Ab initio MO Theory – An Important Tool in Foldamer Research: Prediction of Helices in Oligomers of ω-Amino Acids

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Dedicated to Professor Dr. *Dieter Seebach* on the occasion of his 75th birthday

The enormous developments of computer technologies allow the broad employment of *ab initio* MO theory in foldamer research. In this review, we demonstrate the efficiency and reliability of *ab initio* MO methods for the description of the helix formation in oligomers of ω-amino acids on the basis of representative examples. Thus, *ab initio* MO theory successfully accompanies foldamer research by confirmation and interpretation of experimental results and stimulation of future experiments. The high predictive power of the methods opens the way to novel structure classes with special properties. Nowadays, *ab initio* MO theory has become an inherent part in the arsenal of methods applied in foldamer research.

1. Introduction. – The first reports on helices with 14-membered and 12-membered H-bonded rings in short sequences of β-amino acids from the groups of *Seebach* [1] and *Gellman* [2] in the mid-nineties were the decisive stimulus for the establishment of the field of foldamer research. The notation 'foldamer' was introduced by *Gellman* already in his first papers and became rapidly popular by his review 'Foldamers – A Manifesto' a short time later [3]. In this review, foldamers are considered to be 'polymers with a strong tendency to adopt a specific, compact conformation'. It is obvious, that this definition has some shortcomings to separate foldamers from other polymers with ordered structure and does not account for the fact that the formation of ordered structures occurs already at the oligomer level. *Moore* and co-workers [4] have extensively discussed several aspects of the foldamer definition. Knowing that a generally satisfactory definition can anyway not be given, one may follow their suggestions in most points and consider foldamers as oligomers of unnatural chemical constituents which fold into conformationally ordered and compact states. On the basis of this definition, it becomes clear that a wide variety of chemical compounds could be the starting point to build oligomers with foldamer properties. Corresponding to this, the field of foldamers has enormously been extended into many directions in less than two decades of research. The elaboration of new methods for the synthesis of oligomer constituents, the structure determination of the foldamers employing various methods of structure analytics, and the examination of possible applications of foldamers in biology, pharmacology, and material sciences became important aspects of foldamer

research. Numerous reviews and monographs document the progress in this field [4–6].

Among the numerous classes of foldamers, a special fascination emanates from oligomers of nonproteinogenic amino acids, as those from *Seebach* and *Gellman* at the beginning of the foldamer era. The fact that ordered secondary structures are formed in sequences of β-amino acids leads straight to a comparison with the secondary structures of native peptides and proteins consisting of α-amino acids. It also induces ideas of mimicking natural peptides or parts of proteins by ω-peptides [5t][5u–5w][6f][6g][7]. It could even be to find peptide foldamers that elicit biological effects of their own [5y][6e][6g]. Attracted by all these aspects, numerous groups contributed to the extension of the field of peptide foldamers going far beyond β-peptides, by employing the homologation principle, which means the continuous extension of the amino acid backbone by stepwise insertion of methylene groups. Thus, after the β-peptides, which were reached in the first homologation step starting from α-peptides, homooligomers of the higher ω-amino acids gained great attention. Finally, a considerable extension of the peptide foldamer pool resulted from the combinatorial variety of sequences consisting of different ω-amino acid building blocks, leading to peptide foldamers with heterogeneous backbones [5w][6g].

From the very beginning, theoretical methods were employed in foldamer research. Here, we want to give a review on the application of the methods of *ab initio* MO theory for the description of the structure and properties of foldamers. The enormous development of computational technologies with respect to speed and storage capacity enables nowadays routine calculations on foldamers at reliable levels of *ab initio* MO theory. The importance of theoretical methods, in particular the methods of *ab initio* MO theory, arises from their general applicability on molecules to calculate various chemical and physical properties. It is even possible to estimate the stability and the properties of hypothetical structures in 'computer experiments' ('*in silico*'). The methods have reached a status that goes far beyond the mere confirmation of experimental findings. The explanation of chemical effects, the elaboration of chemical models, and especially the reliable prediction of properties of molecules still to be synthesized, thus establishing the basis for future experiments, are the current challenges for theoretical methods. The methods of *ab initio* MO theory have been applied to various foldamer classes in the meantime. In this review, we confine ourselves on the illustration of their efficiency and reliability describing peptide foldamers composed of ω-amino acid constituents and their derivatives. Moreover, the focus is limited to the helix formation in these oligomers, which is a particularly interesting phenomenon, since it directly leads to one of the possible fields of application of foldamers, *viz.*, the mimicry of secondary structures of native peptides. Of course, there are further impressive examples for the successful application of *ab initio* MO theory to other secondary structure elements [8].

2. Efficiency and Reliability of Theoretical Methods to Describe Peptide Structures. – The determination of the structure of peptides and proteins is essentially a conformational problem. The knowledge of the backbone torsion angles of the amino acid constituents of a sequence and their side chains provides the three-dimensional structure of a peptide or protein. For the theoretical solution of conformational

problems, a great number of methods of molecular mechanics employing empirical force fields and of semiempirical and *ab initio* quantum chemistry is available. Quantum and molecular mechanics methods may even be combined to QM/MM methods.

The computational efforts increase considerably going from molecular mechanics to *ab initio* MO theory. Therefore, the less time-consuming empirical force fields will still remain the method of choice for calculations on larger peptides and proteins or for molecular dynamics studies on smaller peptides in condensed phase, where hundreds and thousands of atoms have to be considered. To the best of our knowledge, the first study on the conformation of simple β-peptide constituents with the general background of secondary structure formation was performed in 1992 by *Rao* and co-workers employing the MM2 force field [9]. Unfortunately, essential conclusions drawn from these calculations by the authors were wrong. This was partially caused by obvious shortcomings of the force field. Numerous contributions of *Alemán* and co-workers [10], who employed molecular mechanics to interpret structure data for various helix types in the fibres of L-β-aspartate polymers found by *Muñoz-Guerra* and co-workers [11], were more important for foldamer research. From our present point of view, these helices show close relationships to the β-peptide helices later found by *Seebach* and *Gellman* in short β-amino acid oligomers, which were even shorter than α-helix sequences in native peptides.

The problems and limitations of empirical force fields for biomolecular systems were extensively discussed by *van Gunsteren* and co-workers [12]. Referring to foldamer structures, at least the following aspects should be emphasized. The wide structural variety of oligomer constituents leads often to the problem of missing force-field parameters for special structure elements in well-established force fields. A consistent derivation of these parameters for a given force field is not always easy and demands considerable care. Even if all parameters are formally available within a force field, they may not be transferable to a new structure class. This can even occur if empirical force fields originally developed for natural α-peptides are employed for peptides composed of nonnatural amino acids. Thus, the parameter sets need revision [12][13]. Since experimental data for novel classes of foldamers are obviously not available for such a revision, the comparison with *ab initio* MO data offers a way out of this dilemma. A great challenge for empirical force fields is the correct description of the delicate relationships between the numerous competitive secondary-structure elements in short oligomer sequences. Here, the results can be rather contradictory. Finally, it should be mentioned that too many conformers on the conformational energy hypersurface of peptides may result from a molecular mechanics treatment [14]. Nowadays, empirical force fields are predominantly employed in foldamer research for molecular-dynamics simulations and for the translation of NMR data into structure information [15].

Semiempirical quantum-chemical methods seem to be promising to overcome shortcomings of empirical force fields as a good compromise between molecular mechanics and *ab initio* MO theory concerning accuracy and computational costs. Well-established semiempirical methods like MNDO, AM1, and PM3 were successfully developed for the description of the properties of organic molecules [16]. *Alemán* and co-workers employed such methods for the investigation of helices of poly(β-aspartate)s as mentioned above in the context of empirical force fields [17].

Nevertheless, it is disappointing that semiempirical methods often fail to correctly predict important secondary structures in peptides and proteins and their energetic relationships [18], which makes their application for oligomers of peptide foldamers questionable. Suggestions to change this situation were helpful but not really satisfactory [16][19]. These aspects have to be considered in QM/MM calculations as well, where the combination of a semiempirical MO method showing problems to describe the structure of peptides with an empirical force field suffering for its part from drawbacks is out of the question.

In view of the somewhat disillusioning statements on the availability of parameters in standard force fields for the many possible foldamer constituents and on the accuracy of semiempirical methods in the description of basic structural properties of peptides and peptide-derived foldamers, our hope rests with the methods of *ab initio* MO theory. Of course, we are aware of the necessary reduction of the size of molecular systems that can be treated by such methods in comparison to semiempirical and force-field methods. Indeed, many shortcomings of force-field and semiempirical MO methods are overcome by the various *ab initio* MO models. The hierarchy of *ab initio* MO methods is essentially determined by the size of the basis set in the LCAO approximation and the extent of consideration of correlation energy. Both factors determine the computational efforts necessary to get reliable results for a given molecular system.

For our purposes of calculating foldamer structures, it may be useful to be guided by the progress of the methodological developments of *ab initio* MO methods for the description of conformational states of peptide sequences consisting of native α-amino acids. When the first *ab initio* MO methods were developed for the treatment of larger molecular systems, the concept of secondary structure of peptides and proteins was already established and confirmed by comprehensive experimental data. The first *ab initio* MO calculations on the conformation of the simplest peptide-bond models $HCONH_2$ (formamide) and MeCONHMe (*N*-methylacetamide) and on the diamides For-Gly-NH_2 (*N*-formylglycinamide), For-Ala-NH_2 (*N*-formylalaninamide), and Ac-Ala-NHMe (*N*-acetyl-*N*′-methylalaninamide) as simple peptide models were performed around the year 1980 [20]. They were above all a test for the capacity of the methods employed. The aim of all these activities was the refinement of the famous *Ramachandran* plot [21], which indicates the sterically allowed conformational regions of an amino acid constituent within a peptide sequence in a two-dimensional diagram of its backbone torsion angles φ and ψ and correlates them with the experimentally found protein-secondary-structure elements, to a *Ramachandran* energy surface (RES). The successful reproduction of some of the important protein secondary structures at the level of the basic amino acid units raised the question if the typical secondary-structure elements can generally be derived from the available conformational space of the constituents, or if a critical sequence length is required for their formation, a question which is permanently actual in structure studies on foldamers, too.

The first *ab initio* MO calculations on peptides were performed at very low levels of minimum and simple split-valence basis sets [20] (*e.g.*, STO-3G, 4-21G). Among the following activities at higher basis-set levels, a paper by *Head-Gordon* and co-workers has played a key role [22]. In this work, the *Ramachandran* plot was systematically searched for all minimum conformations and transition states between them for For-Gly-NH_2 and For-Ala-NH_2 at the *Hartree–Fock*(HF)/3-21G and HF/6-31 + G* levels

of *ab initio* MO theory. The more elaborated split-valence basis set 6-31 + G* considers additional diffuse and polarization functions. Employing this basis set, the authors found six conformers for For-Ala-NH_2, which they denoted as C_{7eq}, C_5, C_{7ax}, β_2, α_L, and α'. The given order reflects the stability order. In view of only minuscule barriers of the β_2 and α_L conformers to the more stable C_{7eq} and C_{7ax} forms, respectively, these minima might even be neglected. *Fig. 1* illustrates the *Ramachandran* enery surface for the model compound Ac-L-Ala-NHMe [23]. Some of the mentioned conformers can directly be related to peptide secondary structures. Thus, the C_{7eq} conformer corresponds to the γ'-turn, the C_5 form can be considered as the parent conformation for β-sheet structures, and the C_{7ax} conformer represents the γ-turn. The torsion angles of the α_L conformer reflect approximately those of left-handed α- or 3_{10}-helices, which occur sometimes as a single turn at the end of a normally right-handed α-helix. The native α-helix (or the right-handed 3_{10}-helix nearby) itself is not a conformer on the conformational hypersurface at this approximation level.

