1956.409114$ a.u. f) $E_T = -1956.361656$ a.u. g) $E_T = -1956.413644$ a.u.

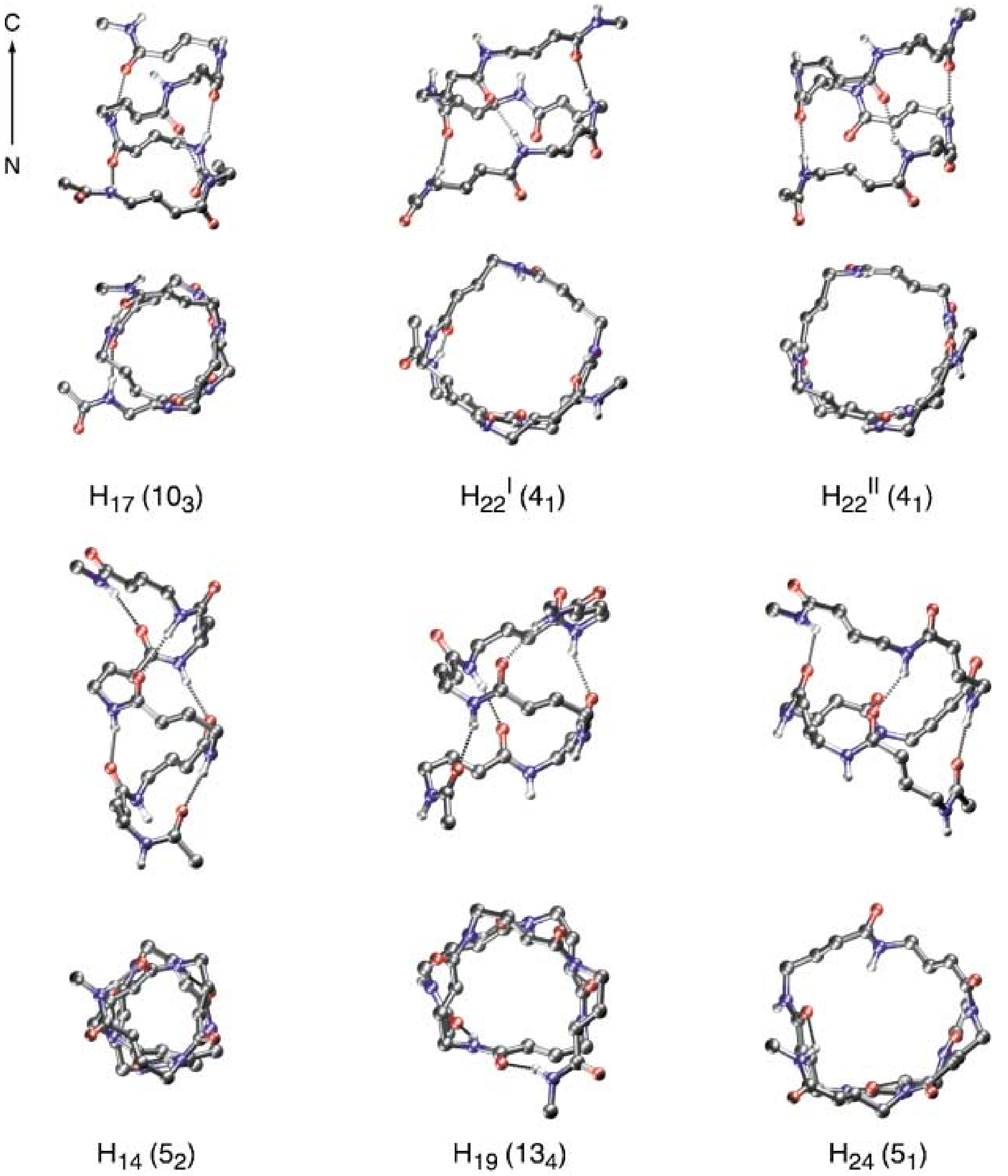
moment of $\mathbf{H}^{\mathbf{I}}_{12}$ ($\mu = 30.5$ D) in comparison to $\mathbf{H}^{\mathbf{I}}_{14}$ ($\mu = 24.8$ D) and $\mathbf{H}^{\mathbf{I}}_{9}$ ($\mu = 25.4$ D). The global dipolar component is of considerable importance in the *Onsager* reaction-field model and may be overestimated in the estimation of the solvation energy in relation to local solvation effects. The SCRF model, which simulates the solute in a sphere when contacting the solvent continuum, may anyway be too simple for such linear structures like those investigated here. The PCM model, however, should be more advantageous in such cases since the electrostatic interactions between solute and solvent are calculated on the basis of the actual molecular surface area in contact with the solvent continuum, thus describing local electrostatic effects much better. The PCM model predicts $\mathbf{H}^{\mathbf{I}}_{14}$ again as the most stable helix, followed by $\mathbf{H}^{\mathbf{I}}_{12}$ only 1.8 kJ/mol above and $\mathbf{H}^{\mathbf{I}}_{9}$ by 13.3 kJ/mol less stable. Obviously, these three forms are those most probably to be found in structure determinations on γ-peptides.

