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δ-Peptides and δ-Amino Acids as Tools for Peptide Structure Design—A Theoretical Study

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An overview on all possible helix types in oligomers of δ-amino acids (δ-peptides) and their stabilities is given on the basis of a systematic conformational analysis employing various methods of ab initio MO theory (HF/6-31G*, B3LYP/6-31G*, PCM//HF/6-31G*). A wide variety of novel helical structures with hydrogen-bonded pseudocycles of different size are predicted. Since a δ-amino acid constituent may replace a dipeptide unit in α-peptides, there are close relationships between the secondary structures of peptides with δ-amino acid residues and typical secondary structures of α-peptides. However, the preference of gauche conformations at the central C(β)−C(γ) bonds of δ-amino acids, which correspond to the peptide linkages in α-peptides, over staggered ones makes completely novel structure alternatives for helices and turns more probable. The peculiarities of β-turn formation by sugar amino acids derived from δ-amino acids are compared with the turn formation in δ-amino acid residues and in α-peptides. The considerable potential of secondary structure formation in δ-peptides and single δ-amino acid constituents predicted by ab initio MO theory may stimulate experimental work in the field of peptide and foldamer design.

Introduction

In the past years, numerous examples of unnatural oligomeric sequences have been found that fold into well-defined conformations in solution.[1] It is popular to denote such oligomers as foldamers.[1a] In particular, studies on oligomers of β- and γ-amino acids (β- and γ-peptides) demonstrated their ability to adopt ordered secondary structures, e.g., helices, strands, and turns.[2,3] Thus, these homologues of α-peptides are candidates for mimicking the structure and function of their natural counterparts. In the meantime, experimental hints were also obtained for the formation of ordered structures in oligomers of δ-amino acids (δ-peptides),[4] although detailed structure information is still missing.

From the very beginning of peptide foldamer research the experimental investigations were accompanied by systematic investigations of the conformational space of β- and γ-peptides employing theoretical methods.[5] The results of these studies contributed essentially to a better understanding of the origin and features of the novel

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(1) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Barron, A. E.; Zuckermann, R. N. *Curr. Opin. Chem. Biol.* **1999**, *3*, 681. (c) Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530. (d) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714. (e) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (f) Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650. (g) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (h) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649.

(2) (a) Fernández-Santín, J. M.; Aymamí, J.; Rodríguez-Galán, A.; Muñoz-Guerra, S.; Subirana, J. A. *Nature (London)* **1984**, *311*, 53. (b) Chandrakumar, N. S.; Stapelfeld, A.; Beardsley, P. M.; Lopez, O. T.; Drury, B.; Anthony, E.; Savage, M. A.; Williamson, L. N.; Reichman, M. *J. Med. Chem.* **1992**, *35*, 2928. (c) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071. (d) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. (e) Krauthäuser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719. (f) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015. (g) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1595. (h) Motorina, I. A.; Huel, C.; Quiniou, E.; Mispelter, J.; Adjadj, E.; Grierson, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 8. (i) Martinek, T. A.; Fülöp, F. *Eur. J. Biochem.* **2003**, *270*, 3657.

(3) (a) Rydon, H. N. *J. Chem. Soc.* **1964**, 1328. (b) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569. (c) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983. (d) Hanessian, S.; Luo, X. H.; Schaum, R. *Tetrahedron Lett.* **1999**, *40*, 4925. (e) Brenner, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 1181. (f) Brenner, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 2155. (g) Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573.

(4) (a) Smith, M. D.; Claridge, T. D. W.; Tranter, G. E.; Sansom, M. S. P.; Fleet, G. W. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2041. (b) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parrill, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074. (c) Claridge, T. D. W.; Long, D. D.; Hungerford, N. L.; Aplin, R. T.; Smith, M. D.; Marquess, D. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2199. (d) Long, D. D.; Hungerford, N. L.; Smith, M. D.; Brittain, D. E. A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2195. (e) Brittain, D. E. A.; Watterson, M. P.; Claridge, T. D. W.; Smith, M. D.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3655. (f) Hungerford, N. L.; Claridge, T. D. W.; Watterson, M. P.; Aplin, R. T.; Moreno, A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3666. (g) Karig, G.; Fuchs, A.; Busing, A.; Brandstetter, T.; Scherer, S.; Bats, J. W.; Eschenmoser, A.; Quinkert, G. *Helv. Chim. Acta* **2000**, *83*, 1049. (h) Schwalbe, H.; Wermuth, J.; Richter, C.; Szalma, S.; Eschenmoser, A.; Quinkert, G. *Helv. Chim. Acta* **2000**, *83*, 1079. (i) McReynolds, K. D.; Gervay-Hague, J. *Tetrahedron: Asymmetry* **2000**, *11*, 337. (j) Jiang, H.; Léger, J. M.; Dolain, C.; Guionneau, P.; Huc, I. *Tetrahedron* **2003**, *59*, 8365. (k) Jiang, H.; Léger, J. M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448. (l) Gregar, T. Q.; Gervay-Hague, J. *J. Org. Chem.* **2004**, *69*, 1001. (m) Ying, L.; Gervay-Hague, J. *Carbohydr. Res.* **2004**, *339*, 367. (n) Zhao, X.; Jia, M.-X.; Jiang, X.-K.; Wu, L.-Z.; Li, Z.-T.; Chen, G.-J. *J. Org. Chem.* **2004**, *69*, 270. (o) Jiang, H.; Dolain, C.; Leger, J.-M.; Gornitzka, H.; Huc, I. *J. Am. Chem. Soc.* **2004**, *126*, 1034.