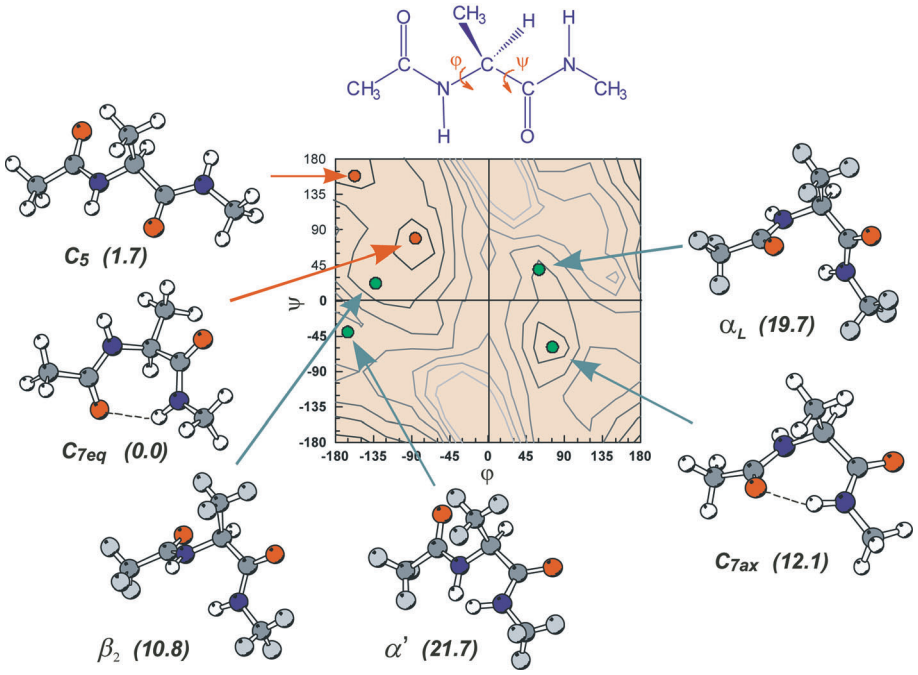

Fig. 1. Ramachandran *energy surface for Ac-L-Ala-NHMe at the HF/6-31G* level of* ab initio *MO theory.* Relative energies (in parentheses) in kJ/mol, most important experimental structures in red, data from [23].

The results obtained at the smaller 3-21G basis-set level are similar, but a seventh minimum appears denoted as α_D. The barrier between this relatively unstable conformer and the much more stable C_{7ax} form is extremely low. The work of *Head-Gordon* and co-workers stimulated a great number of further activities either on the

same model compounds or their blocked derivatives bearing terminal acetyl and *N*-methyl groups to improve the 'quantum chemical' *Ramachandran* plot. A wide variety of basis sets within the framework of the *Hartree–Fock* theory and various correlation energy models were employed in these calculations [23][24]. They confirm essentially the conformer list given above. An often successfully employed approximation level was HF/6-31G*, which is superior to HF/3-21G and still less time-consuming. The HF/6-31G* geometries of the conformers were sometimes the starting point for single-point calculations at much higher levels of *ab initio* MO theory. A thorough study of the influence of basis-set size and correlation effects on peptide structures was performed by *Perczel* and co-workers [24h]. They tested eleven basis sets between 3-21G and 6-311++G** within the *Hartree–Fock* theory on the For-Gly-NH_2 and For-Ala-NH_2 model compounds. The influence of correlation energy was estimated on the basis of the second order *Møller–Plesset* (MP2) perturbation theory. A profound comparison of *ab initio* MO data obtained at various approximation levels for alanine diamide models can also be found in [24n].

For the application of *ab initio* MO methods in foldamer research, it is encouraging to see in all these studies that the search for the most important conformers and the determination of their energetic order was rather successful at the *Hartree–Fock* level employing relatively low basis sets, *e.g.*, 6-31G* and 6-31G**, and neglecting correlation effects. Even the 3-21G basis set may be helpful for a first orientation. To refine the calculations by consideration of correlation effects, the B3LYP density functional [25] in combination with the 6-31G* or 6-31G** basis sets may be sufficient without a noteworthy increase of computational expense, even if some shortcomings of this density functional concerning the description of dispersion effects have to be considered [26]. Some further aspects have to be stressed. The number of conformers found at the lower and higher basis-set levels may differ. The calculations at lower approximation levels provide sometimes more conformers than at higher basis-set levels. However, these differences concern mostly higher-energy conformers, which may anyway be of lesser importance for further discussions. The molecular geometries of the conformers agree rather well at all levels. Stronger deviations can occur for the energy differences between the conformers. The stability order of the conformers may even change. In particular, HF/3-21G energy data have to be critically evaluated in this context. To avoid considerable computational efforts for a check of the stability order in larger systems, it is sometimes sufficient to perform single-point energy calculations at a higher approximation level based on the geometry from lower-basis-set optimizations. Consideration of correlation effects and extension of the basis set often stabilize higher-energy conformers relative to the most stable conformers.

The quantum-chemical results for various α-peptide constituents discussed so far reflect the conformational situation *in vacuo* or, in part, in an apolar solvent. Many experimental data indicate a substantial influence of polar solvents, in particular H_2O, on the structure of peptides. Thus, a comparison of vacuum data with data for polar solvents may provide differences. The explicit consideration of a sufficiently great number of solvent molecules in *ab initio* MO calculations of peptides leads quickly to an increase of the computational costs, which prevents such a supermolecule treatment. Moreover, it is difficult to localize the stationary points on the energy hypersurface in such a solute/solvent system due to the increased number of degrees of freedom.

Sometimes, at least few solvent molecules representing a first solvation sphere are explicitly considered in such calculations.

Continuum models represent a more feasible approximation to consider solvent effects, neglecting the explicit structure of the solvent molecules and describing the solvent as a continuum with global dielectric properties. In the quantum-chemical continuum models, the solvation effects are introduced into the semiempirical and *ab initio* MO *Hamiltonians* leading to the self-consistent reaction field MO (SCRF-MO) methods. Nowadays, various polarizable continuum models (PCM) represent the most popular form of the continuum theory of solvents in *ab initio* MO calculations [27].

Since the reaction-field methods estimate only the electrostatic part of the solute–solvent interactions, terms for the estimation of the energy of the *van der Waals–London* interactions between solute and solvent molecules and the cavitation energy, which describes the energy costs for the creation of a cavity of the size of the solute in the solvent, are complemented. It is obvious, that specific solute–solvent interactions are not considered by continuum models. Nevertheless, these computationally rather effective methods are often able to correctly describe solvent effects in a qualitative or semiquantitative manner, provided that specific interactions can be neglected or, better, do not essentially change in the various molecular states to be compared. Thus, PCM models estimate satisfactorily the change of molecular properties such as the conformational stability and the geometry going from the vacuum to the condensed phase. It is important to consider that new conformational minima may appear in the condensed phase, and vacuum minima may disappear. A thorough conformational analysis demands, therefore, both a vacuum and a condensed-phase search, which can be time-consuming. Thus, the PCM treatment is often limited to the vacuum conformers, which might be misleading in detail. Unfortunately, there are sometimes convergence problems in the geometry-optimization procedure of larger peptides employing PCM models. In view of the still insufficient possibilities to consider solvent effects in quantum-chemical calculations, the development of adequate methods remains a challenge for *ab initio* MO theory [28].

Continuum models were also extensively applied to the above discussed *Ramachandran* energy surface [29]. The vacuum conformers are essentially confirmed for the solvent H_2O. However, the stability order changes considerably. Dependent on the basis set, the originally most stable C_{7eq} conformer (γ'-turn) may even disappear. Most important is the additional appearance of two rather stable conformers corresponding to the right-handed α-helix/3_{10}-helix and the poly(proline) helix II (PP_{II}) on the *Ramachandran* surface. This reflects the experimental structure data of peptides and proteins for the condensed phase much better. Moreover, the reproduction of the right-handed α-/3_{10}-helical conformer demonstrates that this important secondary-structure element belongs already to the pool of conformers of the basic peptide units. Its formation does not require longer sequences, where H-bonding becomes possible.

The methodological aspects described and discussed in this paragraph may serve as a guideline for the application of *ab initio* MO methods to peptide foldamers. Considerations of the ratio between accuracy and computational costs become crucial in the field of foldamer research, where especially the backbone elongation leads to a combinatorial explosion of the conformational degrees of freedom for a given system. Thus, a systematic conformation search represents a great challenge.

3. *Ab initio* MO Theory and the Helices of ω-Peptides. – *3.1. Preamble.* The discovery of helix formation in β-peptide oligomers by *Seebach* and *Gellman* and their co-workers was as if the blinders were removed from our eyes. It provokes the question, why this was not found earlier. Obviously, helices like those in the native α-peptides were not expected by many chemists and biochemists in short oligomers of β- or other ω-amino acids. One reason for this could have been a misunderstanding of what is called 'free rotation around single-bonds' with the implicit understanding that the additional single-bond in β-amino acids leads to higher flexibility preventing the formation of stable ordered structures in oligomers. In reality, the third single-bond seems to reduce strain on the backbone, when realizing a given H-bonding pattern. Basically, a rotation around this bond generates conformers of comparable quality as those resulting from the rotation around the other single-bonds. Thus, we can expect a greater diversity of backbone structures in β-peptides in the first line, when comparing the conformational situation in β- and α-peptides [5b]. Another barrier makes us possibly more resign if looking for secondary structures in ω-peptides: the entropy aspect. Popular textbooks on peptides like that of *Creighton* [30] discuss in their chapters on protein secondary structures the conformational entropy contribution to the formation of a secondary structure element like an α-helix according to the equation for the conformational entropy $\Delta S_{conf} = R \ln N$, where R is the gas constant and N means the number of conformers for an amino acid constituent. In an example, *Creighton* assumes eight conformers for an α-amino acid constituent, which corresponds reasonably to the conformer pool of the *Ramachandran* plot given above. In a periodic secondary structure element, all amino acid constituents assume the same conformation. According to the equation for the conformational entropy, this means a contribution of *ca.* -123 kcal/mol for $T\Delta S$ to the free enthalpy in a sequence of 100 amino acids, which has to be compensated by enthalpy contributions, such as H-bonds, *etc.*, to generate a stable structure with these backbone angles. Even if we are not so ambitious to generate helices of 100 amino acids length, the relation between entropy and enthalpy contributions to the free enthalpy is about kept in shorter sequences, too. Bearing this example in mind, it is rather discouraging to look for secondary structures in β- or still higher ω-amino acid oligomers with much more conformers of the basic constituents, and it remains indeed a surprise to have found them. In any case, it is not astonishing that the inspiration for β-peptide secondary structures did not come so much from analogy considerations to native α-peptides, even if this has become a driving force in foldamer research nowadays. Instead, hints for ordered structures in sequences of ω-amino acids came from other fields, in particular material sciences, *e.g.*, nylon derivatives, partially already decades ago [31]. Unfortunately, the structure of such polymers remained often contradictory. Such uncertainties concerned also the above-mentioned results of *Muñoz-Guerra* and co-workers for poly(β-aspartate)s at first. *Seebach* and co-workers pointed out that their activities in the field of β-peptides were originally not inspired by native peptides but by their finding of helical structures in poly(3-hydroxybutanoate) (PHB) [32], which opened the access to β-peptide secondary structures *via* ideas of isosterism. Lastly, the unequivocal finding of helices in short oligomers of β-amino acids was the decisive impact for foldamer research.

