INSTITUTE OF PHYSICS PUBLISHING PHYSICAL BIOLOGY

Phys. Biol. **3** (2006) S1–S9 doi:10.1088/1478-3975/3/1/S01

Helices in peptoids of α- and β-peptides

Carsten Baldauf, Robert Günther and Hans-Jörg Hofmann

Institute of Biochemistry, Faculty of Biosciences, Pharmacy and Psychology, University of Leipzig, D-04103 Leipzig, Germany

E-mail: hofmann@uni-leipzig.de

Received 30 September 2005
Accepted for publication 3 November 2005
Published 2 February 2006
Online at stacks.iop.org/PhysBio/3/S1

Abstract

Peptoids of α- and β-peptides (α- and β-peptoids) can be obtained by shifting the amino acid side chains from the backbone carbon atoms of the monomer constituents to the peptide nitrogen atoms. They are, therefore, N-substituted poly-glycines and poly-β-alanines, respectively. Due to the substituted nitrogen atoms, the ability for hydrogen bond formation between peptide bonds gets lost. It may be very interesting to see whether such non-natural oligomers could be regarded as foldamers, which fold into definite backbone conformers. In this paper, we provide a complete overview on helix formation in α- and β-peptoids on the basis of systematic theoretical conformational analyses employing the methods of *ab initio* molecular orbital (MO) theory. It can be shown that the α- and β-peptoid structures form helical structures with both trans and cis peptide bonds despite the missing hydrogen bonds. Obviously, the conformational properties of the backbone are more important for folding than the possibility of hydrogen bonding. There are close relationships between the helices of α-peptoids and poly-glycine and poly-proline helices of α-peptides, whereas the helices of β-peptoids correspond to the well-known helical structures of β-peptides as, for instance, the 3_1-helix of β-peptides with 14-membered hydrogen-bonded rings. Thus, α- and β-peptoids enrich the field of foldamers and may be used as useful tools in peptide and protein design.

M This article features online multimedia enhancements

1. Introduction

Important biological functions such as enzyme catalysis, molecular recognition and information storage are realized on the basis of special biomacromolecules that form definite three-dimensional structures [1]. The three major polymers in nature are proteins, nucleic acids and polysaccharides [2]. It is a great challenge in chemistry and biochemistry to look for possibilities for mimicking these native structures employing unnatural chemical constituents, in particular, by the development of novel oligomers that are able to adopt stable secondary structures. Numerous activities in this field are stimulated by the intention of influencing the properties of peptides and proteins. Native peptides often make poor drugs due to their low bioavailability as they are not resistant against proteases and suffer from bad transport properties. Another aim of modification might be the increase in specificity of enzymes and the improvement of receptor selectivity towards special substrates and drugs. Outside the biomimetic aspects, the search for non-natural oligomeric sequences with definite solution structure may lead to compounds with novel properties which make them interesting for material sciences. Moreover, they could be utilized as scaffolds for nanotechnology.

It is popular to denote oligomers of non-natural chemical constituents, which fold into stable definite solution structures, as foldamers [3]. Foldamer research has developed enormously over the last decade [4–7]. A great number of experimental and theoretical studies deal with the formation of secondary structure elements and indicate the importance of various foldamer classes for a rational molecular design. Essential stimulation in this field came from the investigation of peptide foldamers composed of homologous amino acids. In particular, the results for sequences exclusively composed of β-amino acid constituents (β-peptides) were extremely encouraging and indicate a wide variety of definite secondary structures, which are comparable with those in the native α-peptides [8–22]. In the meantime, the concept of homologation was transferred to γ- and

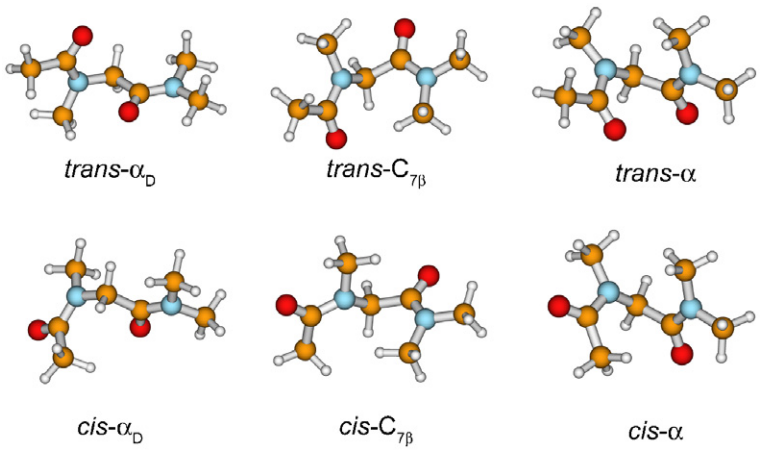


Figure 1. Conformers of blocked trans and cis α-peptoid monomer models.

Table 1. Torsion angles, relative energies in the gas phase and in solution and relative free enthalpies for the trans and cis conformers of the blocked α-peptoid monomer models **Ia** and **Ib** at the HF/6-31G* level of *ab initio* MO theory[a].

Conformers[b]	ω	φ	ψ	ω_2	ΔE	ΔE_s	ΔG
trans (**Ia**)							
α_D	−171.1	79.2	−174.6	174.3	**0.0**[c]	**0.0**[d]	**0.0**[e]
$C_{7\beta}$	−171.8	−128.4	79.8	−177.8	5.4	10.4	5.2
α	−172.1	−60.0	−42.7	174.4	27.3	15.8	26.6
cis (**Ib**)							
α_D	−15.9	−76.9	−171.1	8.0	8.3	2.7	7.2
$C_{7\beta}$	17.5	−153.1	59.1	16.7	20.9	20.6	18.5
α	−17.7	67.2	48.7	10.5	23.3	24.5	21.8

[a] Torsion angles in degrees, energy values in kJ mol^{-1}.
[b] Cf. structure formulae **Ia** and **Ib**.
[c] $E_T = -531.869\,079$ au.
[d] $E_T = -531.874\,971$ au.
[e] $E_T = -531.677\,775$ au.

