Theoretical Prediction of Substituent Effects on the Intrinsic Folding Properties of β-Peptides

by **Robert Günther**[1]) and **Hans-Jörg Hofmann***[2])

Fakultät für Biowissenschaften, Pharmazie und Psychologie, Institut für Biochemie, Universität Leipzig, Talstraße 33, D-04103 Leipzig

Dedicated to Prof. Dr. *Peter Welzel* on the occasion of his 65th birthday

A systematic conformational analysis on blocked β-amino acids as constituents of β-peptides by *ab initio* MO theory reveals that the conformer pool of β-peptide monomers is essentially determined by the conformation of simple submonomer fragments. The influence of single and multiple substitutions at the C(α) and C(β) backbone atoms on the intrinsic folding properties of the monomers was estimated both in the single-molecule approximation and in a polar solvent continuum, applying a quantum-chemical SCRF model. Substitution at C(β) has a higher impact on the β-amino acid conformation than a substitution at C(α). It can be shown that the conformations of important periodic secondary structures in β-peptides belong to the conformer pool of the monomers, even for those secondary-structure elements where H-bond formation appears only in longer sequences. Rules for design of special secondary-structure types by selection of an actual substituent pattern in the β-amino acid constituents have been derived within the monomer approach.

1. Introduction. – In recent years, oligomers of β-amino acids, called β-peptides, have gained much attraction because of their ability to form well-ordered secondary structures [1–6], *e.g.*, β-strand-like conformers [7–9], reverse turns [10–14], and, in particular, helices with differing H-bonding patterns [15–34]. Some representatives are stable against proteases [35–37] and can be translocated across the cell membrane [38][39], which makes β-peptides possible candidates for pharmacological applications [40–49]. In comparison to α-amino acid constituents, β-amino acids offer a much greater number of different substituent patterns, which should influence the secondary-structure formation in peptide sequences. Therefore, it might be useful to look for the intrinsic folding properties in β-peptide models with substituents in various positions.

It is a tempting approach to derive the characteristic secondary structures in peptide sequences from the conformational properties of the monomer constituents (monomer approach). Numerous systematic conformational analyses on blocked α-amino acids and unnatural amino acids have been reported [50–74]. These theoretical studies, employing molecular-orbital (MO) theory and empirical force fields, indicate that most of the typical secondary structures found in peptides and proteins already belong to the conformer pool of the monomers. This concerns even those secondary-structure elements that are characterized by H-bond formation between amino acid residues that are more or less distant in the sequence. Obviously, H-bonds may significantly influence the stability relationships between competing folding alternatives, but they are not the driving force for the formation of the corresponding conformers themselves.

---

[1]) Part of the Ph. D. Thesis of *R. G.*, Universität Leipzig, 2001

[2]) e-mail: hofmann@rz.uni-leipzig.de

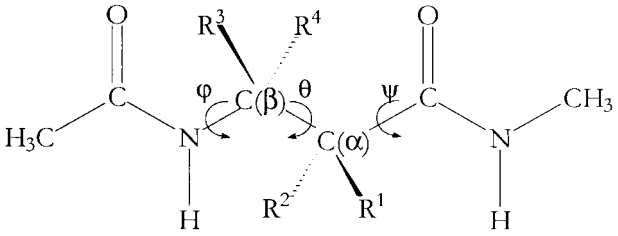
As in the case of α-peptides, theoretical conformation analyses on selected monomers of β-peptides provided a good overview of the possibilities of secondary-structure formation and enabled particularly the prediction of periodic secondary structures in this class of compounds [68–74]. It is an advantage of the monomer approach to realize complete conformational analyses at relatively high levels of *ab initio* MO theory. Of course, one has to keep in mind that further secondary-structure elements might appear only in longer sequences providing novel possibilities of structuring. Besides, the stability relations between various structure alternatives might cooperatively change with increasing sequence length as a comparison of the 2.2_7-ribbon, the 3_{10}-, and the α-helices shows [59][75–77]. However, since a β-peptide constituent has three backbone-conformation angles, φ, θ, and ψ (*cf. Table 1*), a systematic grid-based conformational search on β-amino acid oligomers becomes more and more difficult at higher levels of MO theory. The employment of empirical force fields might be an useful alternative in a search for secondary-structure elements in longer sequences that were not found in the monomer approach, or in investigations of cooperativity effects. This was successfully shown in numerous molecular-dynamics simulations on various β-peptide oligomers [78–80].

In this paper, a systematic conformational analysis was performed on blocked β-amino acids, considering all possible substituent patterns, employing *ab initio* MO theory. In particular, we focused on the influence of multiple substitutions on the intrinsic folding propensities of the various β-peptide monomers. The role of single substitutions was partially described in preceding papers [70–72], but is considered here again to generalize and to understand the influence of the various substituent patterns on folding in this novel class of peptide mimetics. The derivation of some general rules of β-peptide folding, which might be useful for the design of special structure types, is attempted.

2. Methods. – To examine the influence of disubstitution, systematic conformational analyses on the blocked β-amino acid monomers **aA**, **bB**, **aB**, and **AB** were performed in analogy to the procedure previously described in the investigations of the unsubstituted compound **U** and the monosubstituted derivatives **A** and **B** [70]. In our notation, the small letters **a** and **b** designate Me substituents in (*R*)-configuration at the C(α) and C(β) backbone atoms, respectively, and the capital letters **A** and **B** Me substituents in the corresponding (*S*)-configurations (*cf. Table 1*). All combinations of values of $-180°$, $-120°$, $-60°$, $0°$, $60°$, and $120°$ were assigned to the three dihedrals φ, θ, and ψ. The resulting 6^3 starting conformations were optimized at the HF/3-21G level of *ab initio* MO theory followed by re-optimization of the obtained conformers at the HF/6-31G* level. The resulting stationary points were characterized by the eigenvalues of the force constant matrices. Thus, calculation of the free energy differences between the various conformers becomes possible, too. For selected minimum conformations, the influence of correlation energy was estimated at the B3LYP/6-31G* level of density-functional theory (DFT).

Whereas pairs of energetically equivalent conformers with torsion-angle values differing only by sign exist in the **aA** and **bB** series for identical substituents, only approximated backbone mirror-image conformers can be expected for the model compounds **aB** and **AB**. In all cases, where such an approximated mirror image of any

Table 1. *Substituent Patterns of the Investigated β-Amino Acid Model Compounds*



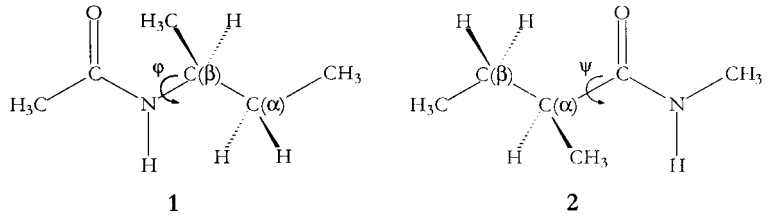
Compound	R^1	R^2	R^3	R^4	Symbol
Ac-[β-hAla]-NHMe	H	H	H	H	**U**
Ac-[(*S*)-β^2-hAla]-NHMe	Me	H	H	H	**A**
Ac-[(*S*)-β^3-hAla]-NHMe	H	H	Me	H	**B**
Ac-[$\beta^{2,2}$-hAla]-NHMe	Me	Me	H	H	**aA**
Ac-[$\beta^{3,3}$-hAla]-NHMe	H	H	Me	Me	**bB**
Ac-[(*R*,*S*)-$\beta^{2,3}$-hAla]-NHMe	H	Me	Me	H	**aB**
Ac-[(*S*,*S*)-$\beta^{2,3}$-hAla]-NHMe	Me	H	Me	H	**AB**
Ac-[$\beta^{2,2}$-(*S*)-β^3-hAla]-NHMe	Me	Me	Me	H	**aAB**
Ac-[(*S*)-$\beta^2\beta^{3,3}$-hAla]-NHMe	Me	H	Me	Me	**AbB**
Ac-[$\beta^{2,2}\beta^{3,3}$-hAla]-NHMe	Me	Me	Me	Me	**aAbB**

determined conformer was not found in the grid-based conformational search, the signs of the torsion angles of the obtained conformers were reversed, and the corresponding structure was optimized to test for alternate handedness. Additionally, all conformers obtained by the *ab initio* calculations on the unsubstituted and substituted β-amino acids in previous studies [67][70–73], but not found in the other series by the above-described procedures, served also as starting points for complete geometry optimizations of all other model compounds. Finally, conformational-grid searches for the (φ, θ, ψ) conformation space in 30° intervals were performed with the CHARMm 23.1 all-atom force field [81][82] as it is incorporated in the Quanta98 program package (*Molecular Simulations*, *Inc.*, San Diego, CA) with atom charges calculated according to *Gasteiger* and *Marsili* [83]. Minimum conformations additionally found in this way served again as starting points for HF/3-21G and HF/6-31G* optimizations. On the basis of all these calculations, the conformer search in the (φ, θ, ψ) space of the various β-peptide models might be considered as complete.

Solvation effects are expected to have a remarkable influence on the stability and conformation of molecules. Therefore, a quantum-mechanical version of the *Onsager* model (self-consistent reaction field, SCRF) was employed for the estimation of these effects. Although the medium influence on peptide properties might considerably be realized by specific solute-solvent interactions, such a continuum approach could provide at least a reliable trend estimation of the solvation influence on the stability and geometry changes of the conformers. A dielectric constant of $\varepsilon = 78.4$ was selected to model an aqueous environment. The molecular radii necessary for the solute molecules in these calculations were estimated from the *Connolly* surface areas of the gas-phase conformers. Starting from the HF/3-21G and HF/6-31G* gas-phase minimum conformations, complete geometry optimizations at the HF/6-31G* level were also performed in the SCRF calculations.