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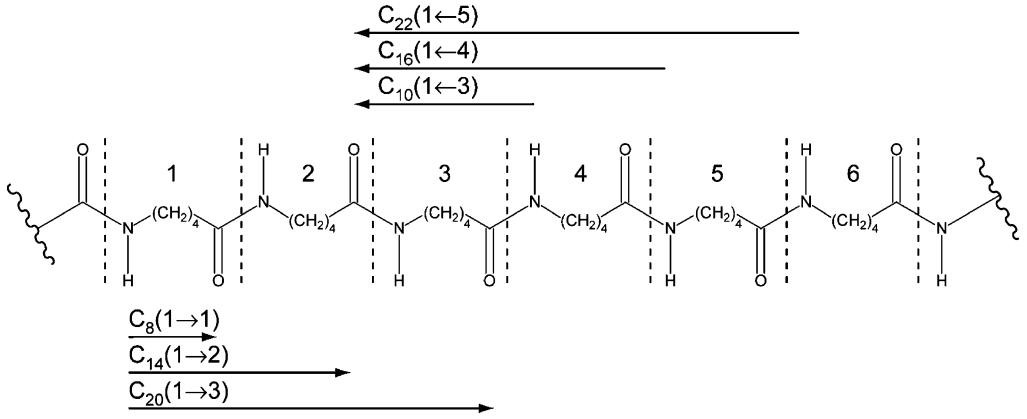
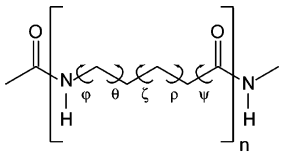


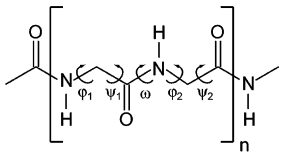
FIGURE 1. Possible hydrogen-bonding patterns in δ-peptides (C_x denotes the hydrogen-bonded pseudocycles with x atoms).

secondary structure types and predicted further possibilities of secondary structure formation. In the case of β-peptides, it was shown that all typical folding patterns can be derived from the conformers of the monomer constituents.[5b,d,i] On the contrary, the most favored helices of γ-peptides do not correspond to conformers of blocked γ-amino acids. They can only be localized by a detailed examination of longer oligomeric sequences.[5k]

Since experimental data on the secondary structure formation in oligomers of δ-amino acids (δ-peptides) **1** are still scarce, we extend our studies to this class of compounds following the same strategy as for the other homologues.[5d,h,j,k] Our aim is to get a complete overview on the possible folding alternatives and compare them with those of α-peptides due to the close correspondence between δ-amino acid residues and dipeptide elements in α-peptides **2**.



1



2

Methodology

To examine the helix formation in δ-peptides, a pool of 5184 periodic conformations of the δ-peptide hexamer **1** ($n = 6$) was generated by a systematic variation of the backbone torsion angles φ, ψ, θ, ζ, and ρ in steps of 60°. All structures exhibiting the hydrogen-bonding patterns of Figure 1 were selected as starting points for geometry optimizations at the HF/6-31G* level of ab initio MO theory. The resulting minimum structures were reoptimized at the B3LYP/6-31G* level of density functional theory to consider correlation energy effects. Finally, the influence of an aqueous environment (dielectric constant $\epsilon = 78.4$) was estimated on the basis of the polarizable continuum model (PCM//HF/6-31G*). The solvation energy includes the electrostatic, van der Waals, and cavitation energy contributions. All turn conformers derived from δ-amino acid constituents were examined at the same levels of ab initio MO theory.

The quantum chemical calculations were performed employing the Gaussian98, Gaussian03 and the Gamess-US program packages.[7]

Results and Discussion

Helix Formation in δ-Peptides. Our search for periodic structures in the δ-peptide hexamer provided a large number of helices with a different size of the

(5) (a) Daura, X.; Jaun, B.; Seebach, D.; van Gunsteren, W. F.; Mark, A. E. *J. Mol. Biol.* **1998**, *280*, 925. (b) Wu, Y.-D.; Wang, D.-P. *J. Am. Chem. Soc.* **1998**, *120*, 13485. (c) Daura, X.; van Gunsteren, W. F.; Mark, A. E. *Proteins: Struct. Funct. Genet.* **1999**, *34*, 269. (d) Möhle, K.; Günther, R.; Thormann, M.; Sewald, N.; Hofmann, H.-J. *Biopolymers* **1999**, *50*, 167. (e) Wu, Y.-D.; Wang, D.-P. *J. Am. Chem. Soc.* **1999**, *121*, 9352. (f) Aleman, C.; Leon, S. *J. Mol. Struct. (THEOCHEM)* **2000**, *505*, 211. (g) Wu, Y.-D.; Wang, D.-P. *J. Chin. Chem. Soc.* **2000**, *47*, 129. (h) Günther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247. (i) Günther, R.; Hofmann, H.-J.; Kuczera, K. *J. Phys. Chem. B* **2001**, *105*, 5559. (j) Günther, R.; Hofmann, H.-J. *Helv. Chim. Acta* **2002**, *85*, 2149. (k) Baldauf, C.; Günther, R.; Hofmann, H.-J. *Helv. Chim. Acta* **2003**, *86*, 2573. (l) Baldauf, C.; Günther, R.; Hofmann, H.-J. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1594. (m) Beke, T.; Csizmadia, I. G.; Perczel, A. *J. Comput. Chem.* **2004**, *25*, 285.