The first important contribution of *ab initio* MO theory to the foldamer field was the study by *Alemán* and co-workers [33] on the conformation of the repeating unit α-

methyl-L-β-aspartyl (modeled by *N*-acetyl-*N*′,α-dimethyl-L-aspartamide) of the above-mentioned special poly(L-β-aspartate)s. In *Alemán*'s study, some conformational properties of β-peptide constituents become visible, but the focus is again on the helix formation in these special polymers. Thus, more general aspects are kept to the sidelines. Publication of this paper in 1996 coincides with the appearance of the papers from the groups of *Seebach* [1] and *Gellman* [2]. This coincidence of the publication of the experimental papers, which initiated foldamer research, with the theoretical contribution of *Alemán* and co-workers demonstrates that *ab initio* MO methods accompany the experimental activities on foldamers from the very beginning, which will be documented by the presentation of further examples on oligomers of ω-amino acids in the following paragraphs.

3.2. *Homooligomers*. 3.2.1. *General*. At first, results of *ab initio* MO theory for the helix formation in oligomers of the same type of ω-amino acid building blocks will be presented. The above-mentioned homologation of the α-amino acid backbone by continuous insertion of methylene groups leads to β-, γ-, δ-, and ε-amino acids, *etc.*, which are the constituents of β-, γ-, δ-, and ε-peptides then. The helical structures and their typical H-bonding patterns in these peptide classes can be classified into three types (*Fig. 2*). The first type of helices is characterized by the formation of H-bonds between the NH and CO groups of peptide bonds in forward direction of the sequence (see **A** in *Fig. 2*). The second helix type forms the H-bonds in backward direction (see **A**). These helices are periodic structures, where all amino acid constituents have the same conformation, represented by equal values of the corresponding backbone torsion angles, and all H-bonded rings have the same size, which may differ dependent on the position of the interacting peptide bonds in the sequence. The third type of helices possesses dimer periodicity, *i.e.*, only every second amino acid in the sequence has the same backbone-torsion-angle values. This dimer periodicity leads to H-bonding patterns, where the H-bond directions alternate in forward and backward direction (see **B** and **C** in *Figs. 2*). The size of the H-bonded rings differs in alternate order, too [34]. Such helices were already found in sequences of alternating D- and L-α-amino acids. Well-known is the structure of gramicidin A with alternating 20- and 22-membered H-bonded rings [35], but also helices with alternating 14- and 16-membered rings were found in DL-α-peptides [36]. Such helices are denoted as β-helices because the H-bonding pattern is similar to that of parallel β-sheet structures. When *Seebach* and co-workers found this helix type in β-peptides [37], they coined the notation mixed helices.

One aim of the theoretical activities is the search for all possible helix types in ω-amino acid sequences. Starting point of a complete theoretical conformational analysis are mostly the basic amino acid constituents of the ω-peptides, performing a systematic variation of the backbone torsion angles (*monomer approach*). Geometry optimization of the starting conformations leads to the possible conformers of the individual constituents. This conformer pool may contain conformers with H-bonds between nearest-neighbor peptide bonds, which can be oligomerized to periodic structures. Besides, there can be conformers without H-bonds leading nonetheless to H-bonded helices after oligomerization. Finally, conformers forming periodic structures without H-bonds, and conformers which are not able to form periodic structures complete the possibilities. As described above, the monomer approach was successfully applied to

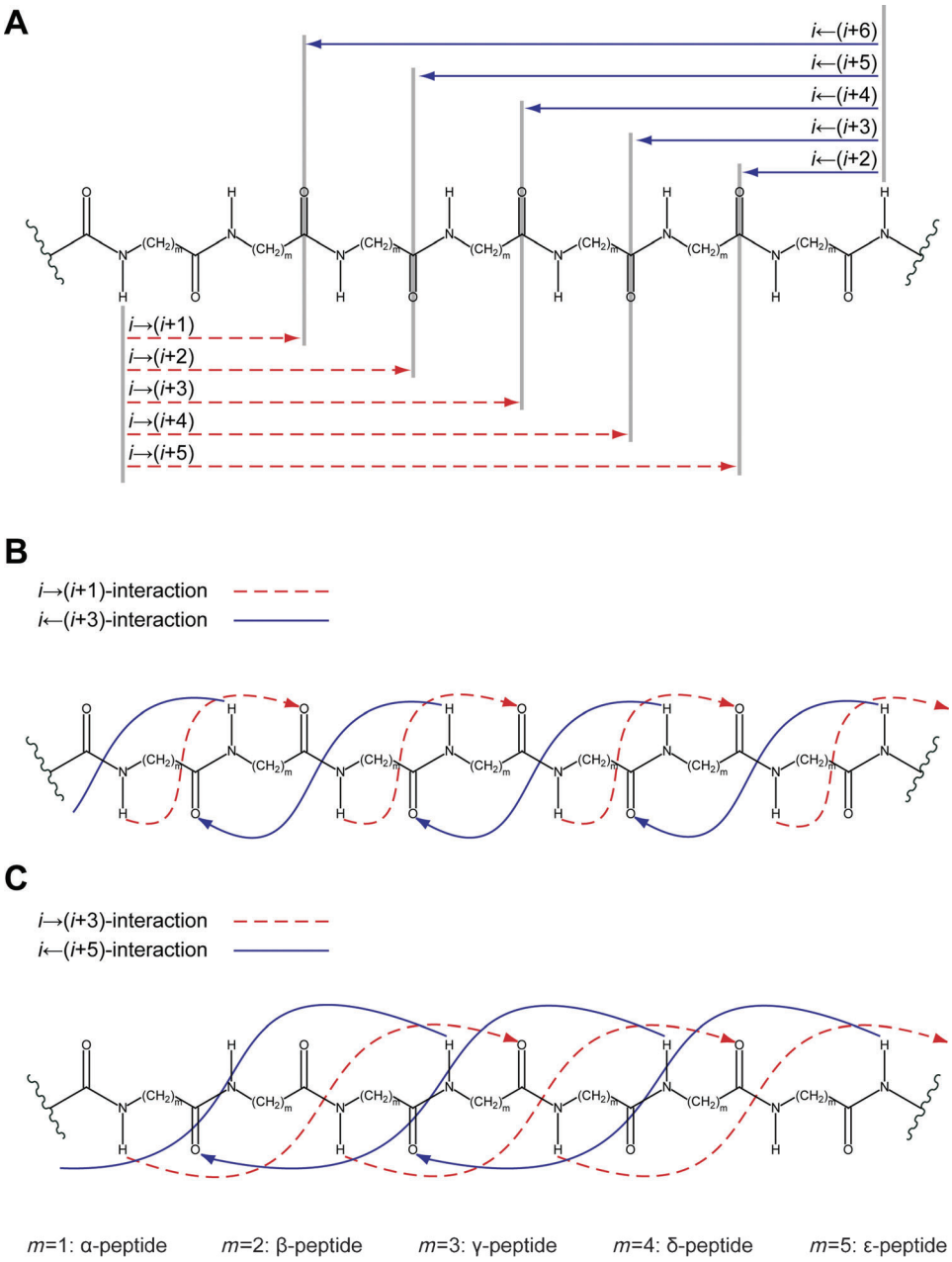

Fig. 2. *H-Bonding types for helices in foldamers of ω-amino acids and their interaction patterns.* **A**: unidirectional helices in forward and backward direction of the sequence; **B**: mixed or β-helices with the basic H-bonded ring combinations; **C**: mixed or β-helices with the next larger H-bonded ring combinations.

get the conformers on the *Ramachandran* energy surface of α-peptides. In higher homologous ω-amino acid constituents with their increasing number of backbone atoms, the probability becomes greater that conformers with H-bonds between nearest-neighbor peptide bonds are preferred, and the conformer pool at the monomer level no longer contains the basic conformations for helices with H-bonds between nonnearest-neighbor peptide bonds. In these cases, the conformational analysis has to be extended to oligomers of sufficient length testing for characteristic H-bonding patterns (*oligomer approach*). This approach is based on the systematic variation of the backbone torsion angles of the oligomer with a given grid size. The possible periodic structures generated in this way are checked on the fly for the presence of H-bonding according to the patterns in *Fig. 2*. Structures with such a pattern are the starting points for geometry optimization then employing *ab initio* MO methods. Although tedious at the *ab initio* MO level, such calculations are possible now. There is a good chance to find all possible periodic structures with and without H-bonds by a combination of the monomer and oligomer approach. The monomer approach provides the periodic structures with nearest-neighbor peptide-bond interactions and without H-bonds from the conformer pool of the basic constituents, and the oligomer approach finds the helices with the larger H-bonded rings. To get a complete overview on all possible helix types, the search should be performed with unsubstituted backbones at first to avoid conformational backbone restrictions by substitution. Afterwards, the examination of the influence of backbone substitution for the generation of special helix types could be complemented. The results presented in the next paragraphs were mostly obtained following these lines.

3.2.2. *β-Peptides.* After the above-mentioned study by *Alemán* and co-workers [33], *ab initio* MO conformational analyses were performed on various blocked and unblocked models of unsubstituted and substituted β-peptide constituents by *Wu* and *Wang* [38] and by our group [39] to generalize the conformational properties for secondary-structure formation in β-peptides. The essential aspects of these studies were later confirmed and extended by various authors, in part at higher approximation levels [40]. Different from α-peptides, the results depend sometimes on the selected terminal groups of the model compounds.

As a representative example for the conformation pool of β-amino acid constituents, a selection of theoretically obtained conformers for the 3-(acetylamino)-*N*-methylbutanamide (Ac-β-Abu-NHMe) constituent with a methyl group in β-position of the basic structure **1**, which are characterized by H-bonds and related to experimentally found structures, is given in *Table 1*. The corresponding information is also available for the unsubstituted 3-(acetylamino)-*N*-methylpropanamide (= *N*-acetyl-*N*′-methyl-β-alaninamide) constituent Ac-β-Ala-NHMe, *i.e.*, **1** and the 3-(acetylamino)-*N*,2-dimethylpropanamide constituent Ac-β-Aib-NHMe, with a Me group in α-position of structure **1** [39].

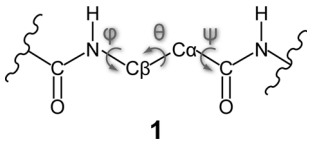

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Table 1. *Backbone Torsion Angles and Energies of H-Bonded Conformers of the β-Peptide Constituent Ac-β-Abu-NHMe* (= AcNHCH(Me)CH_2CONHMe) *and Relationships to Experimentally Found β-Peptide Structures Determined at the HF/6-31G* Level of* ab initio *MO Theory*

Conf.[a])	φ[b])	θ[b])	ψ[b])	ΔE[c])	Type[d])	Experiment[e])
B1	−143.7	−63.8	−144.6	0.0[f])	C_6	[41a][41b][41c][65][66]
B2	−71.9	144.4	−80.9	6.8	C_8	
B2′	60.4	−124.1	86.7	22.8	C_8	
B3	−63.7	−45.0	111.2	7.0	C_8, $H_{10/12}$	[37a][37b]
B3′	55.3	51.1	−116.0	6.2	C_8, $H_{10/12}$	[37a][37b]
B4	63.5	59.3	−159.0	6.9	C_6	
B5	−160.6	56.0	102.6	6.6	C_6	[41a][41b][41c]
B6	−111.9	60.2	25.6	7.2	C_8	[42][43][44]
B9	−91.4	49.8	90.4	9.3	$H_{10/12}$	[37a][37b][45b]
B9′	78.8	−47.0	−95.3	29.4	$H_{10/12}$	[37a][37b][45b]
B10	−155.0	63.4	−129.3	18.9	H_{14}	[1a][2a][2c][45e][67]
B11	−109.4	74.1	−90.8	22.5	H_{12}	[2b][45d][45e]
B18[g])	59.1	51.6	90.5	–[g])	C_{10}	
A15[h])	77.2	55.6	65.7	–[h])	C_{10}	

[a]) For the complete list of conformers, see [39]. [b]) Angles in degrees. [c]) Energies in kJ/mol. [d]) C_x: H-bonded cycle with x atoms; H_x: monomer of a helix with x-membered H-bonded turns; $H_{x/y}$: mixed or β-helix. [e]) Key references for experimental data. [f]) $E_T = -531.897970$ a.u. [g]) Localized for Ac-β-Abu-NHMe at the SCRF/HF/6-31G* level, energy comparison impossible, therefore. [h]) Localized for Ac-β-Aib-NHMe at the HF/3-21G level, energy comparison impossible, therefore.