Table 2. Torsion angles for the blocked hexamer helices of α-peptoids at the HF/6-31G* level of *ab initio* MO theory[a].

Hexamer[b]	ω	φ	ψ	Hexamer[b]	ω	φ	ψ
trans (**Ia**, $n = 6$)				cis (**Ib**, $n = 6$)			
α_D	−170.7	82.0	−176.9	α_D	14.9	78.9	172.6
	−169.2	81.4	−177.8		17.9	74.9	172.8
	−169.0	81.2	−178.0		19.5	72.8	172.7
	−169.0	80.9	−177.9		20.1	72.2	171.8
	−169.3	80.8	−177.6		21.1	71.3	169.0
	−169.3	78.8	−176.7		20.3	71.4	165.2
	174.7				−5.0		
$C_{7\beta}$	172.5	−76.5	170.5	$C_{7\beta}$	20.1	−150.6	61.7
	−171.5	−130.2	75.7		21.4	−162.2	65.0
	−172.2	−129.8	72.8		21.2	−162.2	64.5
	−172.0	−129.4	72.8		21.8	−163.2	64.4
	−172.2	−129.9	71.4		20.5	−162.1	65.3
	−171.8	−129.3	70.0		22.7	−162.2	59.8
	−177.0				12.8		
α	−171.1	−60.5	−43.0	α/α_D	−19.1	67.4	46.9
	−173.3	−57.2	−44.1		18.7	73.2	163.7
	−173.4	−56.2	−44.6		−21.2	66.4	47.9
	−172.8	−56.8	−43.7		19.4	73.6	162.4
	−173.3	−59.3	−43.8		−17.2	67.6	52.6
	−171.3	−56.8	−45.3		19.5	70.8	168.5
	175.6				−7.7		

[a] Torsion angles in degrees.
[b] Derived from the conformers of **Ia** and **Ib** in table 1.

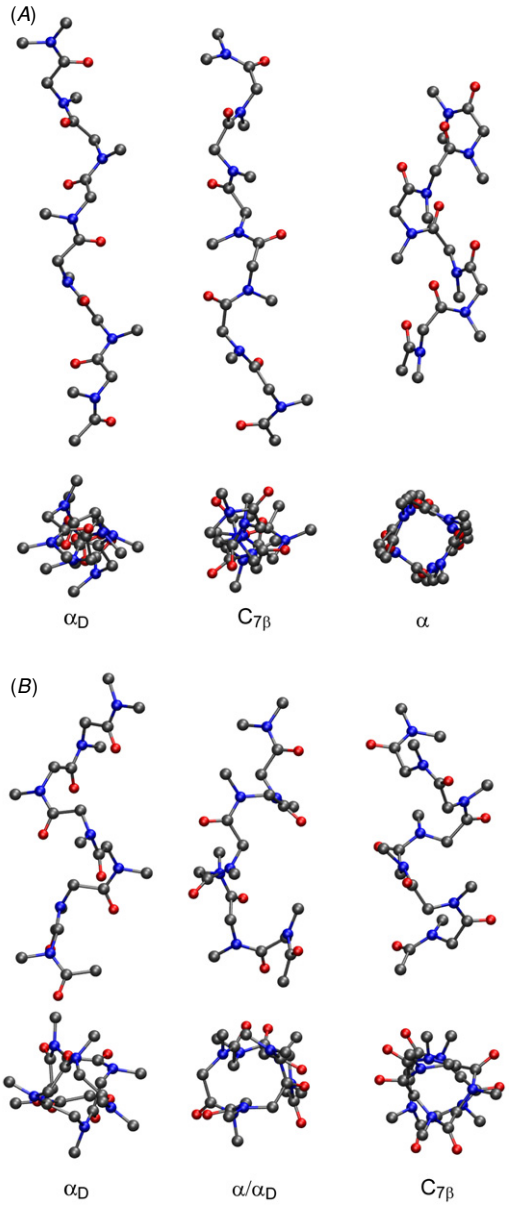


Figure 2. Helices of (*A*) trans α-peptoids and (*B*) cis α-peptoids.

δ-peptides and even to hybrid peptides composed of different homologous amino acids [23–39].

A bit earlier than the systematic activities in the field of β-peptides, another idea of peptide foldamers has got considerable attention. Zuckermann *et al* suggested peptide oligomers composed of α-amino acids bearing their side chains not at the C(α) atoms, but at the peptide nitrogen atoms of a sequence [40–44]. Such peptides can be considered as N-substituted poly-glycines and are denoted as peptoids. Some important consequences result from this structure modification. Because of the lack of chirality, right- and left-handed helices become energetically equivalent. Moreover, the substitution of the peptide nitrogen atoms makes the formation of hydrogen bonds between peptide bonds impossible. These hydrogen bonds are usually considered to

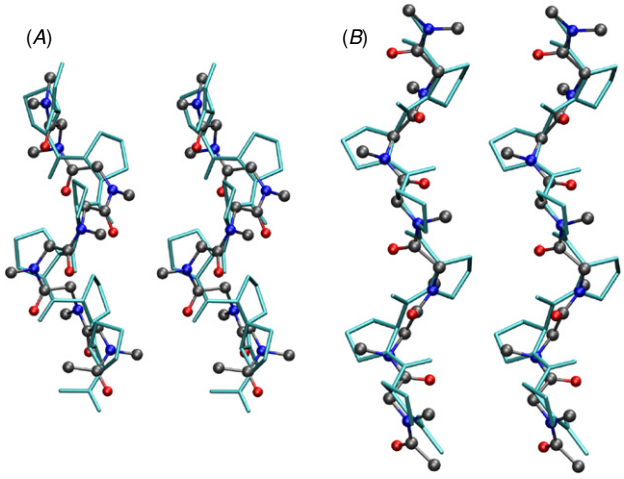


Figure 3. Stereoviews of the superimpositions of (*A*) the cis α_D helix of α-peptoids with the poly-proline I helix PPI and (*B*) the trans α_D helix of α-peptoids with the poly-proline II helix.