(6) (a) Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc., Chem. Commun.* **1980**, 234. (b) Graf von Roedern, E.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 687. (c) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (d) Gardner, R. R.; Liang, G. B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280. (e) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156. (f) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (g) Gardner, R. R.; Liang, G. B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806. (h) Banerjee, A.; Pramanik, A.; Bhattacharjya, S.; Balaram, P. *Biopolymers* **1996**, *39*, 769. (i) Shankaramma, S. C.; Singh, S. K.; Sathyamurthy, A.; Balaram, P. *J. Am. Chem. Soc.* **1999**, *121*, 5360.

(7) (a) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347. (b) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian*, Revision B.04 ed.; Gaussian Inc.: Pittsburgh, PA, 2003.

TABLE 1. HF/6-31G* Backbone Torsion Angles[a] for the Most Stable Helices of Each Ring Size in Hexamers of 1 (n = 6)

conf.[b]	φ	θ	ζ	ρ	ψ	conf.[b]	φ	θ	ζ	ρ	ψ
H_8^I	−178.8	66.5	−143.5	69.1	−171.2	H_{10}^I	−97.3	62.8	68.2	−169.2	86.1
	−179.0	66.4	−142.5	69.2	−172.7		−97.9	62.6	68.3	−168.6	84.7
	−179.5	66.4	−142.2	69.1	−172.5		−98.1	62.4	68.4	−168.5	84.5
	−179.3	66.4	−142.2	69.2	−172.9		−98.2	62.4	68.4	−168.4	84.4
	−179.4	66.4	−142.5	69.3	−173.1		−98.3	62.4	68.4	−168.7	84.5
	−178.7	66.6	−143.9	69.7	−173.8		−99.0	62.6	68.8	−168.7	87.1
H_{14}^I	117.5	−73.5	169.9	−79.9	110.8	H_{16}^I	−77.8	179.8	−170.6	67.3	−113.1
	102.6	−71.9	172.1	−75.4	110.8		−75.3	−179.3	−170.6	70.1	−109.9
	105.9	−73.1	170.5	−77.1	111.5		−76.7	−178.8	−173.4	68.3	−108.0
	106.8	−73.0	170.0	−77.6	111.6		−75.6	−179.0	−173.6	68.5	−108.9
	106.0	−71.1	171.1	−75.0	108.8		−77.5	−177.0	−174.4	70.7	−107.1
	100.3	−74.1	175.8	−76.1	128.9		−78.7	−175.3	178.5	72.6	−105.8
H_{20}^I	158.6	−65.2	−176.6	178.0	129.4	H_{22}^I	−94.1	−175.4	177.0	70.7	−135.9
	130.4	−60.5	−177.5	−176.0	109.2		−91.3	−173.4	179.6	71.3	−136.3
	145.4	−59.5	−176.8	−174.5	132.7		−88.2	−173.7	178.1	72.8	−134.8
	115.7	−55.4	−172.8	−171.0	133.7		−88.5	−173.2	176.5	71.4	−128.4
	112.5	−56.8	−175.7	−174.3	140.2		−96.2	−172.5	175.6	72.2	−120.1
	111.7	−68.1	178.0	179.4	-151.4		−91.5	−179.8	173.2	64.2	−109.8

[a] Angles in degrees. [b] H_x denotes a helix with hydrogen-bonded pseudocycles of x atoms. The superscript Roman number arranges helices of the same ring size according to their stability (cf. Table 2).

hydrogen-bonded pseudocycles. As in the homologous β- and γ-peptides, the hydrogen bonds can be formed in the forward or backward direction along the sequence. Thus, hydrogen-bonding patterns with 8-, 14-, and 20-membered rings in the forward and with 10-, 16-, and 22-membered rings in the backward direction occur according to the general scheme in Figure 1. The same hydrogen-bonding pattern can be realized by various backbone conformations. Consequently, we find two helix alternatives with eight-membered, nine with 10-membered, six with 14-membered, four with 16-membered, and three with 20- and 22-membered hydrogen-bonded pseudocycles. Helix alternatives with the same ring size are denoted by superscript Roman numbers at the helix symbol in the order of decreasing stability. Table 1 lists the backbone torsion angles of the most stable helices of each ring size obtained at the HF/6-31G* level of ab initio MO theory. These helices are also visualized in Figure 2.

The corresponding backbone torsion angles at the B3LYP/6-31G* level and those of the other helix alternatives at both approximation levels are given as Supporting Information. A detailed look at the relative stabilization energies of all helical structures in Table 2 reveals that only a few of them have a chance to be found in experiments. Most stable is the conformer H_{10}^I according to the Hartree−Fock and density functional calculations followed by H_{14}^I, H_{16}^I, and H_8^I. In an aqueous environment, there is a stability increase in favor of helices with nearest-neighbor interactions.