The Gaussian98 (*Gaussian Inc.,* Pittsburgh, MA) and Spartan4.1 (*Wavefunction, Inc.*, Irvine, CA) program packages were employed for all quantum-chemical calculations.

3. Results and Discussion. – 3.1. *General Possibilities of Backbone Folding in β-Peptides.* To get a first idea of the general role of substituents for structuring in a β-peptide constituent, the consequences of monosubstitution at the backbone atoms C(α) and C(β) on the rotation around the N–C(β) and C(α)–C bonds were examined independently from each other. For this purpose, the model compounds **1** and **2** were chosen as the N-terminus of an (*S*)-C(β)-substituted β-amino acid and the C-terminus of an (*S*)-C(α)-substituted β-amino acid, respectively. The energy profiles for the rotation around the N–C(β) bond in **1** described by the torsion angle φ and for the rotation around the C(α)–C bond in **2** described by the torsion angle ψ were calculated at the HF/6-31G* level of *ab initio* MO theory (*Fig. 1*).



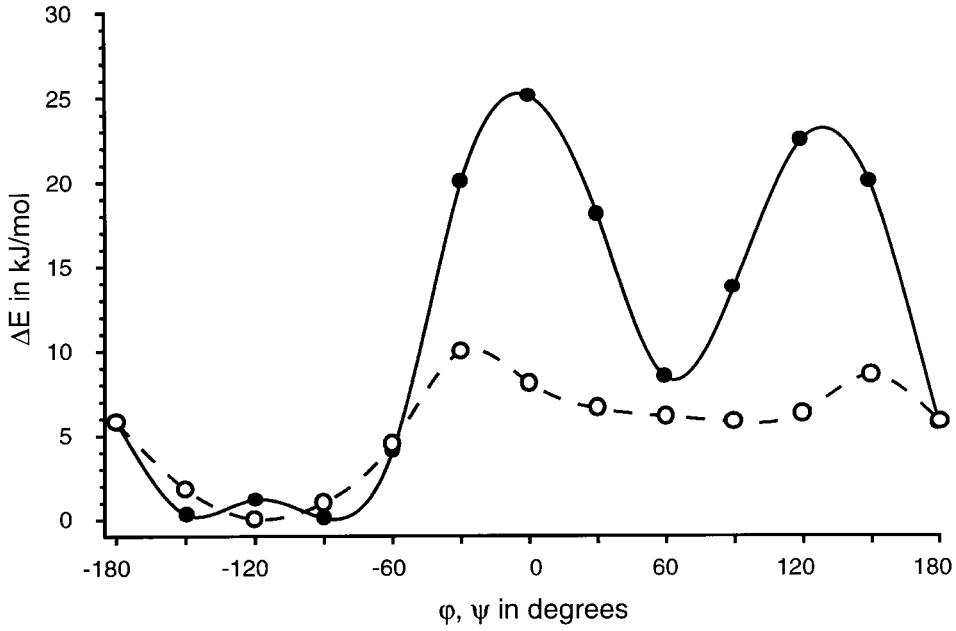


Fig. 1. *HF/6-31G* Energy profiles for the rotation around the backbone dihedrals in the model compounds* **1** (φ, closed circles) *and* **2** (ψ, open circles)

Fig. 1 shows that (*S*)-substitution at C(β) in **1** distinctly favors conformations in between $\varphi = -180°$ and $-60°$ with two shallow minima near $-150°$ and $-90°$, respectively, corresponding to the NH functionality *syn-clinal* (*sc*) to the Me substituent (nomenclature according to [84]). Another minimum region at *ca.* $\varphi = 60°$ is *ca.* 9 kJ/mol above the global minimum and separated by a relatively high barrier of *ca.* 24 kJ/mol. Similar results were obtained in theoretical studies on *N*-isopropylformamide [74]. The rotation around the C(α)–C bond in **2** described by ψ is less hindered. As shown in *Fig. 1*, conformations with ψ at *ca.* $-120°$ are preferred, a second very flat minimum region ranges from 30° to 120°. It is *ca.* 6 kJ/mol above the global minimum and separated by a barrier of only *ca.* 10 kJ/mol. In a first approximation, the conformation characteristics of the two model fragments should essentially be reflected in the conformer pools of the various peptide model compounds provided that linking of the C(α)- and C(β)-atoms does not cause special structuring effects. Possibly, a greater influence on structuring could be expected from substituents at C(β) affecting φ, than from substituents at C(α) influencing ψ. This conclusion is clearly confirmed by the torsion-angle data for the conformers of the monosubstituted β-amino acid model compounds **A** and **B** presented in our preceding paper ([70], *cf.* also [71][72]).

Linking the fragments **1** and **2** leads to a complete β-amino acid constituent. Because of the nature of the connecting C–C single bond, *syn-clinal* (*sc*), *anti-clinal* (*ac*), and *anti-periplanar* (*ap*) orientations should predominate in the rotation profile characterized by the torsion angle θ. In fact, a search in the *Cambridge Structural Data Base* and NMR data reveal that the *sc* and *ap* conformations are distinctly preferred in β-alanine-containing derivatives [67][85]. Thus, the backbone torsion angles of the conformers of the β-amino acid constituents should basically correspond to combinations of those of the various conformers of the fragments **1** and **2**, and the optimum angle values for θ. The results of the systematic conformational searches for **U**, **A**, and **B** [70][71] are in good agreement with this generalization, and it has to be examined whether this can be kept for the disubstituted derivatives.

3.2. *Conformer Pools of Disubstituted β-Amino Acid Constituents.* The conformers of the disubstituted β-amino acid model compounds **aA**, **bB**, **aB**, and **AB**, and the energy differences between them obtained at the HF/6-31G* level of *ab initio* MO theory are presented in *Table 2*. For comparison, the free-energy data, which show close correspondence, are given in the *Supporting Information*. In agreement with the results of the *ab initio* calculations on β-amino acid derivatives [67][70–73], conformers with six- and eight-membered H-bonded pseudocycles (C_6, C_8) are most stable in the four disubstituted model compounds. Interestingly, the global minimum of the blocked β-amino acid **bB** with disubstitution at C(β) realizes a C_8 conformer, whereas the other model compounds prefer a C_6 structure (*Fig. 2*). In the case of disubstitution at C(α) (**aA**), the C_6 structure remains most stable possibly due to a smaller influence of substituents at C(α) on the backbone conformation as already shown in *Fig. 1*.

The global minima of the various monomers are followed by a group of other C_6 and C_8 conformers of comparable energy in all cases. A further group of minimum conformations contains the basic conformers of helical structures with larger H-bonded pseudocycles C_x, although the structural prerequisites for H-bonding are not yet fulfilled in the blocked monomers. Because of their close relationship to the helical

Table 2. *Torsion Angles* (in degrees) *and Relative Energies* (in kJ/mol) *of the Minimum Conformations of the Disubstituted β-Amino Acids Model Compounds Obtained at the HF/6-31G* Level of* ab initio *MO Theory*

Conf.	φ	θ	ψ	ΔE[a)]	Type[b)]	Conf.	φ	θ	ψ	ΔE[a)]	Type[b)]
aA1	−110.1	−61.7	−178.2	**0.0**[c)]	C_6	**bB1**	55.3	47.4	−108.4	**0.0**[c)]	C_8
aA2	−115.1	63.4	22.2	2.8[c)]	C_8	**bB2**	177.7	60.4	118.6	2.4[c)]	C_6
aA3	103.9	176.0	120.9	14.2		**bB3**	56.7	57.3	166.3	5.2	C_6
aA4	−86.8	124.0	−52.1	16.7	C_8	**bB4**	63.7	−171.2	116.4	10.7	
aA5	110.9	54.2	45.6	17.7	H_{10}	**bB5**	−59.0	127.2	−91.4	14.6	C_8
aA6	−144.4	63.1	−124.2	25.5	H_{14}	**bB6**	176.6	57.3	−99.9	20.8	C_N
aA7	−64.9	93.3	−132.0	26.2	H_{12}	**bB7**	77.6	−45.0	−96.6	21.2	
						bB8	−179.2	175.9	−107.7	23.9	
aB1	−146.4	−67.5	−126.0	**0.0**[c)]	C_6	**bB9**	−179.8	70.7	−42.8	25.7	C_N
aB2	−66.9	−47.3	111.9	0.1[c)]	C_8	**bB10**	−95.3	77.7	−23.0	27.0	C_8
aB3	−87.3	−53.1	161.9	0.3[c)]	C_6						
aB3′	90.9	69.4	156.0	11.9	C_6	**AB1**	−144.7	−64.6	−130.6	**0.0**	C_6
aB4	−159.3	57.8	100.0	3.4[c)]	C_6	**AB2**	−75.8	154.9	−83.6	8.2	'C_8'[d)]
aB5	−114.5	72.4	8.4	4.3[c)]	C_8	**AB2′**	71.1	−109.1	70.6	31.4	C_8
aB5′	103.3	−65.5	−6.5	27.9	C_8	**AB3**	59.4	45.6	−115.9	8.6	C_8
aB6	−93.8	54.4	87.7	4.8[c)]		**AB4**	−114.9	49.3	41.9	12.5	C_8
aB6′	81.4	−50.6	−90.0	27.3		**AB5**	−156.0	48.6	84.0	14.9	C_6
aB7	63.3	172.7	129.6	5.7		**AB6**	−112.6	−66.9	81.4	20.6	
aB7′	−105.0	178.0	−65.1	10.3		**AB7**	−154.2	56.7	−120.0	22.1	H_{14}
aB8	−83.2	122.5	−53.1	9.0	C_8	**AB8**	−117.0	69.3	−97.3	27.6	H_{12}
aB8′	63.1	−129.1	87.8	11.8	C_8	**AB9**	80.1	−47.8	−95.1	29.2	
aB9	−108.9	179.0	135.4	9.3		**AB10**	61.4	57.2	95.4	29.4	H_{10}
aB9′	62.7	172.8	−69.6	24.7		**AB11**	−156.5	−66.5	25.8	33.7	C_N
aB10	−66.7	100.9	−127.4	20.3	H_{12}	**AB12**	67.5	136.1	−150.5	34.2	
aB11	−157.9	62.0	−112.2	23.0	H_{14}	**AB13**	87.5	158.2	127.3	34.4	
aB12	−159.0	−72.5	37.7	26.1	C_N						