Table 3. Relative energies in the gas phase and in solution and relative free enthalpies for the blocked trans and cis hexamer helices of α-peptoids at the HF/6-31G* level of *ab initio* MO theory[a].

Hexamer[b]	ΔE	ΔE_s	ΔG
trans (**Ia**, $n = 6$)			
α_D	**0.0**[c]	**0.0**[d]	**0.0**[e]
$C_{7\beta}$	46.9	58.9	52.7
α	124.7	117.8	139.7
cis (**Ib**, $n = 6$)			
α_D	15.3	22.8	18.8
α/α_D	81.8	104.3	85.1
$C_{7\beta}$	151.9	173.6	160.7

[a] Energies in kJ mol^{-1}.
[b] Derived from the conformers of **Ia** and **Ib** in table 1.
[c] $E_T = -1760.462\,092$ au.
[d] $E_T = -1761.073\,082$ au.
[e] $E_T = -1760.462\,092$ au.

be of essential importance for the formation of characteristic secondary structure elements in native peptides and proteins. Finally, the occurrence of cis peptide bonds should increase by nitrogen substitution as it is known for peptide bonds with the amino acid proline. First theoretical estimations of the secondary structure formation in these oligomers revealed the result that helix formation should be possible despite the missing hydrogen bonds [10–12], which was confirmed in several experimental studies afterwards [45–47]. Especially interesting were secondary structures with cis peptide bonds, which are scarce in native peptides and proteins with exception of peptide bonds with the amino acid proline.

Following the development in the field of peptide foldamers, in particular that for the homologous β-, γ- and δ-peptides, it could also be interesting to examine the secondary structure of the peptoids of the higher homologues as promising candidates for peptide and protein design. These compounds did not attract attention until now. In this study, we therefore extend our structure investigations from α-peptoids to oligomers of N-substituted β-alanines as prototype for

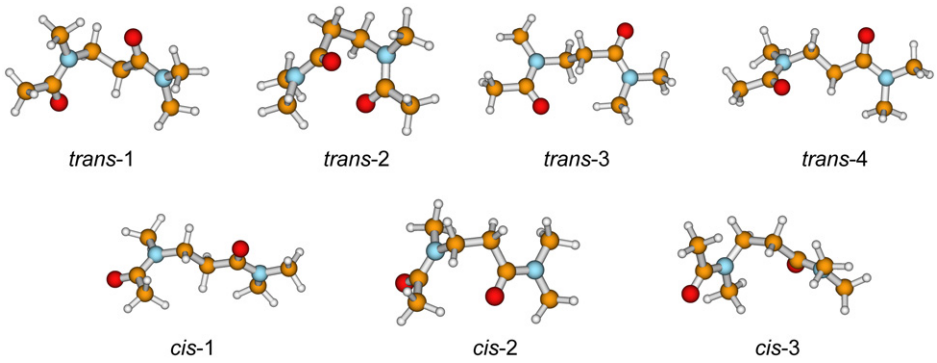


Figure 4. Most stable conformers of the trans and cis monomers of β-peptoids **IIa** and **IIb**.

Table 4. Torsion angles, relative energies in the gas phase and in solution and relative free enthalpies for the trans and cis conformers of the blocked β-peptoid monomer models **IIa** and **IIb** at the HF/6-31G* level of *ab initio* MO theory[a].

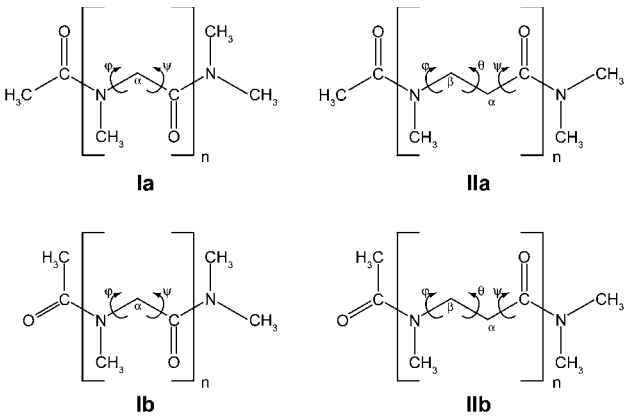
Conformers[b]	ω	φ	θ	ψ	ω_2	ΔE	ΔE_s	ΔG
trans (**IIa**)								
t-**1**	−173.8	−78.2	−70.7	170.4	−175.4	**0.0**[c]	5.0	**0.0**[d]
t-**2**	−173.0	91.7	−50.3	−91.7	174.0	3.9	11.7	10.0
t-**3**	−176.6	−83.8	−179.6	−86.6	−176.9	5.1	6.0	3.0
t-**4**	174.7	81.9	174.8	174.5	−174.4	5.2	**0.0**[e]	1.2
t-**5**	176.1	−78.4	−63.4	−82.9	−175.4	14.7	12.9	13.8
t-**6**	−179.1	−85.0	−177.3	92.7	−178.0	22.7	10.4	20.2
t-**7**	169.4	−122.5	61.3	176.9	−174.4	24.6	13.8	21.6
t-**8**	−170.6	12.9	−79.0	−16.9	−170.8	70.0	60.3	74.4
cis (**IIb**)								
c-**1**	9.9	95.0	−179.6	−179.7	9.9	7.5	0.7	3.7
c-**2**	7.8	116.2	−72.0	163.1	−2.7	9.6	6.4	8.9
c-**3**	7.8	87.5	81.2	−165.2	4.6	14.5	11.5	11.6
c-**4**	4.1	114.2	−56.1	−76.1	−21.6	22.4	15.8	23.2
c-**5**	−5.7	−90.1	−64.2	−74.9	−20.1	25.7	16.3	25.2
c-**6**	12.1	−77.9	−40.4	−76.8	−18.9	29.9	22.9	27.8

[a] Torsion angles in degrees, energies in kJ mol^{-1}.
[b] Cf. structure formulae **IIa** and **IIb**.
[c] $E_T = -570.906\,326$ au.
[d] $E_T = -570.686\,257$ au.
[e] $E_T = -570.909\,863$ au.

peptoids derived from β-peptides (β-peptoids). On the basis of a systematic conformational analysis employing the methods of *ab initio* MO theory, we want to provide a comparison of the helix formation in both α- and the novel β-peptoids and the typical periodic secondary structure elements of native peptides and proteins.