Helices H_{10} and H_{16} deserve special attention with a value of about 180° for the torsion angle ζ, which describes the rotation around the central C(β)−C(γ) bond of the δ-amino acid constituents (cf. Supporting Information). The C(β)−C(γ) bond in a δ-amino acid constituent corresponds to the peptide bond in an α-dipeptide. Thus, it could be possible to find δ-peptide helices that are formal analogues of the 3_{10}- and π-helices of α-peptides with their 10- and 16-membered hydrogen-bonded rings. Among the H_{10} hexamers, only the rather unstable H_{10}^{VII} conformer is similar to the 3_{10}-helix. For a close correspondence (cf. structures **1** and **2**), the torsion angles φ and ρ in the δ-peptide amino acid residues have to be about −60° and the torsion angles θ and ψ between −20° and −30°, which are typical values of φ and ψ in a 3_{10}-

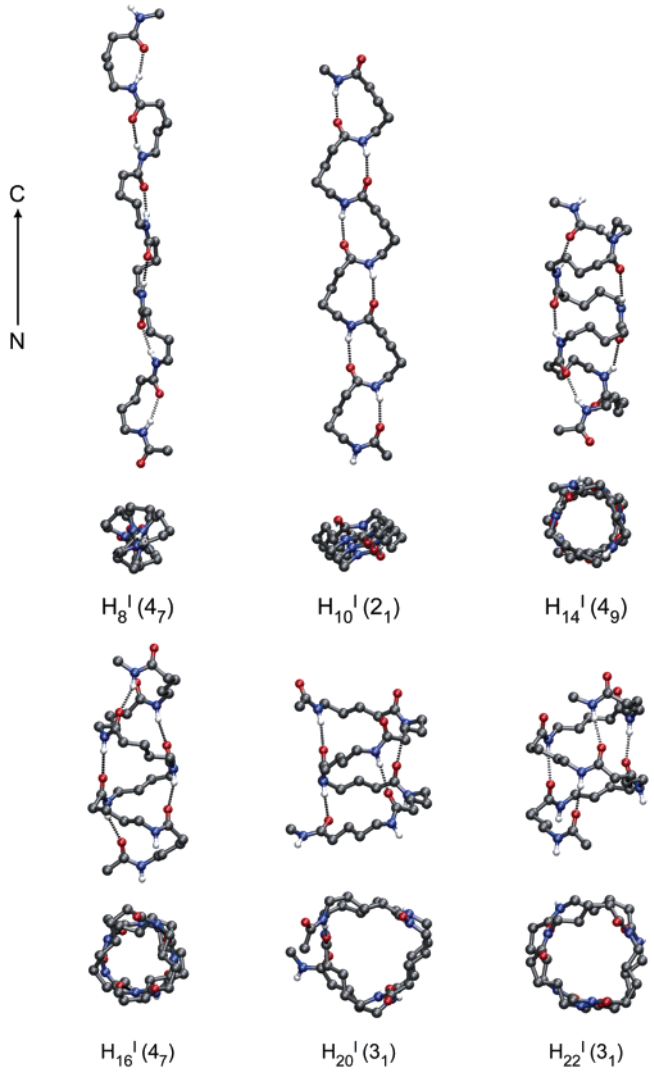


FIGURE 2. Most stable helices of **1** (n = 6) for each type of hydrogen-bonded pseudocycles obtained at the HF/6-31G* level of ab initio MO theory (helix nomenclature in parentheses).

TABLE 2. Relative Energies[a] of the Helix Types in the Hexamer 1 at Various Approximation Levels of ab Initio MO Theory

conf.[b]	ΔE(HF)	ΔE(B3LYP)	ΔE(PCM)[c]
H_8^{I}	19.1	28.2	39.9
H_8^{II}	73.1	41.2	117.3
H_{10}^{I}	**0.0**[d]	**0.0**[e]	50.4
H_{10}^{II}	19.9	9.9	**0.0**[f]
H_{10}^{III}	70.9	55.1	139.7
H_{10}^{IV}	71.9	64.1	130.9
H_{10}^{V}	82.8	66.9	153.8
H_{10}^{VI}	94.5	67.5	151.8
H_{10}^{VII}	100.2	90.3	133.6
H_{10}^{VIII}	105.4	92.7	145.2
H_{10}^{IX}	110.0	95.7	172.3
H_{14}^{I}	10.8	6.8	100.5
H_{14}^{II}	35.8	27.2	126.3
H_{14}^{III}	79.2	75.0	165.3
H_{14}^{IV}	84.1	78.2	176.1
H_{14}^{V}	113.9	108.8	203.1
H_{14}^{VI}	125.9	106.2	214.0
H_{16}^{I}	9.2	9.2	86.1
H_{16}^{II}	16.4	16.0	68.6
H_{16}^{III}	21.6	27.8	107.3
H_{16}^{IV}	95.3	84.2	192.8
H_{20}^{I}	30.1	38.0	81.6
H_{20}^{II}	49.7	64.1	114.2
H_{20}^{III}	60.4	66.7	121.5
H_{22}^{I}	18.7	22.0	76.2
H_{22}^{II}	33.2	37.1	81.7
H_{22}^{III}	61.8	52.8	123.0

[a] Relative energies in kJ/mol. [b] Cf. footnote *b* in Table 1. [c] $\epsilon = 78.4$. [d] $E_T = -2190.562661$ au. [e] $E_T = -2204.282712$ au. [f] $E_T = -2190.558820$ au.