[a]) Total energies of the most stable conformers. **aA**: $E_T = -570.927948$ a.u., **bB**: $E_T = -570.929923$ a.u., **aB**: $E_T = -570.928331$ a.u., **AB**: $E_T = -570.931911$ a.u. [b]) C_x: H-bonded cycle with x atoms. C_N: six-membered H-bonded pseudocycle with an NH···N H-bond. H_x: monomer of a helix with x-membered H-bonded turns. [c]) Relative energies at the DFT/B3LYP/6-31G* level. **aA1**: 3.0 kJ/mol, **aA2**: 0.0 kJ/mol (−574.480159 a.u.); **bB1**: 0.0 kJ/mol (−574.481805 a.u.), **bB2**: 0.4 kJ/mol; **aB1**: 0.0 kJ/mol (−574.480652 a.u.), **aB2**: 3.1 kJ/mol, **aB3**: → **aB1**, **aB4**: 4.6 kJ/mol, **aB5**: 0.9 kJ/mol, **aB6**: 9.2 kJ/mol. [d]) *Cf.* text.

structures, these conformers are denoted by H_x. Some special conformers denoted by C_N exhibit H-bonds between two N-atoms, the one as a proton donor and the other as a proton acceptor. Since these conformers are of relatively high energy in comparison to the global-minimum structure, they should not play an essential role in the formation of characteristic secondary structures in β-peptides. The fully extended form of **bB** was found to be a stationary point of higher order on the potential hypersurface. Therefore, it deserves no further consideration. Some of the conformers are less than 5 kJ/mol above the corresponding global minimum. These structures were reoptimized at the DFT/B3LYP/6-31G* level. The data in *Table 2* reveal that the inclusion of correlation energy does not significantly change the stability order.

As already mentioned, the central torsion angle θ corresponds closely to *sc, ap*, and *ac* conformations, respectively, with the *sc* and *ap* ones preferred in the majority of

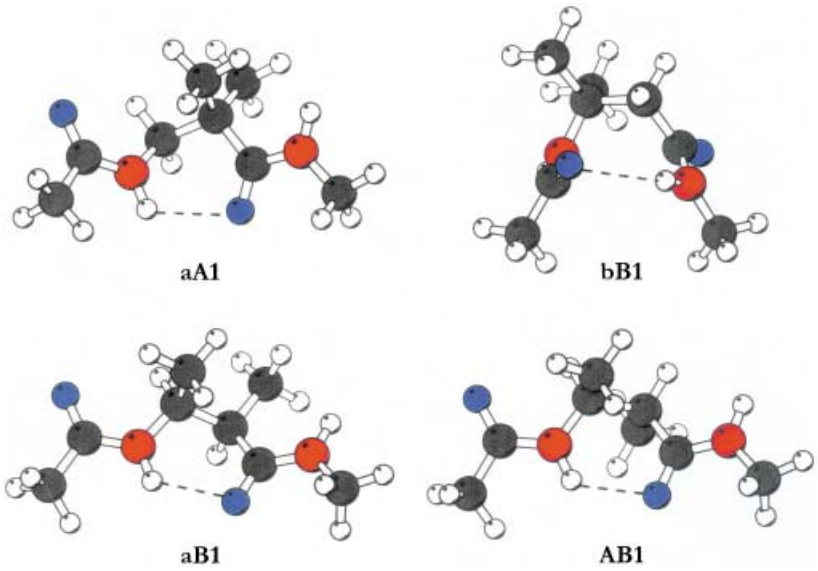


Fig. 2. *Global-minimum conformations of the disubstituted β-amino acid model compounds* **aA**, **bB**, **aB**, *and* **AB**

cases. Nearly two-thirds of all conformers with θ close to 180° were obtained for the (*R,S*)-C(α),C(β)-disubstituted model compound **aB**. In this β-amino acid derivative, the minimum structure with $\theta \approx 180°$ (**aB7**) is only by 5.7 kJ/mol less stable than the global-minimum conformer. This is in excellent agreement with experimental data showing an extended conformation of an (*R,S*)-C(α),C(β)-disubstituted β-amino acid as the preferred structure with the side chains pointing in opposite directions [7–10][86]. This situation is completely different in the alternate vicinally disubstituted model compound **AB**. Here, conformers with an extended structure were not found. Almost all conformers exhibit the *sc* conformation for θ. Interestingly, there is also a low-energy conformer of this β-amino acid model compound with the central backbone dihedral in between the *ac* and *ap* orientations (**AB2**). Although rather similar to a C_8 structure, the distance between the C-terminal peptide O-atom and the N-terminal peptide H-atom is much longer than in typical H-bonds, due to the repulsion of the Me side chains. Consequently, θ corresponds to a more-extended conformation in comparison to an ideal C_8 conformer. Despite the missing H-bond, this conformer is still by *ca.* 23 kJ/mol more stable than the approximate mirror image conformer **AB2′**, which exhibits H-bonding (*Fig. 3*). This is caused by the preference of negative φ values for this type of a C(β)-substitution.

Analyzing the results obtained for the geminally disubstituted β-amino acid derivatives, the conformational flexibility seems to be less restricted in **aA** than in **bB** indicated by the smaller number of conformers. This reflects well the conclusions drawn from the energy profiles for the rotations around the N–C(β) and C(α)–C bonds in the model fragments **1** and **2**, respectively (*cf. Fig. 1*). Moreover, these data support considerably the results from previous studies showing that substitutions at C(β) have a higher impact on the backbone flexibility than substitutions at C(α) [70]. Due to the

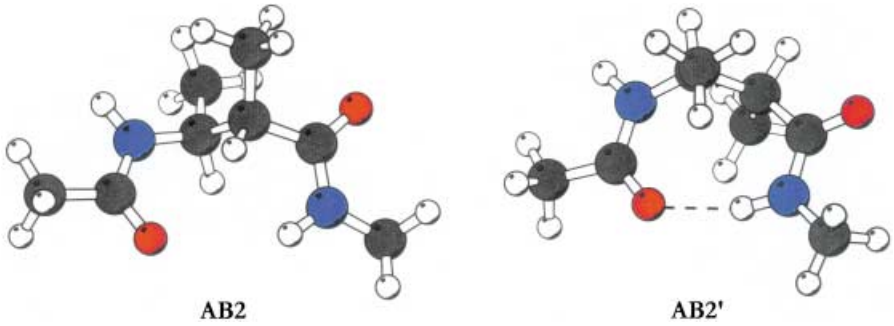


Fig. 3. *Comparison of the* C_8 *minimum structures* **AB2** *and* **AB2′**

geminal disubstitution with the same substituents in **aA** and **bB**, each minimum conformation of these compounds has an energetically equivalent mirror-image conformer, whose torsion angles differ only by sign. Thus, helices of alternate handedness have also the same energy and are formed with the same probability. This equivalence gets lost in the disubstituted β-amino acid models **aB** and **AB**, and, of course, for geminal disubstitution with different substituents. In these cases, the position of the side chains should have a great influence on the formation of secondary-structure elements, as it was already shown in the comparison of the conformers **AB2** and **AB2′**. Thus, it could be possible to determine not only the helix type, but also its handedness by the selection of the substitution pattern.

Our theoretical results for the conformation characteristics of mono- and disubstituted β-amino acid constituents are in good agreement with experimental data collected on numerous β-amino acid derivatives. Since most of the structural features are valid for different substitution patterns of β-peptide monomers, only selected minimum conformations will be discussed. The C_6 and C_8 conformers can be assigned to two and three structure families denoted by (C_6^{I}, C_6^{II}) and (C_8^{I}, C_8^{II}, C_8^{III}), respectively (*Fig. 4*). C_6 Conformers have not been observed in linear β-peptides so far. Investigations on various polyamides show that nearest-neighbor interactions in H-bond formation, although relatively stable according to the calculations, seem to be of minor importance in reality [87–89]. In fact, most of the experimental data hint to the larger C_8 pseudocycles, which can be compared with the γ-turns in α-peptides. The C_8^{II} minimum structure **aA2**, which corresponds formally to the minimum structures **aB5**/**aB5′** and **AB4** in *Table 2*, was confirmed by X-ray diffraction experiments on the C(α),C(α)-disubstituted 1-(aminomethyl)cyclopropanecarboxylic acid [90]. This type of C_8 conformation is also reflected in the corresponding C(β),C(β)-disubstituted model compound **bB** (**bB10**). Here, the (*R*)-side chain is in a *pseudo-equatorial* position due to the H-atom at the N-terminal peptide group. However, the alternate C_8^{III} conformer (**bB1**) is much more favored and is the most-stable structure in **bB**. It was also observed in the β-amino acid analogue of proline as part of a turn structure [91].