2. Methodology

Two strategies were applied to get a complete overview on the periodic secondary structures of the oligomer sequences [25]. In the monomer approach, the conformers of the blocked monomer units of the trans (**Ia**, **IIa**) and cis (**Ib**, **IIb**) α- and β-peptoids were determined by a systematic variation of the torsion angles φ and ψ in **I** and φ, θ and ψ in **II** in intervals of 30° and subsequent geometry optimization of the resulting starting conformations at the Hartree–Fock (HF) level of *ab initio* molecular orbital theory employing the 6-31G* basis set (HF/6-31G*). For an estimation of electron correlation effects, density functional theory (DFT) was applied using the B3LYP functional and the 6-31G* basis set (B3LYP/6-31G*).



Scheme 1

Then, the obtained conformers of the monomers were extended to blocked hexamers, which were re-optimized at the same theoretical levels to check whether the periodic

Table 5. Torsion angles for the blocked hexamer helices of trans β-peptoids at the HF/6-31G* level of *ab initio* MO theory[a].

Hexamer[b]	ω	φ	θ	ψ	Hexamer[a]	ω	φ	θ	ψ
t-**1**	−170.9	−78.9	−70.7	168.6	t-**4**	170.4	81.8	175.3	178.1
	−174.8	−78.9	−71.4	168.6		175.6	81.8	175.4	178.7
	−174.8	−78.9	−71.4	168.8		175.6	82.0	175.4	178.8
	−174.9	−78.9	−71.3	168.8		175.6	82.2	176.3	173.8
	−174.9	−78.9	−71.3	168.6		−177.8	79.5	176.0	178.6
	−174.9	−78.3	−71.9	170.0		175.4	81.9	175.0	175.1
	−179.9					−174.5			
t-**2**	−175.5	93.9	−51.6	−86.1	t-**5**	178.6	−78.4	−66.7	−92.4
	173.3	122.8	−45.1	−72.3		177.1	−77.2	−59.7	−94.4
	176.1	98.9	−52.9	−83.3		178.6	−78.5	−60.9	−94.8
	173.4	120.7	−41.7	−79.8		178.5	−78.0	−60.0	−94.9
	−177.8	102.1	−51.6	−78.9		179.1	−77.7	−60.9	−96.5
	176.6	98.3	−53.0	−88.0		177.9	−79.8	−56.5	−86.6
	173.5					−175.1			
t-**3**	−171.1	−83.1	178.6	−92.8	t-**7**	158.6	−124.0	60.8	−163.0
	−176.7	−83.6	178.5	−92.0		168.2	−125.4	62.6	−162.7
	−176.9	−83.5	178.5	−91.9		169.2	−124.0	62.2	−163.8
	−176.9	−83.5	178.5	−91.9		168.8	−123.7	61.8	−163.3
	−176.9	−83.6	178.9	−92.0		169.7	−123.6	61.5	−163.5
	−177.0	−84.0	179.9	−85.6		171.2	−123.6	65.0	−177.7
	−177.0					−174.8			

[a] Torsion angles in degrees.
[b] Derived from the conformers of **IIa** in table 4.

Table 6. Torsion angles for the blocked hexamer helices of cis β-peptoids at the HF/6-31G* level of *ab initio* MO theory[a].

Hexamer[b]	ω	φ	θ	ψ	Hexamer[b]	ω	φ	θ	ψ
c-**1**	8.6	95.8	−179.6	−178.2	c-**3**	12.4	83.9	71.5	−143.6
	7.7	96.7	−180.0	−179.0		−10.2	92.9	80.2	−171.9
	8.0	97.0	−179.4	−178.3		−7.0	100.1	87.2	177.3
	7.6	97.2	−179.3	−178.3		11.1	90.7	77.8	−152.4
	7.6	97.2	−179.2	−178.8		−5.4	92.1	79.2	−162.8
	8.1	97.5	−178.9	−178.6		−4.9	95.4	85.3	−172.7
	9.4					3.1			
c-**2**	12.1	116.2	−72.0	165.0	c-**5**	−0.3	−90.2	−62.2	−83.0
	13.5	112.5	−70.7	167.4		−9.9	−85.2	61.2	−83.5
	13.0	112.8	−70.5	168.1		−9.7	−84.9	−60.4	−84.0
	13.0	112.7	−70.4	167.9		−9.6	−84.6	−59.8	−84.3
	13.0	112.8	−70.2	168.0		−9.6	−84.6	−59.7	−83.5
	12.7	112.9	−70.4	167.6		−10.7	−84.8	−61.9	−76.2
	−3.3					−19.5			

[a] Torsion angles in degrees.
[b] Derived from the conformers of **IIb** in table 4.

structures are kept or not. In the case of peptoids, the monomer approach has a good chance to provide all possible helices, since hydrogen bond formation is impossible. Thus, definite structures, which become possible if a critical sequence length is reached for the realization of special interactions, are improbable. Nevertheless, we also employed the oligomer approach to exclude further conformers. In this case, the backbone torsion angles of blocked peptoid hexamers were systematically varied in steps of 30° considering the periodicity in the monomer constituents of the sequence followed by geometry optimization of the conformations. As expected, this approach did not provide more helices than already obtained by the extension of the monomer structures. All stationary points on the potential hypersurfaces of the monomers and hexamers were confirmed as minimum structures by frequency calculations, which also provided the free enthalpy values. An estimation of the solvent influence was performed for an aqueous environment with a dielectric constant of $\varepsilon = 78.4$ on the basis of a polarizable continuum model (PCM) [48]. The program packages GAUSSIAN03 [49] and GAMESS [50] were employed for all quantum chemical calculations.