TABLE 3. Idealized and Calculated Backbone Torsion Angles[a] for the βI/I′ and βII/II′ Turns in α-Peptides

turn	φ_1	ψ_1	φ_2	ψ_2
βI	−60/−73	−30/−18	−90/−102	0/12
βI	60/73	30/18	90/102	0/−12
βII	−60/−60	120/136	90/96	0/−12
βII	60/60	−120/−136	−90/−96	0/12

[a] Angles in degrees; first values idealized;[8a] second values calculated for a blocked glycine dipeptide.[8b]

helix. The actual values of about $\varphi = -51°$, $\theta = -47°$, $\rho = -72°$, and $\psi = 0°$ in H_{10}^{VII} (cf. Supporting Information) show that the δ-peptide helix H_{10}^{VII} is more similar to a periodic arrangement of βI-turns in α-peptides (cf. Table 3). The δ-peptide counterpart for the postulated but not convincingly indicated π-helix in α-peptides is conformer H_{16}^{III} with torsion angles of about $\varphi = -77°$, $\theta = -59°$, $\rho = -58°$, and $\psi = -65°$ (cf. Supporting Information). These values agree with torsion angles of $\varphi = -57°$ and $\psi = -70°$ postulated for a π-helix in α-peptides. The two examples illustrate the general capacity of δ-peptide structures to fit approximately secondary structures of α-peptides. This was also demonstrated by the group of Balaram,[6h] who introduced a δ-aminovaleric acid constituent into a sequence of α-amino acids and found that the δ-amino acid adopts the 3_{10}-helix conformation. However, this structure seems to be essentially enforced by the surrounding α-amino acids of the sequence. The stability relations in Table 2 show that helix alternatives with gauche conformations at the C(β)−C(γ) bonds are distinctly favored over the staggered arrangements in oligomers of δ-amino acids.

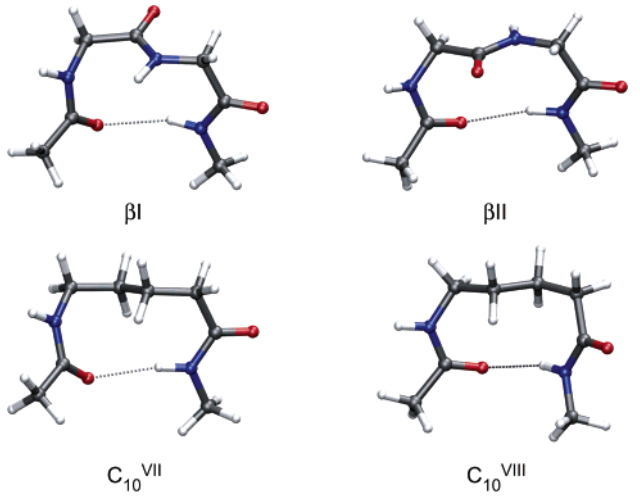


FIGURE 3. Comparison of the βI- and βII-turns of α-peptides with the two turn conformers C_{10}^{VII} and C_{10}^{VIII} of a blocked δ-amino acid constituent.

δ-Amino Acid Constituents as β-Turn Mimetics. The typical β-turns of α-peptides consist of four consecutive α-amino acids. Most of them are characterized by a hydrogen bond between the peptidic CO bond of the first and the peptidic NH bond of the fourth amino acid, thus forming a 10-membered hydrogen-bonded pseudocycle (Figure 3). Since the first and the fourth amino acids of a β-turn are mostly part of periodic structures, the β-turn structure is determined by the conformation of the second and third amino acid. It is obvious that replacement of the central α-dipeptide unit by a δ-amino acid residue may be suited to mimic β-turns. In this case, the C(β)−C(γ) bond of the δ-amino acid replaces the peptide linkage between the second and third α-amino acids (cf. structures **1** and **2**). Turns in proteins are often exposed to the surrounding medium. Therefore, turns with δ-amino acid residues may be attractive because of a higher resistance against proteases due to the missing central peptide bond. Besides, it is possible to design the interaction and recognition functions by special substitutions at the additional carbon atoms. The idealized backbone torsion angles[8a] for the predominating βI- and βII-turns of α-peptides and their approximate mirror images βI′ and βII′ are given in Table 3 together with the calculated values.[8b]

Since the typical β-turns of α-peptides are characterized by a 10-membered hydrogen-bonded pseudocycle, one loop of the nine predicted H_{10} δ-peptide conformers (Table 1 and Supporting Information) could potentially be a β-turn. A search for conformers with 10-membered hydrogen-bonded pseudocycles on a blocked δ-amino acid monomer **1** with $n = 1$ in steps of 30° for the backbone torsion angles φ, ψ, θ, ζ, and ρ confirms the loops of the helices H_{10} as conformers with about the same values of the backbone torsion angles and the same stability order (Tables 4 and 5). Further conformers of this type were not found. However, only conformers C_{10}^{I}, C_{10}^{II}, C_{10}^{VII}, and C_{10}^{VIII} are suited to be β-turn mimetics. This was proved by attachment of three α-amino acids at the N- and

(8) (a) Venkatachalam, C. M. *Biopolymers* **1968**, *6*, 1425. (b) Möhle, K.; Guβmann, M.; Hofmann, H.-J. *J. Comput. Chem.* **1997**, *18*, 1415.