The formation of periodic secondary structures in oligomers of β-amino acids, in particular helices with characteristic H-bonding patterns, was one of the most important findings in β-peptide research. Remembering that the conformational properties of monomer units already reflect structural features of characteristic

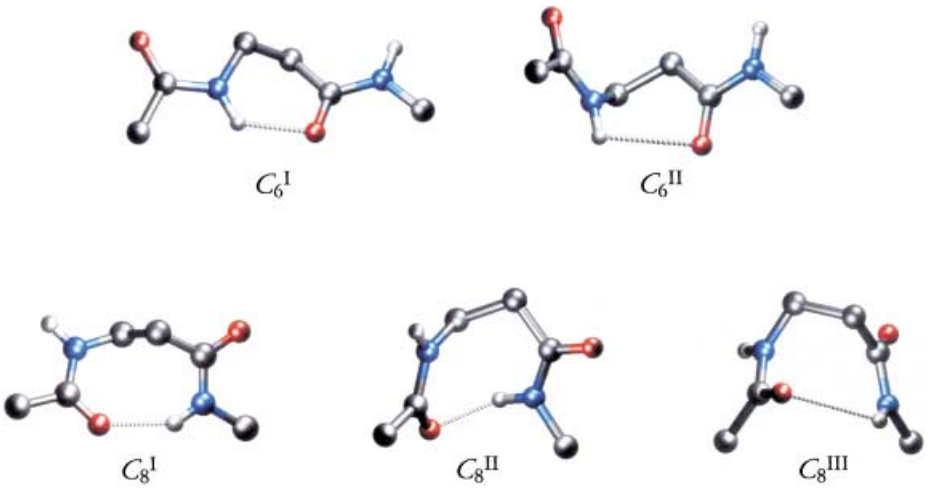


Fig. 4. *Basic* C_6 *and* C_8 *conformations of β-peptide constituents*

secondary structures formed in longer sequences, it might be interesting to look at whether these β-peptide structures could be derived from the monomer properties presented in *Table 2*. The formal possibilities of H-bonding in forward (N- to C-terminal) and backward (C- to N-terminal) direction along the sequence are illustrated in *Fig. 5*. As already pointed out in our previous study on the **U**, **A**, and **B** monomers [70], oligomers of the various C_6 conformations could easily be thought of, since H-bonding occurs within the same β-amino acid unit ($1 \rightarrow 1$ interaction, nomenclature according to [92]). Periodic structures of C_6 conformers could formally be described as H_6 helices, although they are more sheet- or ladder-like. Molecular-dynamics studies revealed an H_6 structure for oligomers of the C_6 conformer **bB2** in *Table 2* as a free-energy minimum [78], which resembles common β-strand structures of α-peptides. Other sheet-like alternatives in β-peptides are oligomers of C_8 conformers with the H-bonds formed in backward direction. Although the H-bonded pseudocycle involves three residues ($1 \leftarrow 3$ interaction), nonperiodic and periodic oligomers can be constructed from all C_8 conformers in any combination. A periodic secondary structure consisting of four C_8^{I} units (H_8) of the C(β)-monosubstituted β-amino acid **B** was predicted by *ab initio* calculations to be of comparable stability to the experimentally determined H_{14} and H_{12} helices [70]. Oligomerization of C_8^{II} conformers such as **aA2** leads to a twisted sheet-like structure, which formally could also be considered as an H_8 helix. This secondary structure was indeed realized in crystals of oligomers consisting of 1-(aminomethyl)cyclopropanecarboxylic acids [90]. Oligomers of α-aminoxy acids and α-hydrazino acids, derived from β-amino acids by replacement of the C(β)-backbone atom by O- and N-atoms, respectively, adopt an equivalent secondary structure [64][65][93–95]. Thus, this secondary-structure type can be considered a general conformational feature of oligomers of β-amino acids and their derivatives.

Although the prerequisites for the formation of a 14-membered H-bonded ring, where the H-bond is formed between the peptidic NH of amino acid *i* and the peptidic

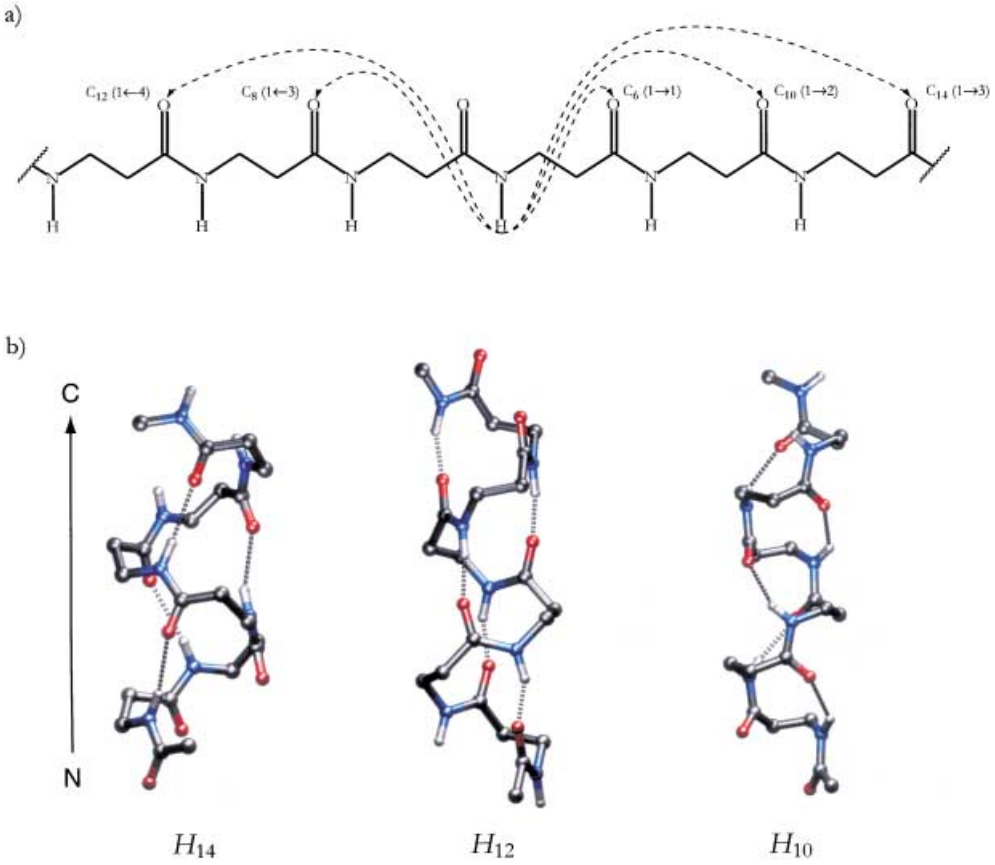


Fig. 5. *Possible H-bonding patterns in β-peptide sequences* (a) *and representatives of selected β-peptide helix models* (b)

CO of amino acid *(i+2)* ($1 \rightarrow 3$ interaction), are not yet fulfilled in the blocked β-amino acids, the basic unit of a H_{14} helix (*cf. Fig. 5*) can be localized as a conformer in the model compounds **aA**, **aB**, and **AB**. The calculated torsion-angle values of the minimum structures **aA6**, **aB11**, and **AB7** are in excellent agreement with experimental data obtained for oligomers of β-amino acid derivatives of the type **B** and **AB**, respectively [15–22][25–33]. Furthermore, X-ray studies on peptides with single β-amino acids incorporated into α-peptide sequences showed that the β-amino acid residue exhibits values of the backbone torsion angles similar to those found in H_{14} helices, although the structural prerequisites for H-bonding are still missing [96–98]. This confirms that the origin of helix formation is basically founded in the conformational properties of the backbone. However, at the monomer level, such conformers are often of higher energy than competing structures and are, therefore, not experimentally observed. Only in longer sequences, where appropriate H-bonds can be formed, these secondary structures predominate.

As already mentioned, substituents at C(β) should influence the formation of characteristic minimum structures more strongly than substituents at C(α). Thus, substituents at C(β) in (*S*)-position lead to a significant preference of conformers with negative values for the dihedral φ according to the energy profile in *Fig. 1*. As a consequence, the left-handed (*M*)-conformation of the H_{14} monomer is preferred. It should be emphasized, that **aA** is the only model compound investigated without C(β)-substitution that exhibits an H_{14} conformer as a minimum structure. Contrary to this, no corresponding conformer was obtained for the C(β),C(β)-disubstituted β-amino acid **bB**. Regarding a monomer unit in a H_{14} conformation, one substituent at C(α) in **aA** is oriented parallel to the N–H bond of the C-terminal peptide bond. In the corresponding idealized H_{14} conformation of **bB**, one C–Me bond would be parallel to the C–O bond of the N-terminal amide group. Considering the different atom sizes of the H- and O-atoms, the (*R*)-Me group in **bB** is too close to the O-atom. This could also explain why a right-handed conformer was not found for the (*S*)-substituted β-peptide monomer until now, which is in good agreement with the substituent influences on the backbone dihedrals φ and ψ discussed for the model compounds **1** and **2** (*Fig. 1*). Another periodic secondary structure, which can immediately be derived from the conformers in *Table 2*, is the H_{12} helix [26–29] (*Fig. 5*) with twelve-membered H-bonded pseudocycles formed between the peptidic NH of amino acid *i* and the peptidic CO of amino acid *(i–3)* ($1 \leftarrow 4$ interaction). With exception of the geminally disubstituted derivative **bB**, all model compounds investigated show the basic unit of this helix in their conformer pool (*Table 2*). Up to now, this helical structure was only observed in oligomers of conformationally restricted β-amino acid derivatives, where the central rotation angle θ is locked to values of *ca.* 90° [26–29][99][3]). Nevertheless, similar to the situation of the H_{14} monomer, this conformation could also be observed in crystals of Boc-[Aib]$_2$-[β-hGly]-NHMe, where a single β-amino acid is incorporated into an α-peptide sequence [100]. In those cases, where both the H_{14} and the H_{12} conformers were located, the H_{14} conformers are energetically favored over the H_{12} ones. This does not hold for the (*R,S*)-C(α),C(β)-disubstituted model compound **aB**. However, it is not possible to decide whether the H_{12} conformation (**aB10**) is *per se* preferred over the H_{14} conformation (**aB11**) in this case, or whether the H_{14} conformation is destabilized due to sterical hindrance. It is interesting that the H_{12} conformation is right-handed despite the (*R*)-configuration of the substituent at the C(α)-atom, which should normally result in left-handed monomers, as shown for the corresponding monosubstituted model compound **A**. Obviously, the configuration at C(β) dictates the handedness, which supports the postulate that C(β)-substitution significantly influences the conformational characteristics of the investigated β-peptide monomers rather independently of another substitution at C(α).