3. Results and discussion

3.1. α-Peptoid helices

The systematic conformational analysis for the blocked trans and cis α-peptoid monomers **Ia** and **Ib** provides the three conformers α_D, $C_{7\beta}$ and α in agreement with former

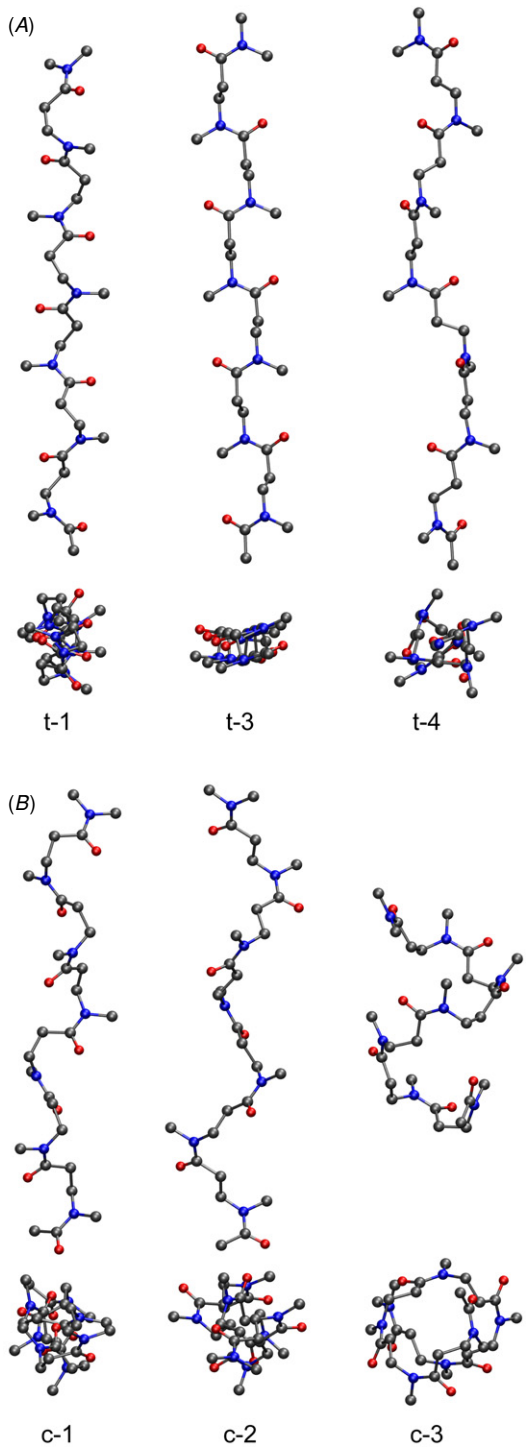


Figure 5. Most stable blocked hexamer helices of (*A*) trans and (*B*) cis β-peptoids.

calculations (table 1, figure 1) [10–12]. The basis for the nomenclature of the conformers is [51]. Interestingly, the values of the backbone torsion angles are nearly the same in the corresponding trans and cis conformers. Most stable are the α_D conformers followed by the $C_{7\beta}$ and α conformers. The comparison with the minimum conformations of

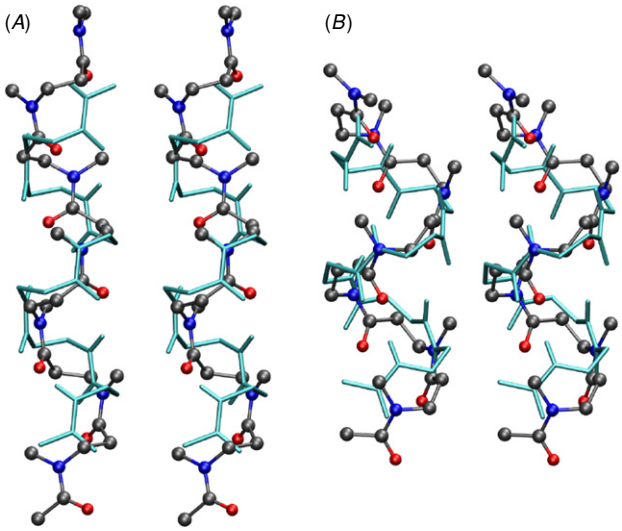


Figure 6. Stereoviews of the superimpositions of (*A*) the trans β-peptoid hexamer t-**5** and the H_{10} helix of β-peptides and (*B*) the trans β-peptoid hexamer t-**7** and the H_{14} helix of β-peptides.

native α-amino acid constituents provides only limited correspondence. In blocked α-amino acids, the C_{7eq} and C_5 conformers [51, 52], which do not appear in the peptoid structures as energy minima, are distinctly more stable than the α_D conformer. The $C_{7\beta}$ form does not exist at all. In the peptoids, this conformer represents a structural compromise between the C_{7eq} and β_2 conformers of the α-amino acid monomers. A very interesting fact is the appearance of the α-conformer in the peptoids. It corresponds perfectly to the α-helix conformation of peptides and proteins. However, in blocked monomers of native amino acids, it does not represent a minimum conformation.