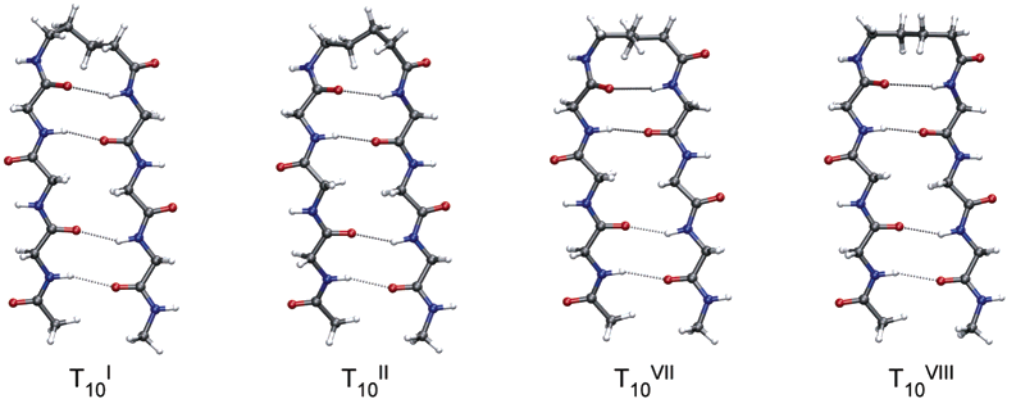


FIGURE 4. Conformers C_{10}^{I}, C_{10}^{II}, C_{10}^{VII}, and C_{10}^{VIII} as β-turn mimetics T_{10}^{I}, T_{10}^{II}, T_{10}^{VII}, and T_{10}^{VIII} embedded in a β-sheet structure after geometry optimization at the HF/6-31G* level.

TABLE 4. HF/6-31G* Backbone Torsion Angles[a] for the C_{10} Conformers of a Blocked δ-Amino Acid Monomer 1

conf.[b]	φ	θ	ζ	ρ	ψ
C_{10}^{I}	98.4	−62.5	−68.4	169.4	−90.4
C_{10}^{II}	83.0	−161.6	72.1	68.3	−104.9
C_{10}^{III}	121.3	−53.5	−46.7	−52.6	129.7
C_{10}^{V}	79.8	−161.8	76.8	−81.8	115.7
C_{10}^{IV}	96.4	−72.0	86.9	−168.3	82.9
C_{10}^{VI}	100.8	−67.9	−96.9	58.7	51.6
C_{10}^{IX}	68.3	52.0	−90.8	−67.7	106.4
C_{10}^{VII}	52.4	48.5	−177.8	69.9	9.8
C_{10}^{VIII}	66.4	−118.5	169.4	−67.5	−20.5

[a] Angles in degrees. [b] C_{10} denotes a conformer with a hydrogen-bonded pseudocycle of 10 atoms. The Roman numbers refer to the corresponding helices in Table 1.

TABLE 5. Relative Energies[a] of the C_{10} Conformers of a Blocked δ-Amino Acid Monomer 1(n = 1) at Various Approximation Levels of ab Initio MO Theory

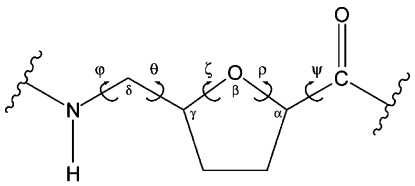
conf.[b]	ΔE(HF)	ΔE(B3LYP)	ΔE(PCM)[c]
C_{10}^{I}	**0.0**[d]	**0.0**[e]	**0.0**[f]
C_{10}^{II}	2.1	1.3	2.8
C_{10}^{III}	6.6	4.5	9.1
C_{10}^{V}	9.9	8.6	16.1
C_{10}^{IV}	10.9	10.0	9.8
C_{10}^{VI}	14.0	10.7	13.7
C_{10}^{IX}	14.3	13.1	13.8
C_{10}^{VII}	16.6	16.1	11.7
C_{10}^{VIII}	18.6	16.7	16.9

[a] Relative energies in kJ/mol. [b] C_{10} denotes a conformer with a hydrogen-bonded pseudocycle of 10 atoms. The Roman numbers refer to the corresponding helices in Table 1. [c] ϵ = 78.4. [d] E_T = −570.930590 au. [e] E_T = −574.481381 au. [f] E_T = −570.935718 au.

C-terminal ends of the 10-membered pseudocycles so that a β-sheet could be formed. Only the above-mentioned conformers were able to reverse the direction of the sequence of α-amino acids and keep the β-sheet structure after geometry optimization (Figure 4). The conformational structure of the turn mimetics C_{10}^{VII} and C_{10}^{VIII} can immediately be related to that of the βI/βI′- and βII/βII′-turns in α-peptides (Tables 3 and 4, Figure 3). A comparison with conformers C_{10}^{I} and C_{10}^{II} shows that gauche conformations at the C(β)−C(γ) bond are more stable than staggered ones in turn-like conformers as it was already found for helical structures. Thus, β-turn alternatives that are impossible in α-peptides are preferred when inserting δ-amino acid constituents into an α-peptide sequence.

However, the less stable C_{10}^{VII} and C_{10}^{VIII} turns become predominant after introduction of a β,γ-double bond in the δ-amino acid constituent mimicking the peptide bond of the α-peptide as it was tried several times.[6a,c,d,f,g]

Sugar Amino Acids as β-Turn Mimetics. Some sugar amino acids can be considered as δ-amino acid derivatives. Oligomers of such sugar amino acids represent pyranose- or furanose-based carbopeptoid foldamers. In several studies sugar amino acids have been inserted into α-peptide sequences to design reverse turns.[6b,e] These sugar amino acids can be derived from both furanose and pyranose residues. In particular, sugar amino acids of the types **3**−**5** might be able to form β-turns since they can be considered as δ-amino acid derivatives representing dipeptide isosteres. It is interesting to compare the β-turns predicted for a blocked δ-amino acid with those formed by these sugar amino acids. The secondary structure in sequences with sugar amino acid constitu-



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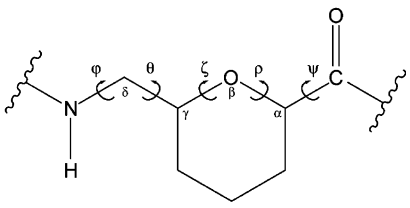