The calculations predict various rather stable conformers forming 6- and 8-membered H-bonded pseudocycles (C_6 and C_8). Recent IR and UV studies in combination with high-level *ab initio* calculations on Ac-β-hGly-NHMe (= AcNHCH_2CH_2CONHMe), Ac-β-hAla-NHMe (= AcNHCH(Me)CH_2CONHMe), and Ac-β-hPhe-NHMe (= AcNHCH(CH_2Ph)CH_2CONHMe) confirm the predominance of these rings with nearest-neighbor peptide-bond interactions in the conformer pool with a preference of C_6 structures in the equilibrium [41]. All C_6 and C_8 conformers can be extended to periodic structures, which can formally be considered as helices, but resemble more ribbon-like structures (*Fig. 3*). A C_8 ribbon was experimentally found in short oligomers of the achiral monomer 1-(aminomethyl)cyclopropanecarboxylic acid [42], in oligomers of (*2R,3S*)-3-amino-2-hydroxyalkanoic acid residues [43], and in oxanorbornene β-peptides [44]. In these cases, the C_8 conformer **B6** in *Table 1* is the theoretical counterpart. The corresponding C_8 rings were also predicted for the unsubstituted and 2-methyl-substituted backbones [39].

Table 1 shows further interesting conformers. The theoretically predicted conformers **B10** and **B11** can immediately be related to the already mentioned and for the stimulation of foldamer research so important 14- and 12-helices [1][2][5o][5r][45]. Conformer **B10** can be regarded as the constituent of a left-handed helix with 14-membered H-bonded rings in forward direction of the sequence. Connecting **B11** conformers, one gets a helix with 12-membered pseudocycles in backward direction. The conformer pairs **B3′**/**B9** and **B3**/**B9′** lead to a mixed helix [5o][5r][37][45b] with 12/10- or, alternatively, 10/12-membered H-bonded rings in alternate order (*Fig. 2*, there **B** and **C**). Although the conformers **B3** and **B3′** represent C_8 rings, only small

changes of the torsion angles allow the adaptation of 12/10- or 10/12-rings in combination with the conformers **B9** and **B9′**, respectively. The basic constituent **1** itself is not able to form the H-bonds of 14-, 12-, and 12/10-helices. Obviously, the helix conformations are already preformed in the conformers of the basic constituents and do not require H-bonds for their formation. This corresponds to the situation in the native α-/3_{10}-helices. As shown above, the α-/3_{10}-conformation range appears as a conformer in the *Ramachandran* plot of For-Ala-NH_2 or Ac-Ala-$NHCH_3$ estimated for a polar environment [23][29].

Among the conformers of Ac-β-Abu-NHMe, we find also a conformer for a stable 10-helix at the SCRF/HF/6-31G* level of *ab initio* MO theory for the solvent H_2O (conformer **B18** in *Table 1*) [39]. However, the torsion angles of $\varphi = 59.1°$, $\theta = 51.6°$, and $\psi = 90.5°$ and also those for the corresponding Ac-β-Aib-NHMe conformer with $\varphi = 77.6°$, $\theta = 49.3°$, and $\psi = 56.8°$ are in a range completely different from that of the 14-helix. According to the theoretical calculations, this 10-helix remains rather stable in oligomers but was never found in experiments up to now. Only a 10-ring turn with about these backbone angles occurs in a β-amino acid dipeptide [42]. Remembering the close conformational relationship between the 3_{10}- and α-helices in native peptides, a comparable relationship could exist between the 14-helix with torsion angles of $\varphi = -155.0°$, $\theta = 63.4°$, and $\psi = -129.3°$ (conformer **B10** in *Table 1*) and a postulated 10-helix with similar torsion angles. *Seebach* and co-workers even discuss a possible equilibrium between such a 10- and the 14-helix [15d][15k]. The existence of this 10-helix in β-peptides remains a bit mysterious. On the basis of the model compounds Ac-β-Ala-NHMe, Ac-β-Aib-NHMe, and Ac-β-Abu-NHMe and the corresponding oligomers, it cannot be localized in the suggested torsion-angle range. Starting geometry optimizations from conformations with an approximate 10-ring pattern leads mostly to the 14-helix. However, *Fülöp* and co-workers found such a 10-helix in NMR studies on *unprotected* oligomers of *trans*-2-aminocyclohexanecarboxylic acid (ACHC) and confirmed it by *ab initio* MO calculations (*Table 2*) [46]. Interestingly, they found this 10-helix only for tetramers, whereas the unprotected pentamers and hexamers form the 14-helix. The terminally protected oligomers form exclusively the 14-helix. This shows the delicate energetic balance between both helix folds and reminds indeed of the situation in α-peptides, where the α-helix gains its energetic preference over the 3_{10}-helix only with increasing sequence length. Other experiments to find a comparable 10-helix stem from the group of *Jagadeesh*, *Chandrasekhar* and co-workers [47]. Here, the formation of the 10-helix is tried in a C_6-strand/14-helix mixed conformation pool. The helix obtained is distorted, but a few turns have the C_{10} geometry with the supposed torsion angles. For completeness, the 10-helix of *Fleet* and co-workers has to be mentioned [48]. The β-peptide constituent contains a four-membered oxetane ring with the amino and carboxy groups in *cis* position at the ring, leading to a backbone conformation which cannot be expected from sequences of β-amino acids with typical amino acid side chains. The experimentally found and theoretically confirmed or predicted 14-, 12-, 10-, and mixed 12/10(10/12)-helices are visualized in *Fig. 3* together with examples for C_6 and C_8 oligomers.

There are hints for helices with larger 16- and 18-membered H-bonded cycles from fibre diffraction studies on poly(aspartate)s [6f][10c][11b], which cannot be obtained by a monomer approach. Rather perfect 16-helices can be localized in blocked

Table 2. *Backbone Torsion Angles of Various Forward and Backward Helices of β-Peptides According to* ab initio *MO Theory*

Helix	φ[a])	θ[a])	ψ[a])	Handedness
H_{10}[b])	– 152.6	51.0	– 128.1	left-handed
H_{12}[c])	– 87.0	92.5	– 112.8	right-handed
H_{14}[d])	– 144.6	59.4	– 135.4	left-handed
H_{16}[e])	– 139.0/ – 92.1	89.7	– 130.9/ – 117.0	right-handed
H_{18}[f])	– 142.8	80.0	– 145.8	left-handed
H_{18}[g])	– 153.8	72.7	– 137.5	left-handed

[a]) Angles in degrees. [b]) 10-Helix of the unprotected tetramer of ACHC at the HF/3-21G level of *ab initio* MO theory [46]; backbone torsion angles from averaging over the two central amino acids. [c]) 12-Helix of Ac-(β-Abu)$_6$-NHMe at the HF/6-31G* level of *ab initio* MO theory; backbone torsion angles from averaging over the two central amino acids. [d]) 14-Helix of Ac-(β-Abu)$_6$-NHMe at the HF/6-31G* level of *ab initio* MO theory; backbone torsion angles from averaging over the two central amino acids. [e]) 16-Helix of Ac-(β-Abu)$_{10}$-NHMe at the HF/6-31G* level of *ab initio* MO theory; torsion angles φ and ψ alternate with the given average values for three alternating residues of the six central residues. [f]) 18-Helix for the octamer of *trans*-ABHC and β^3-hSer [49], re-optimized at the B3LYP/6-31G* level of *ab initio* MO theory; backbone torsion angles from averaging over the four central amino acids. [g]) 18-helix of Ac-(β-Abu)$_8$-NHMe at the B3LYP/6-31G* level of *ab initio* MO theory; backbone torsion angles from averaging over the four central amino acids.

hexamers and higher oligomers of the β-Abu constituent by *ab initio* MO theory. Only the first H-bond in the sequence shows bifurcation with a C_{12} ring. In *Table 2*, average values for the backbone torsion angles for the blocked decamer are given as a representative example. The torsion angles θ of the central six residues exhibit only small deviations from the average value of 89.7°, the angles φ and ψ of these residues assume alternating values of $-139.0°$ and $-92.1°$ for φ on the average and $-130.9°$ and $-117.0°$ for ψ along the sequence. Recently, *Martinek* and co-workers obtained an 18-helix in β-peptides composed of 2-amino-6,6-dimethylbicyclo[3.3.1]heptane-3-carboxylic acid (ABHC) and β^3-hSer and confirmed the structure by *ab initio* MO calculations (*Table 2*) [49]. Such an 18-helix can also be found in blocked octamers of β-Abu constituents by *ab initio* MO theory (*Table 2*). Further theoretical studies on the basis of the oligomer approach could be useful to confirm and characterize helices with still larger H-bonded cycles.

The theoretical calculations on monomers and oligomers of various β-peptide building blocks provide useful insights into the secondary-structure formation in β-peptides. It is striking that the most important helix types can directly be derived from the conformation pool of the constituents, even if the H-bonds are formed between nonnearest-neighbor peptide bonds. The corresponding conformers exhibit *gauche* conformations for the central single-bond described by the backbone torsion angle θ, apparently a prerequisite for helix formation in β-peptides (*Tables 1* and *2*). The preference of this *gauche* arrangement indicates a conformation space of β-peptide constituents more limited than expected. The values of the torsion angle θ for 14-helices are near $\pm 60°$. They tend to $\pm 90°$ for 12-helices and are smaller than $\pm 60°$ for all types of 10-helices.