Two of the investigated model compounds, **aA5** and **AB10** in *Table 2*, realize minimum structures in the gas phase corresponding to monomer units of a helical conformation with ten-membered H-bonded pseudocycles, where the H-bond is formed between the peptidic NH of amino acid *i* and the peptidic CO of amino acid ($i+1$) ($1 \rightarrow 2$ interaction), although, like for H_{12} and H_{14}, this H-bond cannot be

---

[3]) In fact, the substitutions at the C(α) and C(β) backbone atoms reported in [26][27] are both in *(R)*-configuration. Thus, the central dihedral θ exhibits a value of *ca.* $-90°$.

formed in the monomer. Such an H_{10} helix with the three backbone torsion-angle values of the same sign was already predicted for the tetramer of the (*S*)-C(β)-substituted β-amino acid **B** [70] and could be located as a free-energy minimum in molecular-dynamics calculations [78]. It is interesting that the stability of the H_{10} conformer in **aA** (**aA5**) is greater than that of the corresponding H_{14} (**aA6**) and H_{12} (**aA7**) conformers.

Polar solvents might remarkably influence the conformations of **aA**, **bB**, **aB**, and **AB**. *Table 3* presents the conformers of the model compounds, which were obtained by means of the SCRF solvation model at the HF/6-31G* level considering H_2O as the solvent. Comparison with the gas-phase data in *Table 2* shows that some conformers disappear in solution and change into other conformations. There are also some changes in the stability order of the conformers. Whereas, in **aA** and **AB**, the most stable structures in the gas phase remain the preferred ones also in solution, the global minima of **bB** and **aB** are different now (**bB2**^{s} and **aB9**^{s} in *Table 3*). Furthermore, conformers emerge that were not obtained in the gas phase. This might be illustrated on some minimum structures of the (*S,S*)-C(α),C(β)-disubstituted model compound **AB**.

Table 3. *Torsion Angles* (in degrees) *and Relative Energies* (in kJ/mol) *of the Minimum Conformations of the Disubstituted β-Amino Acids Model Compounds Obtained on the Basis of the SCRF Solvation Model at the HF/6-31G* Level of* ab initio *MO Theory*

Conf.[a])	φ	θ	ψ	ΔE[b])	Type[c])	Conf.[a])	φ	θ	ψ	ΔE[b])	Type[c])
aA1^s	−139.7	−60.5	−165.5	**0.0**	C_6	**bB1**^{s}	54.0	52.7	−97.1	11.1	C_8
aA2^s	−113.6	73.2	4.1	4.3	C_8	**bB2**^{s}	173.9	58.3	140.3	**0.0**	C_6
aA4^s	−87.7	117.2	−47.2	9.1	C_8	**bB3**^{s}	56.6	56.2	114.0	13.8	C_6
aA5^s	103.0	48.4	52.4	16.4	H_{10}	**bB5**^{s}	−59.4	120.3	−81.8	11.3	C_8
aA6^s	−148.3	64.5	−130.8	10.8	H_{14}	**bB6**^{s}	179.7	55.4	−115.6	19.3	C_N
aA7^s	−107.9	67.9	−81.9	12.7	H_{12}	**bB7**^{s}	76.8	−52.7	−87.6	33.8	
aA8^s	112.8	−179.6	−121.3	8.8		**bB11**^{s}	63.1	176.4	−101.4	12.6	
						bB12^s	61.7	63.5	−32.8	14.1	C_N
aB1^s	−147.1	−62.3	−143.2	0.7	C_6;	**bB13**^{s}	−83.5	66.4	−97.4	19.9	H_{12}
aB2^s	−59.0	−51.6	98.5	20.8	C_8						
aB2′^{s}	62.9	41.1	−92.1	22.8	C_8	**AB1**^{s}	−146.8	−61.0	−138.3	**0.0**	C_6
aB4^s	−174.2	60.0	134.9	8.2	C_6	**AB2**^{s}	−74.3	138.0	−72.1	11.7	C_8
aB5^s	−105.6	90.5	−21.7	10.8	C_8	**AB2′**^{s}	73.3	−105.3	59.9	21.6	C_8
aB6^s	−93.2	62.7	78.1	24.2		**AB3**^{s}	59.0	47.3	−105.4	22.8	C_8
aB6′^{s}	71.6	−71.9	−56.5	21.3		**AB4**^{s}	−116.2	59.9	23.3	19.0	C_8
aB8^s	−84.7	115.0	−46.8	6.4	C_8	**AB5**^{s}	−168.1	54.0	116.6	17.7	C_6
aB8′^{s}	63.7	−123.0	79.6	12.6	C_8	**AB6**^{s}	−154.1	−62.6	100.8	24.0	
aB9^s	−137.0	179.5	130.7	**0.0**		**AB7**^{s}	−150.5	60.2	−127.5	12.9	H_{14}
aB9′^{s}	64.9	177.5	−63.1	13.8		**AB9**^{s}	80.7	−57.1	−85.5	41.2	
aB10^s	−107.1	71.1	−87.2	14.3	H_{12}	**AB10**^{s}	63.8	46.1	68.9	27.2	H_{10}
aB11^s	−148.7	67.8	−126.7	11.3	H_{14}	**AB11**^{s}	−163.1	−74.6	46.3	45.1	C_N
aB12^s	−155.8	−62.5	109.6	16.1	C_N	**AB12**^{s}	89.0	163.2	−87.6	26.6	
aB13^s	88.2	−70.0	97.8	26.5	H_{12}	**AB14**^{s}	−152.5	158.3	−173.7	19.1	
						AB15^s	89.1	−69.6	92.7	29.5	H_{12}

[a]) Conformer numbering as in *Table 2*. [b]) Total energies of the most stable conformers ($\varepsilon = 78.4$). **aA**: $E_T = -570.935164$ a.u., **bB**: $E_T = -570.933702$ a.u., **aB**: $E_T = -570.938871$ a.u., **AB**: $E_T = -570.939532$ a.u. [c]) *Cf. Footnote b* in *Table 2*.

The basic unit of the H_{14} helix was obtained both in the gas phase and in solution (**AB7** in *Table 2*, **AB7^s** in *Table 3*). **AB7^s** gains some stabilization with respect to the lowest-energy conformer **AB1^s**. The basic conformer with opposite handedness could be located as a minimum structure neither in the gas phase nor in solution. This is completely different for the monomer unit of the H_{12} secondary structure. For the gas phase, only the right-handed conformer (**AB8**) is predicted, whereas the minimum structure with reversed handedness emerges in the H_2O continuum (**AB15^s**). Moreover, the right-handed conformer changes into the more-stable C_8 minimum **AB4^s**. Detailed investigations of the electrostatic properties of these structures reveal that the mirror-image conformation of **AB8** might be destabilized in the gas phase by the Me substituent at C(β). A similar effect was found for the (*R,S*)-C(α),C(β)-disubstituted β-amino acid **aB**. In the gas phase, only the right-handed conformer of the H_{12} helix (**aB10** in *Table 2*) was obtained, whereas the left-handed conformer emerges in solution (**aB13^s** in *Table 3*). However, oligomerization of this conformer of an (*S*)-C(β)-substituted β-amino acid does not consistently result in a left-handed H_{12} helix due to unfavorable contacts between side chains with axial orientations to the helix, which appear only in longer sequences.

Considering the conformation data on the unsubstituted, monosubstituted, and disubstituted β-peptide monomer models, numerous conformers were found, from which well-defined secondary structures could be derived. Quite obviously, the additional CH_2 group in the backbone of a β-amino acid constituent does not so much increase the conformational flexibility of the monomer units as to prevent the formation of ordered structures. This was also pointed out by *Seebach* and co-workers [101]. In other words, rotation around the central C(α)–C(β) linkage is not free, as it was sometimes assumed, but a few discrete conformations are distinctly favored. Therefore, more, but in the same way well-ordered secondary-structure elements could be expected in β-peptides than in the common α-peptides due to the additional conformational degree of freedom.