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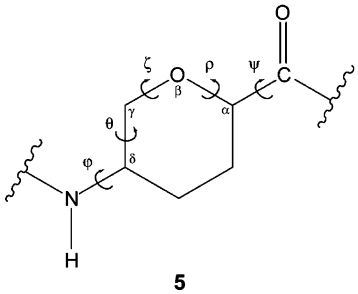

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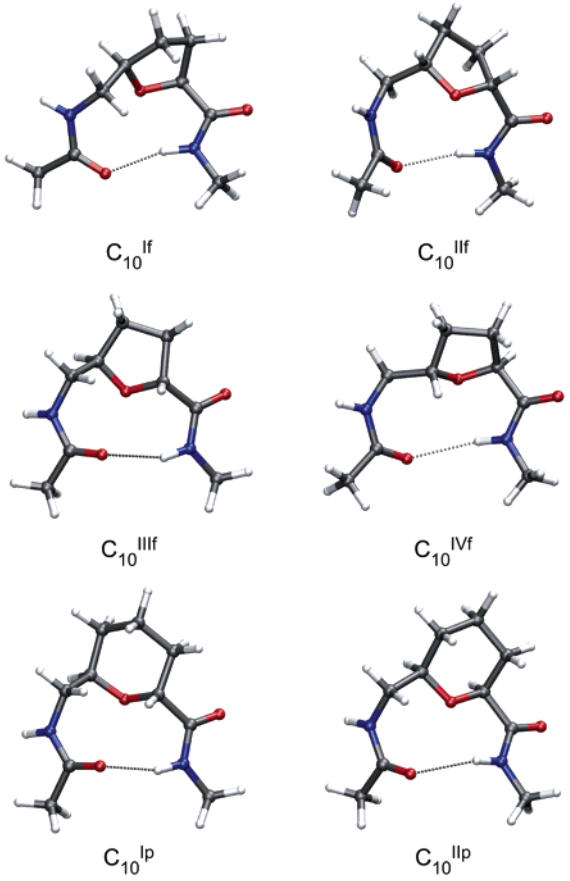


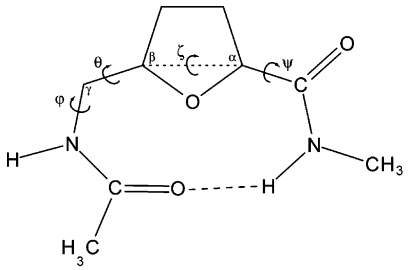
FIGURE 5. β-turns of furanose- and pyranose-based sugar amino acids.

ents depends strongly on the stereochemistry of the ring systems and the substitution type. Contrary to the ordinary δ-amino acids, the torsion angles ζ and ρ in the furanose- and pyranose-based sugar amino acids **3** and **4** and the torsion angles θ, ζ, and ρ in the pyranose-based sugar amino acid **5** are determined by the actual ring conformation. Therefore, the torsion angles in β-turn mimetics with sugar amino acids may differ from those predicted for the aliphatic δ-amino acids. A detailed analysis of the possibilities of β-turn formation with the sugar amino acids **3** and **4** considering different substitution patterns provided four C_{10} ring conformers for **3** and two for **4** with (pseudo)axial/(pseudo)equatorial or (pseudo)equatorial/(pseudo)equatorial orientations of the ring substituents. These pseudocycles are shown in Figure 5. The torsion angles of the six C_{10} rings are given in Table 6. A perfect agreement between a C_{10} conformer of the sugar amino acids and a C_{10} ring of a δ-amino acid constituent can only be seen for pseudocycle C_{10}^{IIp} of the pyranose derivative **4** with the acetyl aminomethylene group in axial and the *N*-methyl amide group in equatorial positions of the chair. The C_{10}^{IIp} conformer corresponds immediately to the most stable pseudocycle C_{10}^{I} in Table 4. All other C_{10} ring conformations of the sugar amino acids are different from those in Table 4. The stability of the pyranose turn C_{10}^{IIp} is surpassed by that of conformer C_{10}^{Ip}, whose conformation is in good agreement with experimental structure data for cyclopeptides having this structure element inserted.[6b,e] The three furanose pseudocycles C_{10}^{I-IIIf} and the pyranose conformer C_{10}^{Ip} of **4** and their mirror images can keep a β-sheet structure in an α-amino acid sequence without notable changes of the original turn conformation. This was again proved by complete geometry optimization of the corresponding β-sheet structures as described for the aliphatic δ-amino acids inserted into an α-amino acid sequence as β-turn elements. The furanose and pyranose turns C_{10}^{IVf} and C_{10}^{IIp} maintain sheet structures only after changes of the torsion angles φ and ψ. In the optimized conformation of the supersecondary structures, the hydrogen bonds in the C_{10} rings get lost. The possibility of β-turns with sugar amino acids of type **5** is more restricted. The only C_{10} pseudocycle obtained is not able to continue ordered secondary structures.