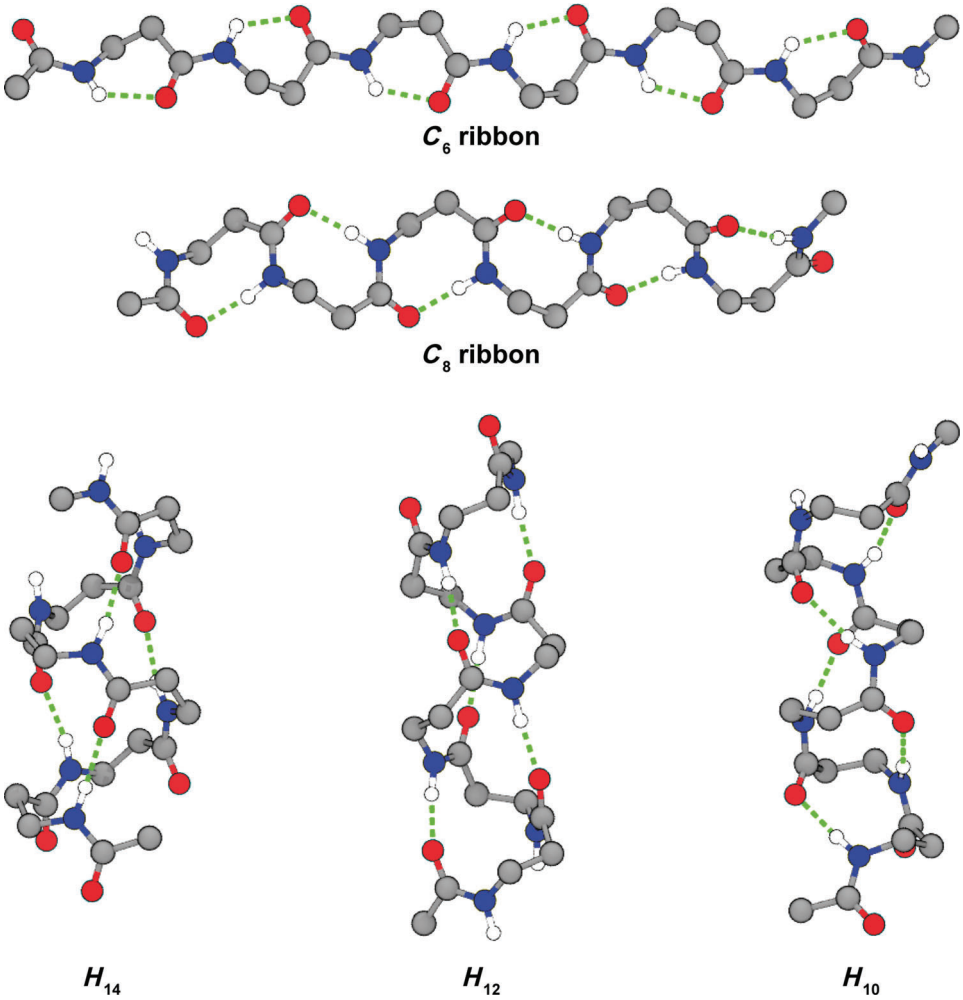


Fig. 3. *Representative ribbon and helix structures of β-peptides predicted by* ab initio *MO theory*

A systematic increase of the length of C_6, C_8, C_{10}, C_{12}, C_{14}, and mixed C_{10}/C_{12} oligomers of unsubstituted β-alanine and the comparison of the energy differences $E(n)-E(n–1)$, where n is the number of monomers, shows cooperative effects in the 14-, 12-, and 10-helices, *i.e.*, the addition of each new monomer leads to a higher stability increase than resulted from the addition of the preceding constituent [5x][40b]. Contrary to this, the energy contributions of the constituents are additive for the C_6 and C_8 ribbons. These calculations also show that the stability order of the various periodic structures changes with increasing sequence length. In shorter sequences, the C_6 and C_8 oligomers with nearest-neighbor peptide-bond interactions are favored. The 10- and 12-helices become more stable than the C_6 and C_8 ribbons in longer sequences. The 14-helix is disadvantaged but is stabilized in polar solvents. The

corresponding results for oligomers of β-Abu are a bit different. They show the C_6 and C_8 trimers still a bit more stable than the 10-, 12-, and 14-trimers, but the stabilities of all tetramers are close together *in vacuo* [39]. In a polar environment, the 14- and 12-helices are distinctly favored. These data demonstrate the high structural sensitivity of β-peptide oligomers. Not quite unexpected, helices with larger H-bonded rings gain gradually more stability in longer sequences than periodic structures with nearest-neighbor peptide-bond interactions or with H-bonded pseudocycles of smaller size as it can also be seen for the native α- and 3_{10}-helices.

Most striking is the high stability of mixed 12/10(10/12)-helices, which are always more stable than the unidirectional helices *in vacuo* or in apolar solvents. However, this situation changes in a polar environment. Mixed helices have a distinctly lower dipole moment due to the compensating dipoles of the alternating H-bonds pointing in opposite direction. Helices with only forward or backward H-bond directions are, therefore, favored in polar solvents by their macrodipoles growing with the sequence length.

It should be mentioned that *ab initio* MO conformational analyses indicate the possibility of another two mixed 12/10(10/12)-helices in β-peptides, which are, however, less stable than *Seebach*'s mixed helix [50]. *Ab initio* MO theory suggests not only several folding alternatives for the same H-bonded ring patterns but additionally mixed helix types with combinations of larger rings. On the basis of *ab initio* MO theory, it could also be demonstrated that the formation of mixed or β-helices is a general folding principle in oligomers of all ω-amino acids [50a].

Table 2 summarizes the backbone torsion angles for 10-, 12-, 14-, 16-, and 18-helices obtained by *ab initio* MO theory. It is remarkable, that the backbone torsion angles of all helices are close to each other. The same sequence of signs (−),(+),(−) induces right-handedness for backward helices and left-handedness for forward helices. The opposite sequence of signs generates the mirror images. Obviously, small structural changes decide on handedness and helix type.

The theoretical data presented in the preceding paragraphs demonstrate the wide variety of secondary structures resulting from the conformer pool of β-peptide constituents. These conformers may be the starting point to search for structure modifications in favor of the one or the other special structure in modelling studies. The aim is mostly to find backbone restrictions in favor of torsion angles for a special secondary structure.

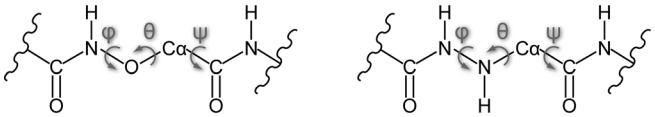
Among the many possibilities of structure modifications to vary helix type and handedness, cyclic side chain constraints proved to be especially useful. Whereas the 14-helix is preferred in protected oligomers of *trans*-2-aminocyclohexanecarboxylic acid [2a][45d], the change to the smaller cyclopentane ring provides the 12-helix in oligomers of the *trans*-2-aminocyclopentanecarboxylic acid monomer [2b][45e]. In the same way, the cyclobutane backbone with its different configurational aspects leading to 14- and 12-helices or to C_6 and C_8 ribbons [51] was successfully tried and the obtained structures partially described by *ab initio* MO theory.

The influence of backbone substitution was extensively examined by *ab initio* MO theory with respect to configurational consequences for helix stability and handedness [5n][38b][52][53]. The theoretical predictions fairly agree with experimental experience. Only a few examples may be given for illustration. Thus, the left-handed 14-

helix is favored with (*S*)-configuration at a 3-substituted constituent or (2*S*,3*S*)-configuration at a 2,3-disubstituted constituent, but the same substitution patterns favor also a right-handed 12-helix. Comprehensive theoretical analyses of backbone substitution exist for *Seebach*'s mixed 12/10(10/12)-helix [50b]. Considering the dimer periodicity, they predict an especially favorable formation of right-handed 10/12-helices with (*S*)-configuration alternating at the 2-position of the first and at the 3-position of the second amino acid constituent in the sequence. (*S*)-Configuration at the 3-position of the first and at the 2-position of the second constituent favor a right-handed 12/10-helix.

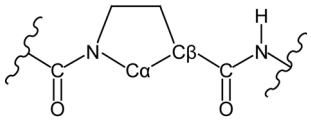
The role of the terminal groups can also be important, as was shown above for the formation of the 10-helix in the unprotected tetramer of *trans*-2-aminocyclohexanecarboxylic acid, whereas the protected oligomers form the 14-helix [46]. Aspects of capping did not attract much attention in theoretical calculations until now.

An interesting extension of the β-peptide concept was introduced by the isosteric replacement of the β-methylene group in the β-amino acid constituents by an O-atom or an NH group. In the first case, we come to α-aminoxy acids **2**, the constituents of oxapeptides. In the second case, we get α-hydrazino acids **3**, which could be constituents of hydrazino or aza-β^3-peptides. Remembering the special conformational properties of hydroxylamine and hydrazine arising from lone-pair interactions, unusual effects could be expected in these constituents and their oligomers. Numerous α-aminoxy peptides were synthesized by *Yang* and co-workers and thoroughly theoretically examined by the *Wu* group [5s][54]. The most stable conformer of the basic constituent **2** is an 8-membered ring structure (α-*N*-*O* turn), which finds its counterpart in conformer **B6** of the β-peptides in *Table 1*, which was already discussed as constituent of a C_8 ribbon in β-peptides. Since the rotation direction of the *N*-*O* turn is determined by the chirality at the $C(\alpha)$-atom, the torsion angles may also have the opposite signs (mirror image). Different from β-peptides, the 8-ring conformer determines also the most stable structure of α-aminoxy acid oligomers. Obviously, nearest-neighbor peptide-bond interactions are preferred in this peptide class.



A comparable situation was found in hydrazino peptides (aza-β^3-peptides), which exhibit also an 8-membered structure (*hydrazino turn*) as their basic unit. This hydrazino turn corresponds to the same C_8 ring of β-peptides **B6** as in the α-aminoxy peptides. The hydrazino turn was predicted by *ab initio* MO theory [55]. Dependent on the approximation level, the hydrazino turn of the basic constituent **3** and its oligomers is the most stable structure or belongs to the most stable structures in the conformer pool. *Le Grel* and co-workers were able to confirm the theoretical predictions in numerous papers by experiment and further theoretical studies [56]. The experimental backbone torsion angles are $\varphi = -133^\circ$, $\theta = 75^\circ$, and $\psi = 14^\circ$ for the basic 8-ring of **3**, the theoretical data are $\varphi = -113.1^\circ$, $\theta = 69.0^\circ$, and $\psi = 18.5^\circ$ [55][56]. Interestingly, *Lelais* and *Seebach* did not find ordered structures in their β^2-oligoazapeptides [57].

In the preceding paragraphs, helices with characteristic H-bonding patterns were presented. Comprehensive *ab initio* MO studies on β-proline oligomers **4**, which cannot form H-bonds, were performed by *Carlson* and co-workers [58]. They indicate left-handed helices with *cis* peptide bonds and right-handed helices with *trans* peptide bonds. These helices behave similarly to α-proline helices. In this context, oligomers of pyrrolidine-4-carboxylic acid have also to be mentioned [59].



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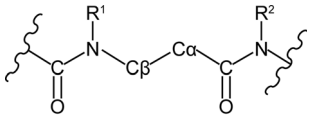

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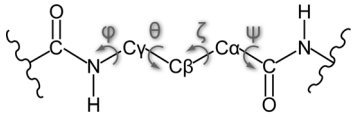
Among the various foldamer classes, peptoids deserve special attention [5c] [60]. The originally as N-substituted oligoglycines suggested foldamers [61] exhibit characteristic secondary structures [62], which were confirmed and partially predicted by *ab initio* MO theory [63]. In the meantime, the peptoid concept was extended to β-peptoids **5** with substituted N-atoms in the β-alanine constituents [64]. The formation of helices in these β-peptoids was extensively examined by *ab initio* MO studies [63d]. All these examples demonstrate the great possibilities for *ab initio* MO methods to support and stimulate experimental activities.

3.2.3. *γ-Peptides.* After early suppositions on helical structures in poly(γ-glutamate)s by *Rydon* [68], the groups of *Seebach* [5o][5r][69] and *Hannessian* [70] showed convincingly in 1998 that oligomers of monosubstituted γ-amino acids are able to form helices. The success of *ab initio* MO theory to predict the main conformers of β-peptides stimulated comparable activities for γ-peptides. Of course, it would have been tempting to derive the essential helical structures of γ-peptides from the conformer pool of the basic constituent **6** on the basis of a monomer approach, which has been so successful in α- and β-peptides.