The extension of the three monomers to blocked hexamers reveals that the corresponding helices of the trans α-peptoids can be localized as minimum conformations at all approximation levels. In the cis α-peptoids, the α-helical conformation does not represent a stable structure. Here, a novel secondary structure type appears with the amino acid constituents alternating in α and α_D conformations (α/α_D). The structures of all helices are visualized in figure 2. Table 2 provides the backbone torsion angles and table 3 the relative energies of the various structures at the HF/6-31G* level of the *ab initio* MO theory. The torsion angles at the B3LYP/6-31G* level of density functional theory (DFT) are given as supplementary data available from stacks.iop.org/PhysBio/3/S1. The most stable helix can be derived from the α_D conformer. As expected for N-substituted poly-glycines, this helix corresponds to the poly-glycine II helix (PGII), for which the α_D conformer is obviously the basic unit. Its left-handed form is related to the left-handed poly-L-proline II helix (PPII) with trans peptide bonds. Figure 3 shows an overlay of the α_D or PGII helix of the peptoids and the PPII helix. In a similar way, the cis α_D conformer is the basis for the most stable helix of the cis α-peptoids, which has to be compared with the poly-proline I helix (PPI) with about the same backbone torsion angle values

as the PGII helix, but cis peptide bonds now. This helix type is the most stable helix according to the calculations. It was also found for peptoid pentamers in x-ray studies [43]. The superimposition of the cis α_D-helix and the PPI helix is also given in figure 3. The trans α-helix of the α-peptoids is less stable than the α_D-helix (table 3). A detailed analysis of the structure reveals that it can only be realized with rather small substituents of the peptide nitrogen atoms, which point into the direction of the original hydrogen bond of the α-helix in native peptides.

Our calculations demonstrate a considerable potential of helix formation in trans and cis α-peptoids despite the missing hydrogen bonds. This reveals that folding into helical structures is basically determined by the conformational properties of the backbone. Hydrogen bonding may support folding into special helical conformations, but is neither the driving force nor a presupposition for helix formation in peptides and proteins.

3.2. β-Peptoid helices

In comparison to α-peptoids, the structure of β-peptoids was not investigated until now. Our calculations on the blocked trans and cis monomers **IIa** and **IIb** provide eight conformers for the trans β-peptoids and six for the cis β-peptoids (table 4). Again, there is close correspondence of the backbone torsion angle values of the trans and cis monomers at the HF/6-31G* approximation level. The B3LYP/6-31G* data are given in the supplementary data available from stacks.iop.org/PhysBio/3/S1. The most stable conformers are illustrated in figure 4.

A comparison between the trans β-peptide conformers and the conformers of the monomers of β-peptides shows some similarities. Thus, the conformers t-**1** and t-**3** (table 4) can be well compared with conformers of β-peptides with six- and eight-membered hydrogen-bonded pseudocycles. The conformers t-**5** and t-**7** (table 4) correspond to the turns of the H_{10} and H_{14} helices in β-peptides. The conformer t-**2** reflects one of the two turns of the mixed $H_{10/12}$ helix [53–55] of the β-peptides. It should also be noted that there are no relationships between the basic conformers of **IIa** and those of β-proline, which was subject of a theoretical conformational analysis [56]. Obviously, values of about $\pm 160^\circ$ for the torsion angle φ found in β-proline conformers are not preferred in the acyclic β-peptoid structures studied here.

After extension of the monomers to blocked hexamers, six helical structures are kept in the trans β-peptoids and four in the cis β-peptoid structures. Their selection is shown in figure 5. The backbone torsion angles of the trans and cis β-peptoid helices are listed in tables 5 and 6. Table 7 provides the stability data for gas phase and solution. Especially interesting are the helices derived from the conformers t-**5** and t-**7**. They represent the analogues of the helices H_{10} and H_{14} in β-peptides [8, 18], which is documented by the superimpositions in figure 6. Like in α-peptides, this confirms the fact that the conformational properties of the backbone and not hydrogen bonding determine the folding in β-peptides. The helices generated from the conformers t-**1** and t-**3** also find their counterparts in β-peptide helices with six- and eight-membered hydrogen-bonded rings. These two helices are most stable in the β-peptoid series.

Table 7. Relative energies in the gas phase and solution and relative free enthalpies for the blocked hexamer helices of α-peptoids at the HF/6-31G* level of *ab initio* MO theory[a].

Hexamer[b]	ΔE	ΔE_s (in kJ mol^{-1})	ΔG
trans (**IIa**, $n = 6$)			
t-**1**	**0.0**[c]	22.3	3.1
t-**3**	23.5	37.1	19.2
t-**4**	24.7	**0.0**[d]	**0.0**[e]
t-**5**	41.6	80.5	60.9
t-**2**	59.8	18.0	62.9
t-**7**	85.9	97.1	95.9
cis (**IIa**, $n = 6$)			
t-**2**	30.1	36.8	33.8
t-**1**	42.1	12.1	18.8
t-**3**	48.6	100.2	57.7
t-**5**	152.0	102.8	148.2

[a] Energies in kJ mol^{-1}.
[b] Derived from the conformers of **IIa** and **IIb** in table 4.
[c] $E_T = -1995.285\,351$ au
[d] $E_T = -1995.284\,257$ au.
[e] $E_T = -1994.508\,360$ au.

4. Conclusions and outlook

The results of our study show that α- and β-peptoids are able to form various helices with both trans and cis configuration of the peptide bonds, although the ability to form hydrogen bonds got lost by the substitution of the peptide nitrogen atoms. This result is remarkable for the understanding of folding in native peptides and proteins, since the conformational properties of the backbone are obviously more important for the formation of definite secondary structure elements than hydrogen bonding. A structure comparison between the helices of α- and β-peptoids and those of native α-peptides and synthetic β-peptides reveals considerable similarities. In particular the possibility to replace the amino acid proline by α-peptoid constituents deserves attention. Both α- and β-peptoids represent interesting foldamer classes, which are promising for a rational peptide and protein design and may also be interesting in material sciences.