TABLE 6. HF/6-31G* Backbone Torsion Angles and Stability Order of the C_{10} Conformers of the Sugar Amino Acid Derivatives 3 and 4[a]

conf.[b]	φ	θ	ζ	ρ	ψ	ΔE
C_{10}^{If} (eq,eq)	94.7	−57.5	−132.4	108.5	4.6	**0.0**[c]
C_{10}^{IIf} (eq,eq)	95.6	−59.6	−123.5	144.0	−20.6	4.8
C_{10}^{IIIf} (ax,eq)	86.6	−55.6	−96.1	−166.7	−61.4	24.0
C_{10}^{IVf} (eq,ax)	63.3	−114.6	−166.9	−97.9	−4.9	26.1
C_{10}^{Ip} (eq,eq)	91.4	−61.1	179.7	−179.1	−3.4	**0.0**[d]
C_{10}^{IIp} (ax,eq)	92.0	−61.8	−76.1	179.6	−78.1	18.8

[a] Angles in degrees. Relative energies in kJ/mol. [b] Nomenclature: The C_{10} pseudocycles are differentiated by superscript Roman numerals in order of decreasing stability followed by "f" for the furanose-based and "p" for the pyranose-based derivatives. The axial or equatorial orientations of the substituents are given in parentheses in the order $CH_3CONHCH_2$ group and $CONH(CH_3)$ group. [c] $E_T = -683.657605$ au. [d] $E_T = -722.693949$ au.



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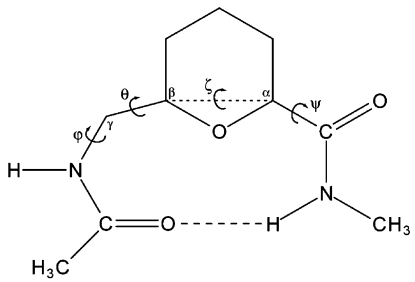

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It is interesting to note that the furanose- and pyranose-based turns of **3** and **4** with the two substituents in equatorial orientations, but not the derivatives with the substituents in axial and equatorial orientations, show a certain similarity to pseudocycles formed in oligomers of γ-amino acids and their vinylogues. Thinking the oxygen bridge of the furanose ring of **3** and the pyranose ring of **4** replaced by a fictive bond between the substituent-bearing ring atoms as indicated by a dotted line in the model structures **6** and **7**, the formal similarity becomes obvious. The turn torsion angles measured via

TABLE 7. Comparison of the HF/6-31G* Backbone Torsion Angles of the C_{10} Conformers of 3 and 4 with Equatorial Substituent Orientations and Those in the Most Stable C_9 Conformers of Blocked γ-Amino Acids and *cis*-Vinylogous γ-Amino Acids[a]

conf.[b]	φ	θ	ζ	ψ
C_{10}^{If}	94.7	−89.8	−24.2	41.9
C_{10}^{IIf}	95.6	−94.0	19.4	8.4
C_{10}^{Ip}	91.4	−60.8	0.8	−4.0
C_9^{I} [c]	99.4	−70.7	−74.6	103.7
C_9^{I} [d]	80.5	−123.7	-0.1	45.7

[a] Angles in degrees. [b] For nomenclature, cf. Table 6. [c] Blocked γ-amino acid monomer.[5k] [d] Blocked *cis*-vinylogous γ-amino acid monomer.

the fictive bond correspond to those of the most stable C_9 pseudocycles found in blocked γ-amino acid derivatives (Table 7).[5k] Due to the equatorial orientation of the substituents, there is a change of torsion angle ζ from a typical value for a gauche conformation to that of a cis orientation in the C_9 ring of a blocked γ-amino acid constituent, as it can be expected for blocked *cis*-vinylogous γ-amino acids. Depending on the sugar ring stereochemistry, the secondary structure formation with sugar amino acids **3** and **4** can obviously be more related to the secondary structures of γ-peptides and their *cis*- and *trans*-vinylogues than to those of δ-peptides. A similar correspondence might also exist between the secondary structure elements of β-peptides and oligomers of sugar amino acids of type **5**. These aspects could be interesting for structure interpretation of the experimentally found helices in oligomers of sugar amino acid derivatives **3**−**5**.[4b,c,d,f,i]

Conclusions

The results of our systematic conformational analysis on δ-amino acid monomers and oligomers demonstrate the considerable potential of secondary structure formation in this class of compounds. As in the homologous β- and γ-peptides, a wide variety of helices with hydrogen-bonded pseudocycles of different size formed between the peptide bonds in the forward or backward direction along the sequence can be expected. This confirms the fact that elongation of the backbone of the amino acid constituents does not prevent the formation of ordered secondary structures due to a higher backbone flexibility but increases the number of folding alternatives due to the well-defined conformational states arising from the additional single bonds. A peculiarity of a δ-amino acid residue is its close correspondence to an α-dipeptide unit.

Thus, δ-amino acid monomers are able to adopt the secondary structures of α-peptide sequences. However, this is considerably enforced by the α-amino acids which the δ-amino acid residue is embedded in. The distinct preference of gauche orientations over staggered ones at the C(β)−C(γ) bond makes novel helix types in oligomers of δ-amino acids more probable than the direct counterparts of α-peptide helices. Even if a β-sheet structure can be maintained in a sequence of α-amino acids via a β-turn with a δ-amino acid constituent instead of the central α-dipeptide unit, novel turn conformations are preferred over those corresponding to the typical β-turns of α-peptides. Keeping in mind the additional possibilities of special backbone substitutions, δ-peptides and δ-amino acids enrich the field of secondary structures considerably and could be a useful tool in peptide and foldamer design.

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Supporting Information Available: Tables with the backbone torsion angles of the most stable helices at the B3LYP/6-31G* level, the backbone torsion angles of the lesser stable helix alternatives at the HF/6-31G* and B3LYP/6-31G* levels, and the backbone torsion angles of the C_{10} conformers at the B3LYP/6-31G* level of ab initio MO theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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