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However, the limitations of the monomer approach discussed above become visible in the γ-peptide class. Conformers with nearest-neighbor peptide-bond interactions forming 7- and 9-membered H-bonded rings, which can be oligomerized to stable periodic structures, are predicted as most stable, together with conformers without H-bonds. However, conformers leading to helices with larger H-bonded pseudocycles after oligomerization were not predicted. Therefore, it was necessary to look for these helices employing the oligomer approach. A wide variety of forward and backward

helices reaching from C_7 and C_9 ribbons/helices up to 24-helices resulted from this conformational search [71]. Besides, several mixed helices with 14/12(12/14)- and 22/24(24/22)-ring alternation were localized [50a]. Helix alternatives with different backbone conformation but the same H-bonding pattern were predicted for forward and backward helices in γ-peptides. Obviously, the longer backbone in the γ-peptide constituents allows for alternative backbone conformations with the same H-bonding pattern. In β-peptides, this occurred only for mixed helices. The 9- and 14-helices with backward H-bond orientation proved to be the most stable unidirectional helices. The backbone torsion angles estimated by *ab initio* MO theory [71] for both helices agree very well with experimental data [69][72] (*Table 3*). The theoretical data for C_7 and C_9

Table 3. *Backbone Torsion Angles and Energies of Selected Secondary Structures of Hexamers of the Basic γ-Peptide Constituent* **6**, *of the* cis *and* trans *Forms of the Vinylogous γ-Peptide Constituents* **7a** *and* **7b**, *and of the β*-N-O Turns **8** *with Relationships to Experimentally Found Helices and Turns Determined at the HF/6-31G* Level of* ab initio *MO Theory*

Helix/Turn[a])	Method	φ[b])	θ[b])	ζ[b])	ψ[b])	ΔE[c])	Ref.
γ-Peptides[d]):							
H_7^{II}	*ab initio*	−94.3	−48.4	−50.2	−103.8	48.4	[71]
C_7	X-ray	−94.9	−47.5	−53.6	−113.6	–	[72c][e])
H_9^{I}	*ab initio*	97.5	−69.7	−75.2	97.0	5.8	[71]
H_9	NMR	125	−68	−65	97	–	[72b]
H_9	X-ray	109	−63	−77	88	–	[72a]
C_9	X-ray	95.2	−64.3	−73.3	80.6	–	[72c][e])
H_9^{II}	*ab initio*	74.9	−161.3	73.4	3.3	50.7	[71]
H_{14}^{I}	*ab initio*	135.7	−61.9	−66.5	141.8	0.0[f])	[71]
H_{14}	X-ray	153.5	−66.4	−55.8	124.9	–	[69b][69c]
H_{19}^{II}	*ab initio*	−74.4	−63.3	169.8	−148.0	60.8	[71]
H_{19}	X-ray	−71.0	−53.0	171.6	−160.6	–	[6f][74]
Vinylogous γ-Peptides:							
C_9 (*cis*)[g])	*ab initio*	−79.8	122.8	0.1	−46.5	–	[76]
C_9 (*cis*)	X-ray	−76	123	0	−57	–	[77]
Ext. (*trans*)[h])	*ab initio*	−91.3	113.9	−177.2	−29.4	–	[76]
Ext. (*trans*)	X-ray	−82	128	−179	−22	–	[77]
β-Aminoxy Turns:							
C_9^{Ii})	*ab initio*	−114.9	84.4	71.1	−97.6	0.0[j])	this work[i])
C_9^{I}	X-ray	−120.7	73.9	75.2	−71.6	–	[78b]
C_9^{I}	X-ray	−115.9	70.4	77.5	−70.1	–	[78b]
C_9^{IIi})	*ab initio*	−106.2	173.0	−73.2	16.4	0.5	this work[i])
C_9^{II}	X-ray	−90.2	172.8	−65.0	4.2	–	[78b]
C_9^{II}	X-ray	−97.8	167.2	−71.7	9.8	–	[78b]

[a]) C_x: H-bonded cycle with x atoms; H_x: helix with x-membered H-bonded turns. [b]) Angles in degrees, backbone angles for the helices result from averaging over all constituents neglecting the terminal residues. [c]) Energies in kJ/mol. [d]) For the complete list of γ-peptide helices, see [71]. [e]) For numerous further experimental structures with similar backbone angles, see Table S1 of the Supporting information in [6f]. [f]) $E_T = -1956.361656$ a.u. [g]) γ-Methyl-substituted derivative **7b** (most stable conformer *G*1 in [76]). [h]) γ-Methyl-substituted derivative **7a** as extended form (most stable conformer *G*2c in solution according to [76]). [i]) Structure **8** re-optimized for this work at the HF/6-31G* level; for extensive calculations on β-aminoxy turns, see [78b]. [j]) $E_T = -567.651343$ a.u.

rings agree also with the torsion angles found in many experimental studies on peptides with single γ-amino acid constituents [6f][73]. The catalogue of theoretically predicted structures includes also a 19-helix, which finds its counterpart in an experimental structure [6f][74]. *Table 3* informs about the backbone torsion angles of important γ-peptide conformers estimated by *ab initio* MO theory and compared with experimental data. *Fig. 4* shows the predominating 9- and 14-helices.

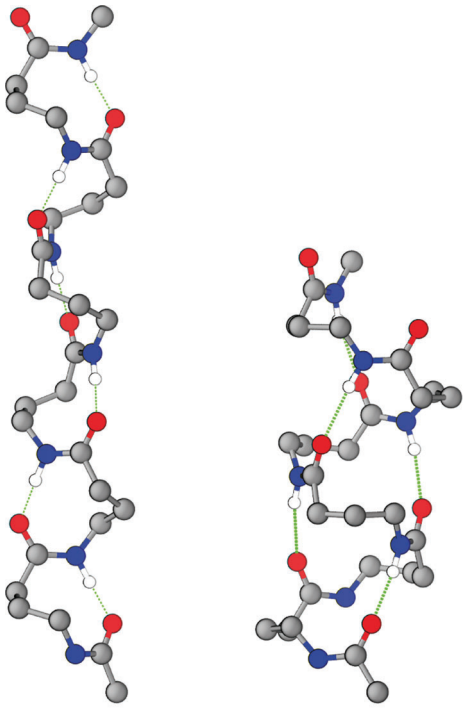
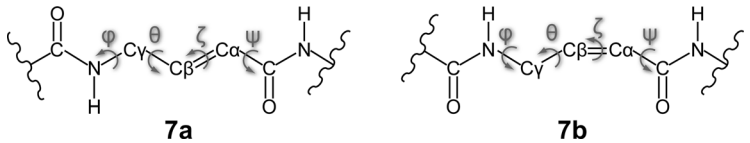


Fig. 4. *Most stable* H_9 *and* H_{14} *helices of* γ*-peptides predicted by* ab initio *MO theory*

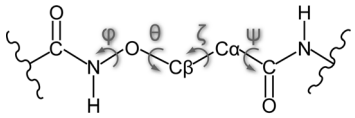
The greater number of backbone atoms in γ-amino acids increases the possibilities to influence structure formation. There are some theoretical estimations of substituent influence on mixed γ-peptide helices [50b], but systematic *ab initio* MO studies on backbone substitution in γ-peptides are still missing.

An interesting backbone variation is the introduction of a C=C bond between the $C(\alpha)$- and $C(\beta)$-atoms, providing vinylogous γ-amino acids **7a** or **7b** as constituents for vinylogous γ-peptides [75]. Due to the C=C bond, (E)/(Z)-(*trans*/*cis*-) isomerization occurs in the building blocks. In oligomers of *trans*-constituents **7a**, the formation of the smaller H-bonded rings should be disadvantaged for steric reasons. Thus, only helices with larger H-bonded pseudocycles or extended structures can be expected. In an *ab initio* MO conformational search, the conformational space of the *trans*- and *cis*-constituents **7a** and **7b** and their oligomers was systematically investigated [71][76]. The 9-membered ring structures are favored in *cis*-oligomers **7b**. Experimental data are

still scarce, but the X-ray studies by *Grison* and co-workers [77] for *cis*-constituents confirm the formation of 9-membered turns (cis-*vinylogous γ-turns*). The theoretical and experimental backbone torsion angles fairly agree (*Table 3*). As expected, *trans*-oligomers tend to extended structures or helices with larger H-bonded rings. The X-ray analysis for *trans*-constituents [77] provides extended conformers without H-bonds in good correspondence with the theoretical data (*Table 3*). Further experimental studies on longer oligomers are necessary to get deeper insight into this concept.



7a **7b**



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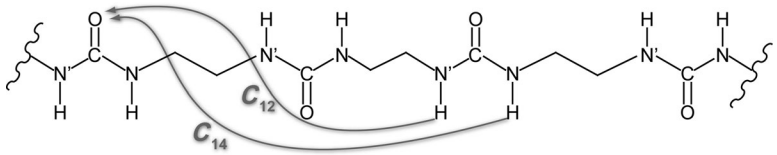
The γ-amino acid backbone can be transformed into β-aminoxy acids **8** by replacement of C(γ) by an O-atom. These systems were experimentally studied and accompanied by *ab initio* MO calculations [5s][78]. As found for the α-aminoxy peptides, nearest-neighbor peptide-bond interactions are favored which generate 9-membered *β-N-O* turns. The geometry of these rings is confirmed by theory and is closely related to the two 9-ring conformers of the parent γ-peptides in *Table 3*. One of the experimentally found geometries corresponds to the ring of the most stable 9-helix of γ-peptides, which represents the most stable helix of γ-peptides, at all together with the 14-helix (*Table 3*). The other, only a bit less stable 9-membered *β-N-O* turn found in some derivatives by X-ray corresponds to a relatively unstable conformer in γ-peptides according to theory (*Table 3*).

An interesting variation of the γ-amino acid constituent results from the replacement of C(α) by an NH moiety leading to oligoureas **9**, which are also promising foldamer candidates. Indeed, the formation of a 14-helix with a certain similarity to the 14-helix of γ-peptides was found [79]. The H-bonded 14-rings between the NH group of an amino acid residue *i* to the peptidic CO of the residue ($i-3$) are supported by the formation of 12-membered rings formed between the urea N-atom N′ of residue ($i-1$) to the same CO group ($i-3$) (bifurcation). *Ab initio* MO calculations confirm this helix structure.



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3.2.4. *δ-Peptides.* δ-Amino acid constituents are of special interest because they can formally replace a dipeptide unit in α-peptides (*Fig. 5*). The relationships between *δ*-

amino acids and β-turns, the 3_{10}-helix, and the π-helix of α-peptides are obvious, whereas the mimicry of α-helices requiring 13-membered H-bonded rings is excluded. Experimental data support the insertion of single δ-amino acids into 3_{10}-helices without disruption of the helix [80]. Obviously, the α-amino acid residues enforce the δ-amino acid constituent into the native helix conformation.

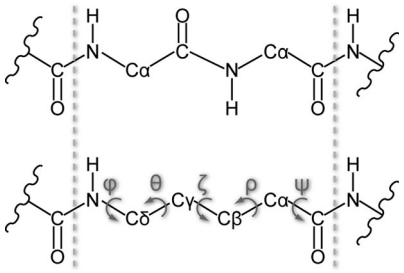


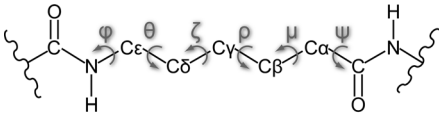
Fig. 5. *Correspondence between an* α*-dipeptide unit* (top) *and a* δ*-amino acid constituent* (bottom)

A systematic *ab initio* MO conformational analysis of δ-amino acid constituents and their oligomers confirms the equivalents for classical β-turns and the 3_{10}- and the π-helix [81]. Secondary structures with 10-membered H-bonded rings are distinctly favored in monomers and oligomers. According to theory, δ-peptide helices should be possible but are not experimentally known yet.