In previous papers, it was shown that the typical secondary-structure elements of β-peptides could be derived from conformers of the monomer constituents, even when H-bonding is still impossible and becomes visible only in longer sequences [46] [53] [54]. It has to be proved whether such a monomer approach might be sufficient to derive the periodic structures also for the γ-peptides. For the C_7 and C_9 pseudocycles, we find three conformers at the monomer level (*cf.* also [84]). In the case of the C_9 pseudocycles, which are more stable than the C_7 rings, these three monomeric conformers are, in fact, the basis for the hexamer structures in *Table 1*, whereas only two of the C_7 conformers are present in the corresponding hexamers. The third conformer changes its oligomer geometry into one of the two other periodic structures. Performing geometry optimizations on blocked monomers with the corresponding torsion-angle values of the helices with the larger pseudocycles provides an indifferent picture. In some cases, *e.g.*, $\mathbf{H^{I}_{14}}$, $\mathbf{H^{I}_{19}}$, $\mathbf{H^{III}_{19}}$, and $\mathbf{H^{II}_{12}}$, we find a change into smaller pseudocycles (C_9 and C_7). In other cases, the geometry optimization provides conformers with considerably different geometry. Only the basic conformation of the $\mathbf{H^{I}_{12}}$ helix is already present at the monomer level. Obviously, most of the higher secondary structures with characteristic H-bonding patterns in γ-peptides cannot immediately be derived from the conformer pool at the monomer level.

After the systematic conformational analysis on a γ-peptide hexamer, which provided a considerable number of conformers, it may be interesting to examine the consequences of the introduction of an (*E*)-double bond between the C(α) and C(β) atoms of the γ-amino acid constituents of the peptide backbone in the resulting vinylogous γ-peptides. In *Table 4*, the HF/6-31G* geometry data of all conformers with periodic H-bonding patterns of the hexamer **2** are summarized. Geometry information obtained at other approximation levels is again part of the *Supplementary Material*. *Table 5* presents the energy relationships between the conformers. Our investigations show some differences in comparison to the situation in the γ-peptides. As expected, structures with nearest-neighbor H-bonds like C_7 and C_9 cannot be formed due to the rigidity of the backbone after the introduction of the (*E*)-double bond. Even periodic structures with the larger C_{12} pseudocycles are not yet possible. Beginning with the pseudocycle C_{14} up to C_{24}, all periodic hexamer structures are again available. They are visualized in *Fig. 4*. None of the vinylogous γ-peptide conformers in *Table 4* can be derived from conformers at the monomer level. Starting geometry optimizations on blocked monomers with the torsion-angle values of the conformers in *Table 4* leads to considerable structure change. In contrast to the γ-peptides, there is only one representative for each ring size with exception of C_{22}, which is realized in the two helices $\mathbf{vH^{I}_{22}}$ and $\mathbf{vH^{II}_{22}}$. In any case, it can be seen that secondary-structure formation can *a priori* be directed to the formation of helices with larger pseudocycles by an appropriate type of rigidification of the peptide backbone. The backbone torsion-angle values are more restricted in the vinylogous γ-peptides in comparison to the γ-peptides. Whereas φ corresponds only to *sc*, and θ to *sp* and *ac* conformations, the torsion angle ψ assumes only values around 0° and 180°, respectively, due to conjugation effects.

In contrast to the γ-peptides, the most-stable conformers are $\mathbf{vH^{I}_{22}}$ at the HF/6-31G* level and $\mathbf{vH_{19}}$ at the B3LYP/6-31G* level (*Table 5*). Independent of the approximation levels, the energies of these two conformers are close together. This relationship is maintained when considering the solvent influence (*Table 5*). Despite the lesser number of H-bonds in the hexamer, the formation of the larger pseudocycles C_{19} and C_{22} is preferred over the formation of C_{14} pseudocycles in the vinylogous γ-peptides, which predominate in the γ-peptides. Besides, the relatively unstable $\mathbf{vH_{14}}$ conformer found in the vinylogous γ-peptide hexamer shows no strict correspondence to one of the three H_{14} conformers of the γ-peptide hexamer.

A detailed look at the structure of the rather stable $\mathbf{vH^{I}_{22}}$ helix of the vinylogous γ-peptides (*Fig. 4*) reveals a large inner diameter of *ca.* 3.5 Å. Thus, such structures could become important for the design of channels and tubes.