3.3. *Substituent Influence on the Intrinsic Folding Properties in β-Peptides.* In the preceding paragraph, the general conformation characteristics in mono- and disubstituted β-peptide monomers were discussed. Now, we turn to the substituent influence on the intrinsic folding properties into the different periodic secondary-structure alternatives. To get a complete overview on all substitution possibilities in β-amino acid constituents, we consider also the tri- and tetrasubstituted monomers **aAB**, **AbB**, and **aAbB** (*Table 1*). For a comparison of the various substituent patterns, the fully extended conformation of all compounds with the backbone torsion angles set to 180° was chosen as a reference point. Thus, the intrinsic folding propensities are characterized by the energy differences between any folded conformer and the corresponding extended structure. The total energies of all extended conformations are given in the *Supporting Information*. The *Tables 4* and *5* show the intrinsic folding tendencies of the investigated model compounds depending on the substituent patterns and on the environmental influence. For completeness, the corresponding data for the blocked β-amino acids **U**, **A**, and **B** ([70] and *cf. Table 1*) are also calculated. Due to the chirality of some model compounds, the conformers in *Tables 4* and *5* can be assigned to structures forming left-handed (*M*) and right-handed (*P*) helices, respectively. The conformers with the highest folding tendency are marked in italics.

Table 4. *Intrinsic Folding Energies* (in kJ/mol) *of Selected Minimum Conformations of the Investigated β-Amino Acid Model Compounds Obtained at the HF/6-31G* Level of* ab initio *MO Theory*[a])

	H_{14}		H_{12}		H_{10}		C_8^{I}		C_8^{II}		C_8^{III}		C_6^{I}		C_6^{II}	
Model	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)
U	–		+ 0.4		–		– 12.3		– 15.3		–		–		– 24.1	
aA	– 7.0		– 6.3		– 14.8		– 15.8		– 29.7		–		–		– 32.5	
bB	–		–		–		– 13.1		– 0.7		– 27.7		– 25.3		– 22.4	
aAbB	–		–		–		– 13.8		– 11.4		– 28.3		– 35.1		– 28.0	
A	–	–	–	– 11.4	–	–	–	– 25.4	– 23.6	– 25.4	–	– 30.5	– 30.7	–	–	– 32.6
B	– 14.7	–	–	– 11.1	–	–	– 10.8	– 26.8	–	– 26.4	– 26.6	– 27.4	– 33.6	– 27.0	–	– 26.7
aB	– 17.1	–	–	– 19.8	–	–	– 28.3	– 31.1	– 12.2	– 35.8	–	– 40.0	– 40.1	– 36.7	*– 39.8*	– 28.2
AB	*– 32.3*	–	–	*– 26.8*	–	– 25.0	– 23.0	*– 46.2*	–	– 41.9	*– 45.8*	–	***– 54.4***	– 39.5	–	–
aAB	– 26.2	–	–	– 24.7	–	– 18.8	– 26.7	–	– 22.1	*– 43.9*	–	–	– 50.7	– 38.8	–	– 33.2
AbB	–	–	–	– 13.3	–	*– 26.6*	– 25.4	–	–	– 13.1	– 44.8	– 26.7	– 42.3	– 32.7	–	–

[a]) Folding energies are given as differences between the energy of the various conformers and the corresponding extended conformation (*cf. Supporting Information*) as reference points. (*M*) and (*P*) refer to left-handed and right-handed helices, resp.

Table 5. *Intrinsic Folding Energies* (in kJ/mol) *of Selected Minimum Conformations of the Investigated β-Amino Acid Model Compounds Obtained on the Basis of the SCRF Solvation Model at the HF/6-31G* Level of* ab initio *MO Theory*[a])

	H_{14}		H_{12}		H_{10}		C_8^{I}		C_8^{II}		C_8^{III}		C_6^{I}		C_6^{II}	
Model	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)	(*M*)	(*P*)
U[s]	+3.6		+7.5		–		+0.6		–		+17.6		−4.0		–	
aA[s]	−4.1		−2.2		+1.5		−5.8		−10.6		–		–		*−14.9*	
bB[s]	–		+4.6		–		−4.0		–		−4.2		−15.3		−1.5	
aAbB[s]	–		−8.8		–		−8.2		–		−2.1		−26.0		–	
A[s]	−10.6	−1.5	−2.0	−7.0	–	−0.5	–	−12.7	−11.2	−8.9	–	+1.5	−17.0	−12.5	–	–
B[s]	−11.0	–	–	−7.0	–	+0.8	−1.8	−13.6	–	−9.6	+2.0	+0.4	−19.8	−10.9	–	–
aB[s]	−20.3	–	−5.1	*−17.3*	–	–	−19.0	−25.2	–	–	−10.8	+8.8	−30.9	−23.4	–	–
AB[s]	*−25.8*	–	−9.2	–	–	–	−17.1	*−27.1*	–	−19.7	–	−15.9	−38.7	−21.0	–	–
aAB[s]	−23.7	–	−9.3	–	–	−8.4	−18.9	−18.1	–	*−26.5*	–	–	***−38.9***	−18.4	–	−11.3
AbB[s]	–	–	−5.7	−8.8	–	*−12.4*	−18.4	−11.5	–	+4.9	−1.1	*−18.5*	−30.4	−19.5	–	–

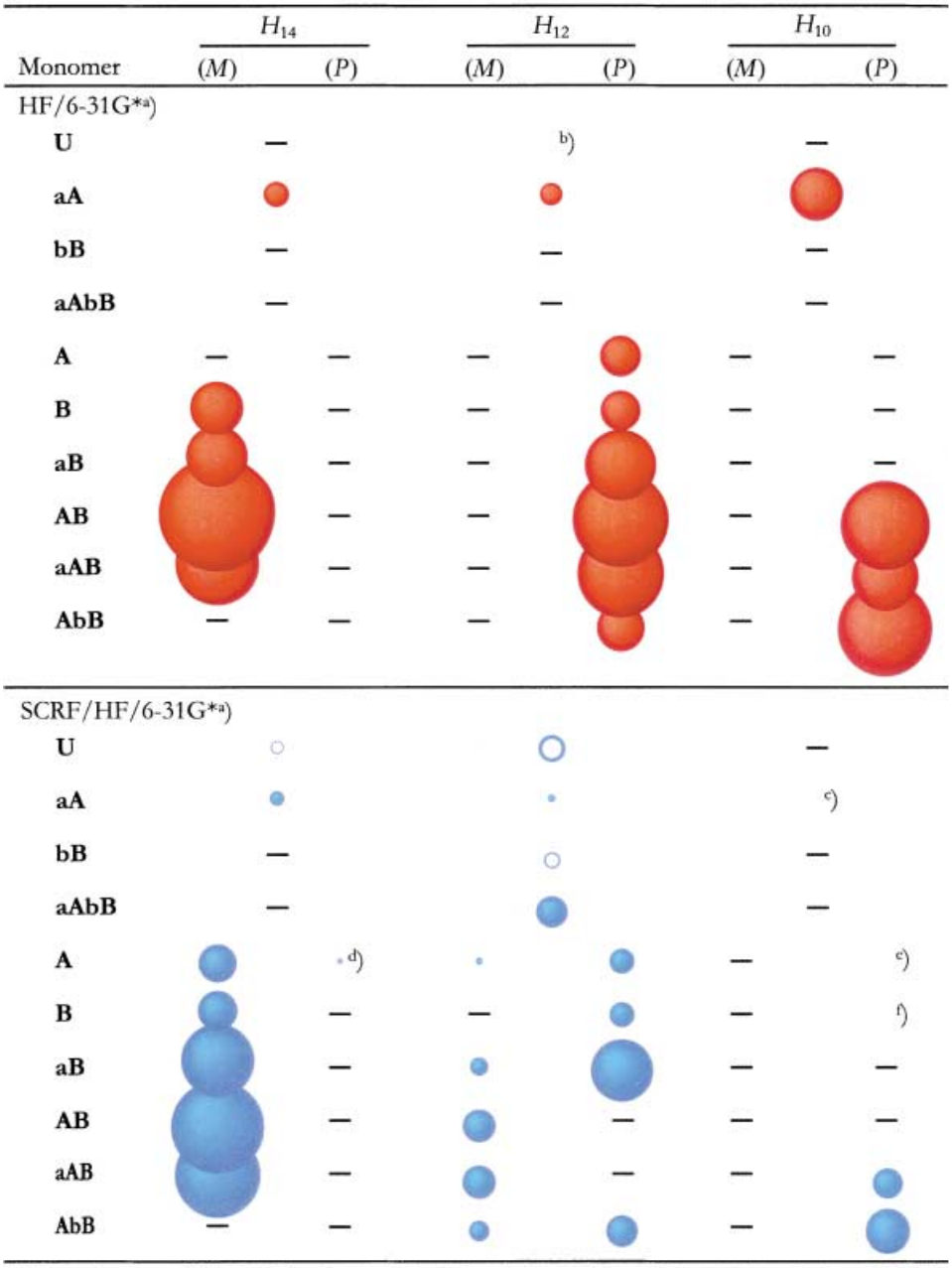
[a]) *Cf. Footnote a* in *Table 4*.