The single-bond between the C(β) and C(γ) atoms of the δ-amino acid building block corresponds formally to the peptide-bond in an α-peptide dimer. However, the calculations show that *gauche* conformations are energetically preferred over perpendicular conformations as the equivalents for the (*E*) peptide bond. Thus, there are two sets of β-turn and helix analogues in δ-peptides, where those with *gauche* torsion angles are more stable than those with a perpendicular conformation [82]. A greater similarity between δ- and α-peptide secondary structures could probably be enforced by introduction of a C=C bond between the C(β)- and C(γ)-atoms [83].

Following the experience with β- and γ-peptides, γ-aminoxy acids were derived from δ-amino acid constituents by introduction of an O-atom in the δ-position. Oligomers of these γ-aminoxy acids are able to form well-defined secondary structures like the α- and β-aminoxy acids [5s][5z].

3.2.5. *ε-Peptides.* Further homologation of the amino acid backbone leads to ε-amino acids **10**. Polymers of ε-amino acids are well-known as polyamide fibres. A comprehensive *ab initio* MO conformational analysis indicates the possibility for many helix and turn types [84]. However, experimental data are not available for comparison yet.



10

3.3. *Heterooligomers.* 3.3.1. *General.* The α-peptides as well as the nonnatural oligomers discussed in the preceding paragraphs are composed of one type of building

block. Hence, they were classified as homooligomers. A logic step of extension of the foldamer concept is the combination of different ω-amino acid building blocks within one sequence resulting in heterooligomers [5w][6g][6h][85]. This higher abstraction from the natural prototype substantially extends the structural possibilities and allows for virtually unlimited combinations. To keep an overview and a systematic classification, theoretical methods are of special importance in this field.

At first, it seems to be advantageous to combine different ω-amino acids in a regular way. In the first successful studies, the α- and β-amino acid constituents were arranged in 1:1 alternation in the sequence [5w][6d][6g][6h]. Meanwhile, some more two-amino-acid combinations of α-amino acid constituents with γ-, δ-, and ε-amino acids and of β-amino acids with γ-amino acids in 1:1 alternation were experimentally investigated. It is obvious that this concept can be extended in various directions, such as the combination of two different ω-amino acids in varying number, *e.g.*, 1:2 or 2:1 alternation, or finally the combination of three or more different ω-amino acids in any number and order.

The experimental data for the combinations mentioned above indicate a great number of novel helix types. It is a nice recommendation for *ab initio* MO theory that numerous of these helix types could correctly be predicted before the peptides were synthesized and their structure analyzed. Various aspects of helix formation in foldamers composed of two ω-amino acids in 1:1 order are described in the following paragraphs.

3.3.2. *α,β-Peptides.* In 2004, the *Reiser* [86a] and the *Gellman* group [86b] found the first helical structures in sequences of α- and β-amino acids in 1:1 alternation. Whereas a 13-helix was obtained by *Reiser* and co-workers, *Gellman* and co-workers obtained 14/15- and 11-helices for their oligomers. The 14/15- and 11-helices are in a relationship similar to those between 3_{10}- and α-helices in native peptides or 10- and 14-helices in β-peptides already mentioned, *i.e.*, the 14/15-helix with larger H-bonded rings predominates with growing sequence length, the 11-helix in shorter sequences [87]. A systematic *ab initio* MO study predicted the possible unidirectional helix structures for an α,β-peptide backbone and also several mixed helix types [88]. The 14/15- and 11-helices helices were confirmed. The postulated mixed 9/11(11/9)-helix was experimentally found by *Sharma* and *Kunwar* and co-workers and *Tomasini* and co-workers [89]. According to the theoretical calculations, the backward 11- and 14/15-helices and the mixed 9/11(11/9)-helices are the preferred structures in a polar environment. The H-bonding patterns for these helices are illustrated in *Fig. 6*. *Reiser*'s 13-helix needs a comment, since a helix with only 13-membered H-bonded rings considering all peptide bonds of the sequence within the H-bonding network is impossible. *Ab initio* MO theory predicts instead a forward 12/13-helix (*Fig. 6*). This helix is relatively unstable in comparison to the other helices already discussed. Obviously, the special cyclopropane backbone of *Reiser*'s β-amino acid constituents supports this helix, but the 12-membered rings are disrupted. Thus, this 13-helix seems to be a distorted 12/13-helix where only every second peptide bond is part of the H-bonding network. In *Table 4*, the theoretically estimated backbone torsion angles for the most important α,β-peptide helices are given and compared with experimental data.

In the meantime, combinations of α-aminoxy acids and α-amino acids [90] and of hydrazino acids and α-amino acids [91] in 1:1 alternation were also investigated in

Table 4. *HF/6-31G* Backbone Torsion Angles of Selected Helical Structures of Hybrid Peptides Composed of Various ω-Amino Acids in 1 : 1 Alternation in Comparison to Experimental Data*

Helix[a])	Method	Residue	φ[b])	θ[b])	ζ[b])	ρ[b])	μ[b])	ψ[b])	Ref.
α,β-Peptides:									
H_{11}	*ab initio*	α	– 70.3					– 18.6	[88]
		β	– 98.6	77.1				– 84.6	
H_{11}	X-ray	α	– 53.5					– 39.9	[87a]
		β	– 95.8	94.5				– 89.9	
$H_{14/15}$	*ab initio*	α	– 72.9					– 26.4	[88]
		β	– 118.0	79.2				– 122.9	
$H_{14/15}$	X-ray	α	– 62					– 38	[87b] [87c]
		β	– 126	83				– 119	
$H_{11/9}$	*ab initio*	α	59.2					– 149.2	[88]
		β	– 78.4	– 59.6				97.0	
$H_{11/9}$	NMR	α	72					– 141	[89b]
		β	– 93	– 58				85	
α,γ-Peptides:									
H_{12}	*ab initio*	α	– 69.7					– 22.7	[93]
		γ	– 123.1	53.0	63.4			– 126.2	
H_{12}	X-ray	α	– 54.6					– 43.3	[94c]
		γ	– 127.4	54.3	60.3			– 114.4	
H_{12}	X-ray	α	– 65.5					– 30.2	
		γ	– 129.9	50.9	63.5			– 116.8	[94e]
H_{12}	X-ray	α	66.5					32.0	[94d]
		γ	134.5	– 57.5	– 53.0			110	
$H_{12/10}^{I}$	*ab initio*	α	– 67.2					147.7	[93]
		γ	65.5	32,4	48.0			– 129.0	
$H_{12/10}$	X-ray	α	– 68.4					132.2	[94b]
		γ	87.8	37.7	45.1			– 129.3	
$H_{12/10}^{II}$	*ab initio*	α	– 61.6					151.1	[93]
		γ	129.4	– 50.5	95.9			– 116.2	
$H_{12/10}$	NMR	α	– 67					140	[94a]
		γ	139	– 55	99			– 104	
$H_{12/10}$	NMR	α	– 69					134	[94a]
		γ	139	– 52	101			– 104	
α,δ-Peptides:									
$H_{13/11}$	*ab initio*	α	– 68.8					151.3	[95]
		δ	139.4	– 79.5	63.8	57.7		– 141.0	
$H_{13/11}$	NMR	α	– 87					133	[95]
		δ	138	– 72	73	56		– 135	
α,ε-Peptides:									
$H_{14/12}^{I}$	*ab initio*	α	– 79.1					143.6	[97]
		ε	110.1	– 72.7	159.7	– 89.1	74.0	– 123.4	
$H_{14/12}$	NMR	α	– 79					111	[97]
		ε	119	– 70	170	– 90	72	– 102	
β,γ-Peptides:									
H_{13}^{I}	*ab initio*	β	– 95.7	92.3				– 113.2	[93]
		γ	– 126.5	60.1	62.2			– 131.2	
H_{13}	X-ray	β	– 133.6	113.5				– 85.7	[98]
		γ	– 141.0	59.0	53.2			– 125.4	

Table 4 (cont.)

Helix[a])	Method	Residue	φ[b])	θ[b])	ξ[b])	ρ[b])	μ[b])	ψ[b])	Ref.
$H_{11/13}^{IIId}$)	*ab initio*	β	173.9	60.5				17.0	[93]
		γ	95.9	– 82.3	70.0			– 148.6	
$H_{11/13}$	NMR	β	142	66				– 10	[94a]
		γ	121	– 81	58			– 101	
$H_{11/13}$	NMR	β	145	68				– 8	[94a]
		γ	123	– 84	63			– 106	

[a]) H_x: helix with x-membered H-bonded turns; $H_{x/y}$: mixed or β-helix. [b]) All theoretical data were obtained at the HF/6-31G* level of *ab initio* MO theory; angles are in degrees; theoretical backbone angles for the helices result from averaging over the two central constituents of each ω-amino acid; experimental data are given as in the references or averaged over the central residues neglecting the terminal ones. [d]) There are two more stable $H_{11/13}$ helices *in vacuo* according to theory, but this helix becomes rather stable in solution [93].

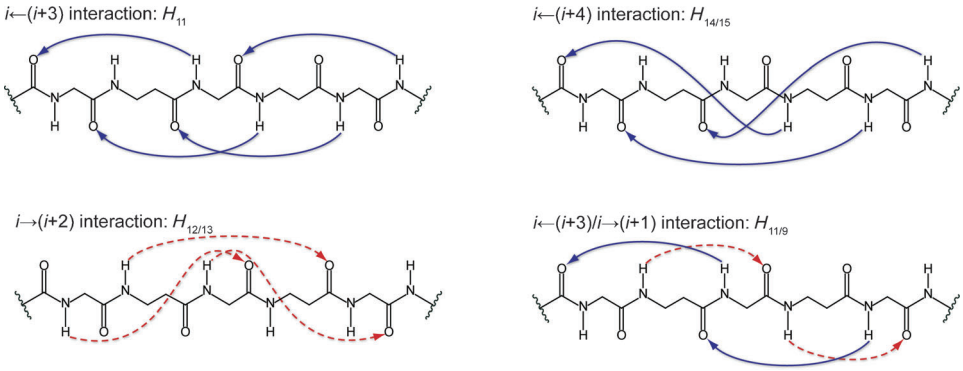


Fig. 6. *H-Bonding patterns of the most important helices in α,β-hybrid peptides predicted by* ab initio *MO theory*

experimental studies supported by *ab initio* MO calculations. Not unexpected, the constituents of these α,β-peptides keep their nearest-neighbor peptide-bond interactions. Thus, 8-membered α-*N*-*O* turns and γ-turns in the one case and hydrazino turns and γ-turns in the other are alternating.

An unusual periodic structure in α,β-peptides was presented by *Sanjayan* and coworkers for oligomers of L-proline and anthranilic acid (=2-aminobenzoic acid), which was supported by *ab initio* MO theory [92]. The conformational restrictions arising from the fixed torsion angles φ in the proline residue ($\approx -60°$) and θ in the β-amino acid constituent anthranilic acid ($\approx 0°$) create an unconventional helical pseudo-β-turn structure with 9-membered rings in forward direction. Usual β-turn H-bonds are pointing in backward direction [82].