H_{17} (10_3) $H_{22}{}^{I}$ (4_1) $H_{22}{}^{II}$ (4_1)

H_{14} (5_2) H_{19} (13_4) H_{24} (5_1)

Fig. 4. *All periodic conformers of the vinylogous γ-peptide hexamer* **2** *obtained at the HF/6-31G* level of* ab initio *MO theory* (helix nomenclature in parentheses)

4. Conclusions. – Our systematic conformational search for periodic structures with characteristic H-bonding patterns in γ-peptides provides a wide variety of structure alternatives. In comparison to β-peptides, the homolongation of the peptide backbone increases the number of structures with definite backbone conformations and H-bonds

Table 4. *Backbone Torsion Angles of Conformers of the Blocked Vinylogous γ-Peptide Hexamer* **2** *with H-Bonds Formed in Backward and Forward Direction Obtained at the HF/6-31G* Level of* ab initio *MO Theory*[a])

Conformer	φ	θ	ψ	Conformer	φ	θ	ψ
vH$_{14}$	71.4	18.2	164.2	**vH$_{17}$**	−166.6	−132.5	24.2
	65.1	15.4	163.7		84.7	−107.1	38.7
	65.6	16.9	160.5		93.6	−100.6	41.0
	66.0	16.8	161.4		83.5	−101.1	49.2
	67.6	15.1	155.1		84.2	−99.0	44.8
	81.6	−3.8	177.3		82.3	−93.9	45.6
vH$_{19}$	79.3	10.9	−175.8	**vH$^{I}_{22}$**	118.5	117.6	165.3
	70.1	33.1	−174.2		74.1	107.3	157.3
	80.0	16.6	−172.6		66.6	109.0	158.4
	83.4	16.1	−179.8		72.1	108.0	158.1
	87.8	14.3	−175.7		70.3	108.5	159.4
	114.5	−2.9	−176.0		73.3	130.5	−174.9
vH$_{24}$	77.2	−125.9	32.9	**vH$^{II}_{22}$**	103.6	−123.5	31.6
	76.3	−127.1	39.2		100.3	−116.7	35.8
	81.7	−116.2	−33.1		96.1	−110.4	37.3
	98.4	−117.3	30.5		90.4	−107.9	38.8
	94.2	−117.3	−18.8		85.9	−106.4	41.6
	103.4	−131.5	−20.6		87.5	−105.1	40.1

[a]) Torsion angles in degrees.

Table 5. *Relative Energies of Conformers of the Blocked Vinylogous γ-Peptide Hexamer* **2** *Obtained at Various Levels of* ab initio *MO Theory*[a])

Conformer	ΔE			
	HF/6-31G*	B3LYP/6-31G*	SCRF/HF/6-31G*[b])	PCM//HF/6-31G*[b])
vH$_{14}$	39.9	25.0	27.5	63.0
vH$_{17}$	67.2	57.2	44.3	82.5
vH$_{19}$	5.3	*0.0*[c])	*0.0*[d])	6.4
vH$^{I}_{22}$	*0.0*[e])	10.8	14.8	*0.0*[f])
vH$^{II}_{22}$	66.9	70.8	70.7	53.3
vH$_{24}$	74.7	77.4	55.1	53.3

[a]) Relative energies in kJ/mol. [b]) $\varepsilon = 78.4$. [c]) $E_T = -1960.996152$ a.u. [d]) $E_T = -1949.245753$ a.u. [e]) $E_T = -1949.211533$ a.u. [f]) $E_T = -1949.283589$ a.u.

formed in forward and backward directions along the sequence. All H-bonded pseudocycles with ring sizes between C_7 and C_{24} are formally represented. In most cases, there are several possibilities to realize identical H-bonding patterns. In good agreement with experimental data, periodic structures with 14- and 9-membered pseudocycles are most stable.

It can be shown that the introduction of a (*E*) double bond into the backbone of the γ-amino acid constituents supports the formation of helices with larger H-bonded pseudocycles in the corresponding vinylogous γ-peptides, since closer rings cannot be formed any longer by this type of backbone modification. Special influence on the folding properties of γ-peptides and their vinylogues could also be expected from different substituent patterns at the backbone C-atoms.

Our study demonstrates the enormous potential for secondary-structure formation in γ-peptides and their vinylogues, which is promising for peptide and protein design.

Support of this work by *Deutsche Forschungsgemeinschaft* (Projekt HO 2346/1 '*Sekundärstrukturbildung in Peptiden mit nicht-proteinogenen Aminosäuren*' and SFB 610 '*Proteinzustände von zellbiologischer und medizinischer Relevanz*') is gratefully acknowledged.

Supplementary Material Available. Tables of the backbone torsion angles in conformers of the γ-peptide hexamer **1** and its vinylogue **2** at the SCRF/HF/6-31G* and DFT/B3LYP/6-31G* levels. See any current masthead page for ordering information and Internet access instructions.

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Received January 29, 2003