Acknowledgment

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

References

[1] Fersht A 2003 *Structure and Mechanism in Protein Science* (New York: Freeman)

[2] Vosset D, Voet J G and Pratt C W 1999 *Fundamentals of Biochemistry* (New York: Wiley)

[3] Gellman S H 1998 Foldamers: a manifesto *Acc. Chem. Res.* **31** 173–80

[4] Hill D J, Mio M J, Prince R B, Hughes T S and Moore J S 2001 A field guide to foldamers *Chem. Rev.* **101** 3893–4011

[5] Barron A E and Zuckermann R N 1999 Bioinspired polymeric materials: in-between proteins and plastics *Curr. Opin. Chem. Biol.* **3** 681–87

[6] Kirshenbaum K, Zuckermann R N and Dill K A 1999 Designing polymers that mimic biomolecules *Curr. Opin. Struct. Biol.* **9** 530–35

[7] Cubberley M S and Iverson B L 2001 Models of higher-order structure: foldamers and beyond *Curr. Opin. Chem. Biol.* **5** 650–53

[8] Seebach D, Overhand M, Kühnle F N M, Martinoni B, Oberer L, Hommel U and Widmer H 1996 β-Peptides: synthesis by Arndt-Eistert homologation with concomitant peptide coupling. Structure determination by NMR and CD-spectroscopy and by x-ray crystallography. Helical secondary strcuture of a β-hexapeptide in solution and its stability towards pepsin *Helv. Chim. Acta* **79** 913–41

[9] Appella D H, Christianson L A, Karle I L, Powell D R and Gellman S H 1996 β-Peptide foldamers: robust helix formation in a new family of β-amino acid oligomers *J. Am. Chem. Soc.* **118** 13071–72

[10] Moehle K and Hofmann H-J 1996 Peptides and peptoids: a quantum chemical structure comparison *Biopolymers* **38** 781–90

[11] Möhle K and Hofmann H-J 1996 Peptides and peptoids: a systematic structure comparison *J. Mol. Model.* **2** 307–11

[12] Möhle K and Hofmann H-J 1998 Secondary structure formation in N-substituted peptides *J. Pept. Res.* **51** 19–28

[13] Günther R and Hofmann H-J 2001 Hydrazino peptides as foldamers: an extension of the β-peptide concept *J. Am. Chem. Soc.* **123** 247–55

[14] Wu Y, Wang D, Chan K and Yang D 1999 Theoretical study of peptides formed by aminoxy acids *J. Am. Chem. Soc.* **121** 11189–96

[15] Seebach D and Matthews J L 1997 β-Peptides: a surprise at every turn *J. Chem. Soc., Chem. Commun.* **21** 2015–22

[16] Gademann K, Hintermann T and Schreiber J 1999 β-peptides: twisting and turning *Curr. Med. Chem.* **6** 905–25

[17] Cheng R P, Gellman S H and DeGrado W F 2001 β-peptides: from structure to function *Chem. Rev.* **101** 3219–32

[18] Möhle K, Günther R, Thormann M, Sewald N and Hofmann H-J 1999 Basic conformers in β-peptides *Biopolymers* **50** 167–84

[19] Günther R, Hofmann H-J and Kuczera K 2001 Searching for periodic structures in β-peptides *J. Phys. Chem. B* **105** 5559–67

[20] Wu Y-D and Wang D-P 1998 Theoretical studies of β-peptide models *J. Am. Chem. Soc.* **120** 13485–93

[21] Alemán C and León S 2000 Effects of electron correlation and the environment on the conformational preferences of the β-alanine dipeptide *J. Mol. Struct. (Theochem)* **505** 211–19

[22] Beke T, Csizmadia I G and Perczel A 2004 On the flexibility of β-peptides *J. Comput. Chem.* **25** 285–307

[23] Hagihara M, Anthony N J, Stout T J, Clardy J and Schreiber S L 1992 Vinylogous polypeptides: an alternative peptide backbone *J. Am. Chem. Soc.* **114** 6568–70

[24] Baldauf C, Günther R and Hofmann H-J 2003 Helix formation and folding in γ-peptides and their vinylogues *Helv. Chim. Acta* **86** 2573–88

[25] Baldauf C, Günther R and Hofmann H-J 2004 δ-peptides and δ-amino acids as tools for peptide structure design: a theoretical study *J. Org. Chem.* **69** 6214–20

[26] Baldauf C, Günther R and Hofmann H-J 2005 Control of helix formation in vinylogous γ-peptides by (E)- and (Z)-double bonds: a way to ion channels and monomolecular nanotubes *J. Org. Chem.* **70** 5351–61

[27] Baldauf C, Günther R and Hofmann H-J 2005 Side chain control of folding of the homologous α-, β- and γ-peptides into 'mixed' helices (β-helices) *Biopolymers* **80** 675–87

[28] López-Carrasquero F, García-Alvarez M, Navas J J, Alemán C and Muñoz-Guerra S 1996 Structural study on poly(β-L-aspartate)s with short alkyl side chains: helical and extended crystal forms *Macromolecules* **29** 8449–59

[29] Zanuy D, Alemán C and Muñoz-Guerra S 2000 A microscopic view of a helical poly(γ-peptide): molecular dynamics simulations of a 20-residue unionized poly(γ-D-glutamic acid) in water *Macromol. Theory Simul.* **9** 543–49

[30] Zanuy D, Alemán C and Muñoz-Guerra S 1998 On the helical conformation of un-ionized poly(γ-D-glutamic acid) *Int. J. Biol. Macromol.* **3** 175–84

[31] Seebach D, Brenner M, Rueping M and Jaun B 2002 γ(2)-, γ(3)-, and γ(2,3,4)-amino acids, coupling to γ-hexapeptides: CD spectra, NMR solution and X-ray crystal structures of γ-peptides *Chem.-Eur. J.* **8** 573–84

[32] Hintermann T, Gademann K, Jaun B and Seebach D 1998 γ-peptides forming more stable secondary structures than α-peptides: synthesis and helical NMR-solution structure of the γ-hexapeptide analog of H-(Val-Ala-Leu)(2)-OH *Helv. Chim. Acta* **81** 983–1002