Comparing the relative folding propensities of the different structure patterns, folding is most favorable for substitution type **AB**. Obviously, an (*S,S*)-C(α),C(β)-disubstituted β-amino acid generally promotes the formation of folded structures in agreement with experimental data. Thus β-peptide constituents with an (*S,S*)-C(α),C(β)- or, alternatively, (*R,R*)-C(α),C(β)-disubstitution might act as nucleation points in the folding of longer β-peptide sequences. It should be remembered that the incorporation of an (*S,S*)-disubstituted β-amino acid into the center of a β-peptide hexamer enhances the CD signal of an H_{14} conformation [20]. Moreover, the first detailed crystallographic data of H_{14} and H_{12} helices were obtained from β-amino acid oligomers in which the central C(α)–C(β) bond of each β-amino acid residue is incorporated into an (*S,S*)-disubstituted cyclohexane and (*R,R*)-disubstituted cyclopentane ring, respectively [26][27]. β-Peptide monomers with only one substituent exhibit a significantly smaller folding tendencies. Interestingly, the trisubstituted model compound **aAB** realizes nearly all basic conformers. Their stabilization with respect to the fully extended conformation is comparable with that of the **AB** derivatives. The smallest energy differences are estimated for the achirally substituted β-amino acid models. The preference of extended conformations in these symmetric compounds could be a reason for this. The results in *Table 4* show that the geminal disubstitution at C(β) is the most unfavorable substitution pattern for folding. The situation in the trisubstituted β-amino acid model **AbB** is slightly different. Here, formation of the monomer units of the helices H_{12} and H_{10} can still be observed. For the formation of H_{10}, this type of trisubstitution seems most promising of all substitution patterns.

Table 5 illustrates the influence of a polar-solvent continuum on folding. In comparison with the data in *Table 4*, it is obvious that the solvent continuum favors the formation of H_x secondary structures, where the H-bonds cannot be formed in the monomers, over the C_x conformers. This is most striking for the H_{12} conformer. However, the general folding tendency is smaller in solution than in the gas phase, especially for those conformers that are characterized by *intra*-molecular H-bonds (C_6, C_8). For instance, the difference between the folding tendencies of the most stable H_x conformer and the most stable C_x conformer of **AB**, H_{14} and C_6^{I}, respectively, is smaller in the solvent continuum than in the gas phase. It has to be remembered that the solvent data should not be overestimated due to the neglect of specific solvation effects. They should only be considered as a qualitative estimation of the general trends of solvation.

A graphical overview and generalization of the relations between the substitution patterns of the β-amino acid constituents of β-peptides and their backbone folding into the especially interesting β-peptide helices H_{14}, H_{12}, and H_{10} in the gas phase and in a polar medium is provided by *Table 6*. Here, closed and open circles indicate the existence of minimum conformations. A closed circle represents higher stability of the folded structure over the extended one, open circles describe the opposite situation. The size of the circles correlates with the extent of folding and unfolding, respectively. The diameters of the circles are in relation to the actual energy differences to the extended conformations. The remarkable influence of substitution on the formation of these characteristic secondary structures can immediately be seen. Asymmetrically substituted β-amino acids generally favor folding into the helical conformations as indicated by the larger spheres. In agreement with the results obtained on the model

Table 6. *Graphical Overview on the Intrinsic Folding Properties of the Investigated β-Amino Acid Model Compounds into Basis Conformations of Left-*(M) *or Right-Handed* (P) *Helical Structures*



[a]) For explanation of the symbols, *cf.* text. [b]) 0.4 kJ/mol. [c]) −0.5 kJ/mol. [d]) −1.5 kJ/mol. [e]) −0.5 kJ/mol. [f]) 0.8 kJ/mol.

compounds **1** and **2** representing the N- and C-terminal fragments of a blocked β-amino acid, the configuration at C(β) atom dictates the handedness of the helical structure. Consequently, the (*S*)-configuration enforces folding into a left-handed (*M*)-H_{14} and into a right-handed (*P*)-H_{12} conformer, respectively. Thus, the handedness of a helical structure can already be derived at the monomer level, in some way even at the submonomer level, when regarding the fragments **1** and **2** in that way. In the case of the theoretically predicted (*P*)-H_{10} helix, it is interesting to note that a disubstitution with one substituent at C(α) in (*S*)-configuration may support the formation of this type of secondary structure. These conclusions can essentially be maintained, if the global influence of a polar medium is considered. Obviously, the solvent stabilization of the folded structures is slightly smaller than that of the extended structures.

Summarizing, this rather complete overview of the general influence of substitution on the intrinsic folding properties of β-peptides might be helpful for an understanding of secondary-structure formation in this class of compounds. It could be useful for a rational design of definite three-dimensional structures.

Support of this work by *Deutsche Forschungsgemeinschaft* (Innovationskolleg '*Chemisches Signal und Biologische Antwort*' and SFB *610* '*Protein-Zustände mit zellbiologischer und medizinischer Relevanz*') and by *Fonds der Chemischen Industrie* is gratefully acknowledged. We are obliged to Prof. *Dieter Seebach*, Zürich, for helpful advice.

Supporting Information Available. Tables with backbone dihedrals and energies of selected HF/6-31G*, SCRF/HF/6-31G*, and DFT/B3LYP/6-31G* minimum structures of the investigated β-amino acid model compounds. See any current masthead page for ordering information and Internet access instructions.

REFERENCES

[1] D. Seebach, J. L. Matthews, *Chem. Commun.* **1997**, 2015.
[2] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173.
[3] W. F. DeGrado, J. P. Schneider, Y. Hamuro, *J. Peptide Res.* **1999**, *54*, 206.
[4] K. Gademann, T. Hintermann, J. Schreiber, *Curr. Med. Chem.* **1999**, *6*, 905.
[5] R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219.
[6] D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893.
[7] S. Krauthäuser, L. A. Christianson, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1997**, *119*, 11719.
[8] D. Seebach, S. Abele, K. Gademann, B. Jaun, *Angew. Chem.* **1999**, *111*, 1700; *Angew. Chem., Int. Ed.* **1999**, *38*, 1595.
[9] Y. J. Chung, B. R. Huck, L. A. Christianson, H. E. Stanger, S. Krauthäuser, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **2000**, *122*, 3995.
[10] X. Daura, K. Gademann, H. Schäfer, B. Jaun, D. Seebach, W. F. van Gunsteren, *J. Am. Chem. Soc.* **2001**, *123*, 2393.
[11] D. Seebach, S. Abele, T. Sifferlen, M. Hänggi, S. Gruner, P. Seiler, *Helv. Chim. Acta* **1998**, *81*, 2218.
[12] Y. J. Chung, L. A. Christianson, H. E. Stanger, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1998**, *120*, 10555.
[13] B. R. Huck, J. D. Fisk, S. H. Gellman, *Org. Lett.* **2000**, *2*, 2607.
[14] F. Schumann, A. Müller, M. Koksch, G. Müller, N. Sewald, *J. Am. Chem. Soc.* **2000**, *122*, 12009.
[15] J. M. Fernández-Santín, J. Aymamí, A. Rodríguez-Galán, S. Muñoz-Guerra, J. A. Subirana, *Nature (London)* **1984**, *311*, 53.
[16] J. M. Fernández-Santín, S. Muñoz-Guerra, A. Rodríguez-Galán, J. Aymamí, J. Llovera, J. Subirana, E. Giralt, M. Ptak, *Macromolecules* **1987**, *20*, 62.
[17] F. López-Carrasquero, M. García-Alvarez, J. J. Navas, C. Alemán, S. Muñoz-Guerra, *Macromolecules* **1996**, *29*, 8449.
[18] D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913.