3.3.3. *α,γ-Peptides.* A systematic conformational analysis for the 1:1 α,γ-peptide backbone performed by *ab initio* MO theory is available [93]. Among the numerous predicted folding patterns, mixed 12/10- and 18/20-helices are most stable. As generally found, this situation changes in a polar environment. Here, a 12-helix is distinctly

favored. The preferred mixed 12/10- and 12-helices were confirmed by experimental studies [72c][72d][94]. The theoretically estimated backbone torsion angles are given in *Table 4*. They agree very well with the experimental data.

3.3.4. *α,δ-Peptides.* In a concerted investigation, a mixed 13/11-helix was found in experimental and theoretical studies as a favored periodic structure in α,δ-peptides both *in vacuo* and in a polar environment [95]. The experimental and theoretical data for the backbone torsion angles are compared in *Table 4*. The α,δ-peptide backbone is interesting because it corresponds to an α-peptide trimer and the dimer repeat of β,γ-hybrid peptides (*Fig. 7*).

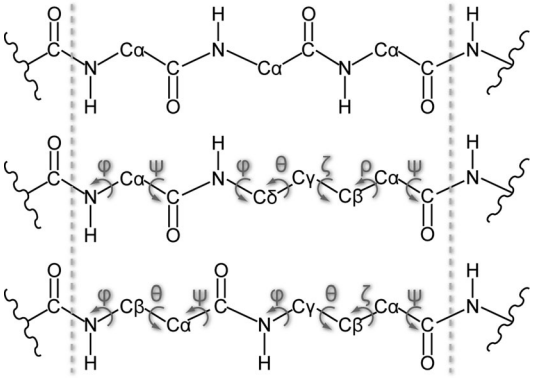


Fig. 7. *Correspondence between an α-tripeptide unit* (top), *an α,δ-dipeptide unit* (center) *and a β,γ-dipeptide unit* (bottom)

Since a 13-helix was predicted by theory as the next stable conformer after the mixed 13/11-helix in polar solution, α,δ-peptides could be able to mimic the native α-helix. There are also close relationships between the mixed 20/22(22/20)-helices of α,δ-peptides and the gramicidin A helix.

A different type of α,δ-peptides was presented by *Gervay-Hague* and co-workers [96]. Due to the special structure of the constituents, the periodic structure does not fit into the general characteristics of α,δ-peptides.

3.3.5. *α,ε-Peptides.* The theoretical conformational analysis for α,ε-peptides predicts several mixed helices as preferred *in vacuo*, whereas two 14-helices of similar energy are most stable in aqueous solution [97]. One of the predicted stable mixed helices with a 14/12-H-bonding pattern is confirmed by experimental studies [97]. The torsion angles of this helix are also listed in *Table 4*.

3.3.6. *β,γ-Peptides.* β,γ-Hybrid peptides were relatively early considered in hybrid-peptide foldamer studies. The *ab initio* MO conformational analysis provided mixed 20/22- and 11/13-helices as most stable for the vacuum [93] (*Table 4*). In a polar solvent, 11- und 13-helices gain considerable stability and become competitive. The 11/13-helix was confirmed by experimental studies [94a].

In *Sect. 3.3.4* on α,δ-peptides, the correspondence between the backbones of α,δ- and β,γ-peptides and an α-peptide trimer was discussed and illustrated in *Fig. 7*. Thus, a similar mimicry of the α-helix seems to be possible by β,γ-peptide sequences [98a].

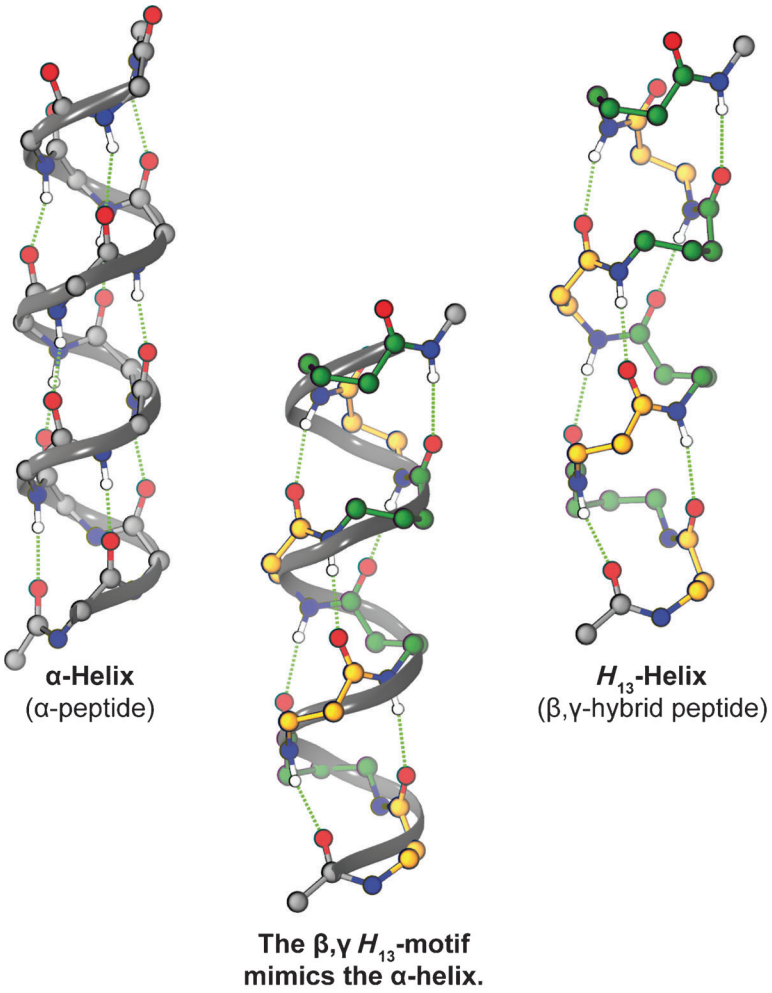


Fig. 8. *Superimposition of the α-helix of native peptides and the most stable* H_{13} *helix of β,γ-peptides*

Fig. 8 shows a comparison of the most stable 13-helix of *β,γ*-peptides predicted by theory and the native *α*-helix.

Indeed, *Gellman* and co-workers [98b] were able to realize this concept by selection of suited *β*- and *γ*-constituents for their hybrid peptides. Thus, a helix with H-bond analogy to the *α*-helix was generated without *α*-amino acids. The geometry of this helix obviously agrees with the theoretically predicted 13-helix. The isosteric replacement of *α*-amino acid residues by *β,γ*-peptide motifs to mimic *α*-helical turns or to design artificial coiled coil motifs was successfully performed by *Koksch* and co-workers [7n][7o].

3.3.7. *β,δ-Peptides.* A comprehensive *ab initio* MO conformational analysis was also performed for β,δ-peptides [99]. However, experimental data for this foldamer class are still missing.

3.4. *Miscellaneous.* In the preceding paragraphs, some examples of backbone correspondence between the various peptide-foldamer classes were mentioned. The first example was the equivalence of a δ-amino acid constituent and an α-dipeptide unit (*Fig. 5*) followed by various examples for backbone correspondences between heterooligomers and homooligomers and between heterooligomers (*Fig. 7*), respectively. On the basis of the numerous helix types obtained by *ab initio* MO theory in our group, we were able to give a general overview on backbone correspondences for various peptide foldamer classes, which may be helpful for peptide and protein design [99]. On the basis of experimental structure data, comparable relationships were established by *Balaram* and co-workers in several papers [6f].

Regarding backbone correspondence of peptide foldamers, it could be useful to distinguish between *ring-size* compatibility and *shape similarity.* Ring-size compatibility occurs if two foldamer types form H-bonded rings of the same size and direction, shape similarity means close correspondence of the ring conformation. The various mixed 12/10-helices of β-peptides or the various 9- and 14-helices of γ-peptides are examples for an ideal ring-size compatibility within the same foldamer class. The helices agree in size, direction, and number of H-bonded rings formed along the sequence. However, it is obvious that these helices cannot show shape similarity because of their different backbone conformation. Comparing different ω-peptide-foldamer classes, ring-size compatibility and shape similarity can only approximately be realized. Often the number of peptide bonds in the corresponding foldamer building blocks differs and thus also the number of H-bonded rings in the sequence. Even if the number of H-bonded rings agrees, peptide bonds could be shifted to each other in the building blocks. These aspects have to be considered when incorporating such isosteric sequences into α-peptide or other foldamer sequences. The correspondence of the building blocks of α-tripeptides, α,δ-, and β,γ-peptides given in *Fig. 7* may illustrate these problems. Thus, α,δ-sequences can reach ring-size compatibility and shape similarity to the native α-helix. They are able to form 13-helices with the same direction of the H-bonds, even if the number of these rings along the sequence is smaller than in the α-helix because of the missing peptide bond in the δ-amino acid constituent of the building block. Additional shape similarity becomes possible if a perpendicular conformation can be realized around the C(β)–C(γ) single-bond of the δ-amino acid constituent. The chance for a still better α-helix mimicry possibly increases in hybrid peptides consisting of alternating α-amino acids and δ-amino acids with a double-bond between the C(β)- and C(γ)-atoms. Contrary to this, β,γ-peptides can only realize an approximate ring-size compatibility. They are able to form 13-helices, but the backbone conformation differs from that of the α-helix since the position of the central peptide bond of the β,γ-building block does not correspond to a peptide bond in the α-tripeptide building block (*Fig. 7*). Nevertheless, the approximate similarity may be sufficient for an α-helix mimicking as some studies impressively show [7n][7o][98b].

In the examples of hybrid peptides discussed so far, two different ω-amino acids were arranged in 1:1 alternation. Recently, peptide sequences with 2:1 or 1:2 alternation of α-amino acids and β- or γ-amino acids, respectively, were synthesized,

which show helix formation [100]. Such examples could stimulate further theoretical activities in this field, which offers nearly unlimited possibilities for the employment of *ab initio* MO theory.

Supported by *ab initio* MO theory, the concept of hybrid helices was introduced by *Sharma*, *Kunwar*, and *Hofmann* and co-workers [101]. The authors demonstrated that continuous helices can be formed in sequences consisting of different hybrid peptide types. Thus, the connection of short β-, α,β-, and α,γ-peptide sequences within the same sequence combines the special characteristics of the 12/10-helix of β-peptides, the 11/9-helix of α,β-peptides, and the 12/10-helix of α,γ-peptides in a continuous H-bonding network. Numerous further examples for such hybrid helices were given.

A very interesting tool for foldamer design denoted as 'stereochemical patterning' approach was suggested by *Fülöp* and co-workers [102]. By correlation of the signs of the torsion angles flanking the peptide-bond unit and the configuration of the building blocks, it is possible to estimate a distinct helical folding.

4. Conclusions. – It was the aim of this review to give an overview on the application of *ab initio* MO theory to describe the helix formation in sequences of ω-amino acids. On the basis of representative examples, the success of *ab initio* MO methods was demonstrated from the very beginning of foldamer research. It was shown that these methods are able to support the experimental activities by confirmation of the obtained structural data, by their interpretation, and by stimulation of further experiments. Moreover, theoretical calculations have a considerable predictive power. The treatment of hypothetical foldamer structures may open the way to novel structure classes. Helix formation in oligomers of ω-amino acids represents only one section of the application of MO methods in peptide foldamer research. Numerous further examples demonstrate and confirm their efficiency for the description of foldamer secondary structures. Besides peptide foldamers, the focus of research is in particular on aromatic foldamers [5v][6a][6g][103], which were not the subject of this review. The permanently increasing number of foldamer classes with their wide variety of structure possibilities, which could easily become confusing, demands downright the application of theoretical methods as an organizing principle. As in many other fields of chemistry and biochemistry, theoretical methods, in particular *ab initio* MO theory, have become an indispensable tool in the meantime.

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