[33] Hook D F, Bindschadler P, Mahajan Y R, Sebesta R, Kast P and Seebach D 2005 The proteolytic stability of 'designed' β-peptides containing α-peptide-bond mimics and of mixed α,β-peptides: application to the construction of MHC-binding peptides *Chem. Biodiv.* **2** 591–632

[34] Seebach D, Beck A K and Bierbaum D J 2004 The world of β- and γ-peptides comprised of homologated proteinogenic amino acids and other components *Chem. Biodiv.* **1** 1111–239

[35] Sadowsky J D, Schmitt M A, Lee H-S, Umezawa N, Wang S, Tomita Y and Gellman S H 2005 Chimeric (α/β+α)-peptide ligands for the BH3-recognition cleft of Bcl-xL: critical role of the molecular scaffold in protein surface recognition *J. Am. Chem. Soc.* **127** 11966–68

[36] Aravinda S, Ananda K, Shamala N and Balaram P 2003 α-γ hybrid peptides that contain the conformationally constrained gabapentin residue: characterization of mimetics of chain reversals *Chem.-Eur. J.* **9** 4789–95

[37] Karle I L, Gopi H N and Balaram P 2001 Peptide hybrids containing α- and β-amino acids: structure of a decapeptide β-hairpin with two facing β-phenylalanine residues *Proc. Natl Acad. Sci. USA* **98** 3716–19

[38] Roy R S, Karle I L, Raghothama S and Balaram P 2004 α,β hybrid peptides: a polypeptide helix with a central segment containing two consecutive β-amino acid residues *Proc. Natl Acad. Sci. USA* **101** 16478–82

[39] Roy R S and Balaram P 2004 Conformational properties of hybrid peptides containing α- and omega-amino acids *J. Pept. Res.* **63** 279–89

[40] Simon R J, Kania R S, Zuckermann R N, Huebner V D, Jewell D A, Banville S, Ng S, Wang L, Rosenberg S, Marlowe C K, Spellmeyer D C, Tan R Y, Frankel A D, Santi D V, Cohen F E and Bartlett P A 1992 Peptoids—a modular approach to drug discovery *Proc. Natl Acad. Sci. USA* **89** 9367–71

[41] Wu C W, Sanborn T J, Huang K, Zuckermann R N and Barron A E 2001 Peptoid oligomers with α-chiral, aromatic side chains: sequence requirements for the formation of stable peptoid helices *J. Am. Chem. Soc.* **123** 6778–84

[42] Wu C W, Sanborn T J, Zuckermann R N and Barron A E 2001 Peptoid oligomers with α-chiral, aromatic side chains:

effects of chain length on secondary structure *J. Am. Chem. Soc.* **123** 2958–63
[43] Wu C W, Kirshenbaum K, Sanborn T J, Patch J A, Huang K, Dill K A, Zuckermann R N and Barron A E 2003 Structural and spectroscopic studies of peptoid oligomers with α-chiral aliphatic side chains *J. Am. Chem. Soc.* **125** 13525–30
[44] Lee Y C, Zuckermann R N and Dill K A 2005 Folding a nonbiological polymer into a compact multihelical structure *J. Am. Chem. Soc.* **127** 10999–1009
[45] Armand P, Kirshenbaum K, Falicov A, Dunbrack R L J, Dill K A, Zuckermann R N and Cohen F E 1997 Chiral N-substituted glycines can form stable helical conformations *Fold. Des.* **2** 369–75
[46] Kirshenbaum K, Barron A E, Goldsmith R A, Armand P, Bradley E K, Truong K T, Dill K A, Cohen F E and Zuckermann R N 1998 Sequence-specific polypeptoids: a diverse family of heteropolymers with stable secondary structure *Proc. Natl Acad. Sci. USA* **95** 4303–08
[47] Armand P, Kirshenbaum K, Goldsmith R A, Farr-Jones S, Barron A E, Truong K T, Dill K A, Mierke D F, Cohen F E, Zuckermann R N and Bradley E K 1998 NMR determination of the major solution conformation of a peptoid pentamer with chiral side chains *Proc. Natl Acad. Sci. USA* **95** 4309–14
[48] Miertus S, Scrocco E and Tomasi J 1981 Electrostatic interaction of a solute with a continuum—a direct utilization of *ab initio* molecular potentials for the prevision of solvent effects *Chem. Phys.* **55** 117–29
[49] Frisch M J *et al* 2003 *Gaussian 03* (Pittsburgh, PA: Gaussian Inc.)
[50] Schmidt M W *et al* 1993 General atomic and molecular electronic-structure system *J. Comput. Chem.* **14** 1347–63
[51] Head-Gordon T, Head-Gordon M, Frisch M J, Brooks III C L and Pople J A 1991 Theoretical study of blocked glycine and alanine peptide analogs *J. Am. Chem. Soc.* **113** 5989–97
[52] Brooks III C L and Case D A 1993 Simulations of peptide conformational dynamics and thermodynamics *Chem. Rev.* **93** 2487–502
[53] Seebach D, Gademann K, Schreiber J V, Matthews J L, Hintermann T and Jaun B 1997 'Mixed' β-peptides: a unique helical secondary structure in solution *Helv. Chim. Acta* **80** 2033–38
[54] Wu Y-D and Wang D-P 1999 Theoretical study on side-chain control of the 14-helix and the 10/12-helix of β-peptides *J. Am. Chem. Soc.* **121** 9352–62
[55] Baldauf C, Günther R and Hofmann H-J 2004 Mixed helices—a general folding pattern in homologous peptides? *Angew. Chem. Int. Ed. Engl.* **43** 1594–97
[56] Sandvoss L M and Carlson H A 2003 Conformational behavior of β-proline oligomers *J. Am. Chem. Soc.* **125** 15855–62