[19] D. Seebach, S. Abele, K. Gademann, G. Guichard, T. Hintermann, B. Jaun, J. L. Matthews, J. V. Schreiber, *Helv. Chim. Acta* **1998**, *81*, 932.
[20] D. Seebach, J. V. Schreiber, S. Abele, X. Daura, W. F. van Gunsteren, *Helv. Chim. Acta* **2000**, *83*, 34.
[21] D. Seebach, A. Jacobi, M. Rueping, K. Gademann, M. Ernst, B. Jaun, *Helv. Chim. Acta* **2000**, *83*, 2115.
[22] P. I. Arvidsson, M. Rueping, D. Seebach, *Chem. Commun.* **2001**, 649.
[23] T. Sifferlen, M. Rueping, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 2067.
[24] T. Hintermann, D. Seebach, *Synlett* **1997**, 437.
[25] D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 13071.
[26] D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi Jr., S. H. Gellman, *Nature (London)* **1997**, *387*, 381.
[27] D. H. Appella, L. A. Christianson, D. A. Klein, M. R. Richards, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1999**, *121*, 7574.
[28] X. Wang, J. F. Espinosa, S. H. Gellman, *J. Am. Chem. Soc.* **2000**, *122*, 4821.
[29] H.-S. Lee, F. A. Syud, X. Wang, S. H. Gellman, *J. Am. Chem. Soc.* **2001**, *123*, 7721.
[30] D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1999**, *121*, 6206.
[31] J. J. Barchi Jr., X. Huang, D. Appella, L. Christianson, S. Durell, S. Gellman, *J. Am. Chem. Soc.* **2000**, *122*, 2711.
[32] R. P. Cheng, W. F. DeGrado, *J. Am. Chem. Soc.* **2001**, *123*, 5162.
[33] B. W. Gung, D. Zou, A. M. Stalcup, C. E. Cottrell, *J. Org. Chem.* **1999**, *64*, 2176.
[34] T. D. W. Claridge, J. M. Goodman, A. Moreno, D. Angus, S. F. Barker, C. Taillefumier, M. P. Watterson, G. W. J. Fleet, *Tetrahedron Lett.* **2001**, *42*, 4251.
[35] D. Seebach, S. Abele, J. V. Schreiber, B. Martinoni, A. K. Nussbaum, H. Schild, H. Schulz, H. Hennecke, R. Woessner, F. Bitsch, *Chimia* **1998**, *52*, 734.
[36] D. Seebach, M. Albert, P. I. Arvidsson, M. Rueping, J. V. Schreiber, *Chimia* **2001**, *55*, 345.
[37] J. Frackenpohl, P. I. Arvidsson, J V. Schreiber, D. Seebach, *ChemBioChem* **2001**, *2*, 445.
[38] N. Umezawa, M. A. Gelman, M. C. Haigis, R. T. Raines, S. H. Gellman, *J. Am. Chem. Soc.* **2002**, *124*, 368.
[39] M. Rueping, Y. Mahajan, M. Sauer, D. Seebach, *ChemBioChem* **2002**, *3*, 257.
[40] K. Gademann, M. Ernst, D. Hoyer, D. Seebach, *Angew. Chem.* **1999**, *111*, 1302; *Angew. Chem., Int. Ed.* **1999**, *38*, 1233.
[41] M. Werder, H. Hauser, S. Abele, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1774.
[42] S. Poenaru, J. R. Lamas, G. Folkers, J. A. L. d. Castro, D. Seebach, D. Rognan, *J. Med. Chem.* **1999**, *42*, 2318.
[43] Y. Hamuro, J. P. Schneider, W. F. DeGrado, *J. Am. Chem. Soc.* **1999**, *121*, 12200.
[44] K. Gademann, T. Kimmerlin, D. Hoyer, D. Seebach, *J. Med. Chem.* **2001**, *44*, 2460.
[45] K. Gademann, D. Seebach, *Helv. Chim. Acta* **2001**, *84*, 2924.
[46] D. Seebach, M. Rueping, P. I. Arvidsson, T. Kimmerlin, P. Micuch, C. Noti, D. Langenegger, D. Hoyer, *Helv. Chim. Acta* **2001**, *84*, 3503.
[47] D. Liu, W. F. DeGrado, *J. Am. Chem. Soc.* **2001**, *123*, 7553.
[48] E. A. Porter, X. F. Wang, H. S. Lee, B. Weisblum, S. H. Gellman, *Nature (London)* **2000**, *404*, 565; E. A. Porter, X. F. Wang, H. S. Lee, B. Weisblum, S. H. Gellman, *Nature (London)* **2000**, *405*, 298.
[49] P. I. Arvidsson, J. Frackenpohl, N. S. Ryder, B. Liechty, F. Petersen, H. Zimmermann, G. P. Camenisch, R. Woessner, D. Seebach, *ChemBioChem* **2001**, *2*, 771.
[50] H.-J. Böhm, S. Brode, *J. Am. Chem. Soc.* **1991**, *113*, 7129.
[51] T. Head-Gordon, M. Head-Gordon, M. J. Frisch, C. L. Brooks III, J. A. Pople, *J. Am. Chem. Soc.* **1991**, *113*, 5989.
[52] R. F. Frey, J. Coffin, S. Q. Newton, M. Ramek, V. K. W. Cheng, F. A. Momany, L. Schäfer, *J. Am. Chem. Soc.* **1992**, *114*, 5369.
[53] I. R. Gould, P. A. Kollmann, *J. Phys. Chem.* **1992**, *96*, 9255.
[54] I. R. Gould, W. D. Cornell, I. H. Hiller, *J. Am. Chem. Soc.* **1994**, *116*, 9250.
[55] C. L. Brooks III, D. A. Case, *Chem. Rev.* **1993**, *93*, 2487.
[56] W. D. Cornell, I. R. Gould, P. A. Kollman, *J. Mol. Struct. (Theochem)* **1997**, *392*, 101.
[57] K. Rommel-Möhle, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1993**, *285*, 211.
[58] K. Möhle, H.-J. Hofmann, *J. Mol. Model.* **1998**, *4*, 53.
[59] K. Möhle, H.-J. Hofmann, W. Thiel, *J. Comput. Chem.* **2001**, *22*, 509.
[60] K. Möhle, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1995**, *339*, 57.

[61] M. Thormann, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1998**, *469*, 63.
[62] M. Thormann, H.-J. Hofmann, *J. Mol. Struct. (Theochem)* **1998**, *431*, 79.
[63] K. Möhle, H.-J. Hofmann, *J. Pept. Res.* **1998**, *51*, 19.
[64] R. Günther, H.-J. Hofmann, *J. Am. Chem. Soc.* **2001**, *123*, 247.
[65] Y. Wu, D. Wang, K. Chan, D. Yang, *J. Am. Chem. Soc.* **1999**, *121*, 11189.
[66] S. N. Rao, V. N. Balaji, K. Ramnarayan, *Peptide Res.* **1992**, *5*, 343.
[67] C. Alemán, S. León, *J. Mol. Struct. (Theochem)* **2000**, *505*, 211.
[68] L. A. Christianson, M. J. Lucero, D. H. Appella, D. A. Klein, S. H. Gellman, *J. Comput. Chem.* **2000**, *21*, 763.
[69] J. Chandrasekhar, M. Saunders, W. L. Jorgensen, *J. Comput. Chem.* **2001**, *22*, 1646.
[70] K. Möhle, R. Günther, M. Thormann, N. Seewald, H.-J. Hofmann, *Biopolymers* **1999**, *50*, 167.
[71] Y.-D. Wu, D.-P. Wang, *J. Am. Chem. Soc.* **1998**, *120*, 13485.
[72] J. J. Navas, C. Alemán, S. Muñoz-Guerra, *J. Org. Chem.* **1996**, *61*, 6849.
[73] Y.-D. Wu, D.-P. Wang, *J. Chin. Chem. Soc.* **2000**, *47*, 129.
[74] Y.-D. Wu, D.-P. Wang, *J. Am. Chem. Soc.* **1999**, *121*, 9352.
[75] C. Alemán, R. Roca, F. J. Luque, M. Orozco, *Proteins: Struct. Funct., Genet.* **1997**, *28*, 83.
[76] R. Improta, V. Barone, K. N. Kudin, G. E. Scuseria, *J. Am. Chem. Soc.* **2001**, *123*, 3311.
[77] Y.-D. Wu, Y.-L. Zhao, *J. Am. Chem. Soc.* **2001**, *123*, 5313.
[78] R. Günther, H.-J. Hofmann, K. Kuczera, *J. Phys. Chem. B* **2001**, *105*, 5559.
[79] X. Daura, B. Jaun, D. Seebach, W. F. van Gunsteren, A. E. Mark, *J. Mol. Biol.* **1998**, *280*, 925.
[80] X. Daura, W. F. van Gunsteren, A. E. Mark, *Proteins: Struct., Funct., Genet.* **1999**, *34*, 269.
[81] F. A. Momany, R. Rone, *J. Comput. Chem.* **1992**, *13*, 888.
[82] F. A. Momany, R. Rone, H. Kunz, R. F. Frey, S. Q. Newton, L. Schäfer, *J. Mol. Struct. (Theochem)* **1993**, *286*, 1.
[83] J. Gasteiger, M. Marsili, *Tetrahedron* **1980**, *36*, 3219.
[84] IUPAC, Commission on Macromolecular Nomenclature, *Pure Appl. Chem.* **1981**, *51*, 733.
[85] F. Gregoire, H. S. Wei, E. W. Streed, K. A. Brameld, D. Fort, L. J. Hanely, J. D. Walls, W. A. Goddard, J. D. Roberts, *J. Am. Chem. Soc.* **1998**, *120*, 7537.
[86] I. A. Motorina, C. Huel, E. Quiniou, J. Mispelter, E. Adjadj, D. S. Grierson, *J. Am. Chem. Soc.* **2001**, *123*, 8.
[87] G. P. Dado, S. H. Gellman, *J. Am. Chem. Soc.* **1994**, *116*, 1054.
[88] B. W. Gung, Z. Zhu, *J. Org. Chem.* **1997**, *62*, 6100.
[89] B. W. Gung, Z. Zhu, D. Zou, B. Everingham, A. Oyeamalu, R. M. Crist, J. Baudlier, *J. Org. Chem.* **1998**, *63*, 5750.
[90] S. Abele, P. Seiler, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1559.
[91] S. Abele, K. Vögtli, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1539.
[92] C. Toniolo, *CRC Crit. Rev. Biochem.* **1980**, *9*, 1.
[93] D. Yang, J. Qu, B. Li, F.-F. Ng, X.-C. Wang, K.-K. Cheung, D.-P. Wang, Y.-D. Wu, *J. Am. Chem. Soc.* **1999**, *121*, 589.
[94] C. Peter, X. Daura, W. F. van Gunsteren, *J. Am. Chem. Soc.* **2000**, *122*, 7461.
[95] A. Cheguillaume, A. Salaün, S. Sinbandhit, M. Potel, P. Gall, M. Baudy-Floc'h, P. Le Grel, *J. Org. Chem.* **2001**, *66*, 4923.
[96] F. Rossi, E. Bucci, C. Iserna, R. Iacovino, P. Di Lello, M. Grimaldi, D. Montesarchio, L. De Napoli, G. Piccialli, E. Benedetti, *Biopolymers* **2000**, *53*, 140.
[97] A. K. Thakur, P. Venugopalan, R. Kishore, *J. Pept. Res.* **2000**, *56*, 55.
[98] A. K. Thakur, R. Kishore, *Biopolymers* **2000**, *53*, 447.
[99] J. D. Winkler, E. L. Piatnitski, J. Mehlmann, J. Kasparec, P. H. Axelsen, *Angew. Chem.* **2001**, *113*, 765; *Angew. Chem., Int. Ed.* **2001**, *40*, 743.
[100] V. Pavone, B. Di Blasio, A. Lombardi, C. Isernia, C. Pedone, E. Benedetti, G. Valle, M. Crisma, C. Toniolo, R. Kishore, *J. Chem. Soc., Perkin Trans. 2* **1992**, 1233.
[101] K. Gademann, B. Jaun, D. Seebach, R. Perozzo, L. Scapozza, G. Folkers, *Helv. Chim. Acta* **1999**, *82*, 1.

Received April 2, 2002