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Synthesis and Secondary Structure of Alternate α,β-Hybrid Peptides Containing Oxazolidin-2-one Moieties

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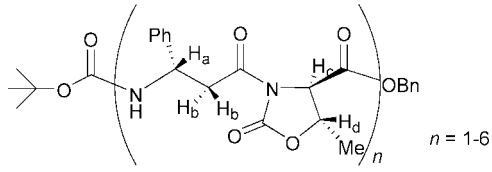
The synthesis and conformational analysis of a novel class of foldamers containing (*S*)-β^3-homophenylglycine [(*S*)-β^3-hPhg] and D-4-carboxy-oxazolidin-2-one (D-Oxd) residues in alternate order is reported. The experimental conformational analysis performed in solution by IR, ^{1}H NMR, and CD spectroscopy unambiguously proved that these oligomers fold into ordered structures with increasing sequence length. Theoretical calculations employing ab initio MO theory suggest a helix with 11-membered hydrogen-bonded rings as the preferred secondary structure type. The few formal helix alternatives can be excluded in particular by steric effects of the oxazolidin-2-one rings. The novel structures enrich the field of peptidic foldamers and might be useful in the mimicry of native peptides.

Introduction

The synthesis of peptide-like oligomers that fold into definite secondary structures is a great challenge for the community of synthetic organic chemists. Such molecules have been defined as foldamers by Gellman.[1] In the last decade, several groups succeeded in the preparation of homooligomers or heterooligomers of homologous amino acids, mainly β-amino acids, with defined secondary structures.[2]

Recently, several examples of foldamers were reported containing a mixture of α- and β-, α- and γ-, or β- and γ-amino acids in alternating order.[3] Besides helical structures with hydrogen bonds pointing only in one direction, either backward or forward along the sequence, also mixed helices (β-helices) with hydrogen bonds alternately changing in the forward and backward directions were found in these regular hybrid peptides.[3,4] In several cases, an increased resistance of the pseudopeptides against proteases was indicated in comparison to their native counterparts. Moreover, even biological activity of such peptidomimetics was found.[5] All these results make peptidic foldamers consisting of homologous amino acids highly attractive for several purposes and stimulate the search for novel foldamer classes.

Here, we report the synthesis of novel foldamers with the general formula Boc-[(*S*)-β^3-hPhg-D-Oxd]$_n$-OR (Figure 1). (*S*)-β^3-hPhg is the abbreviation for (*S*)-β^3-homophenylglycine[6] and D-Oxd is that for *trans*-(4*R*,5*S*) 4-carboxy-5-methyloxazolidin-2-one.[7] Thus, the periodic foldamer unit consists of a β-amino acid constituent followed by the proline mimetic D-Oxd as an α-amino acid. We expect that these molecules have several constraints due to the presence of the cyclic D-Oxd moiety that enforces the peptide bond, actually an imide bond, exclusively into the *trans* conformation owing to the presence of the endocyclic carbonyl group. The possibility of intramolecular hydrogen bonds would favor secondary structure formation as found in the above-mentioned regular α,β-hybrid peptides.



Boc-[(*S*)-β^3-hPhg-D-Oxd]$_n$-OBn

Figure 1. General formula of the oligomers.

Results and Discussion

Synthesis

Oligomers up to the 12-*mer* level (n = 6 in Figure 1) were synthesized in the liquid phase (Scheme 1). At first, the dimer Boc-(*S*)-β^3-hPhg-D-Oxd-OBn (**2**) was prepared by the addition of Boc-(*S*)-β^3-hPhg-OH to D-Oxd-OBn (**1**) in the

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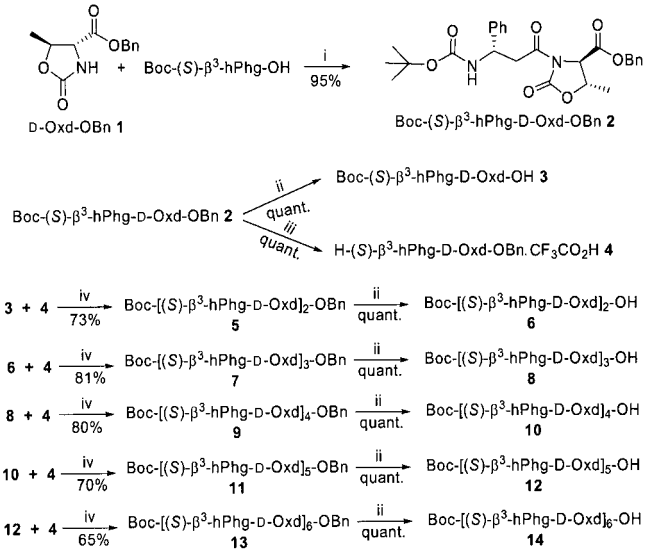
presence of *N*-[(1*H*-benzotriazol-yl)(dimethylamino)methylene]-*N*-methylmethaneiminium hexafluorophosphate *N*-oxide (HBTU) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile in excellent yield. Then, C-deprotected dimer **3** and N-deprotected dimer **4** were obtained by selective deprotection of the C-terminal benzyl ester with H_2 in methanol in the presence of Pd/C (5%) and of the N-terminal Boc moiety with anhydrous trifluoracetic acid (TFA) in dichloromethane, respectively. Treatment of **4** with a weak base ($NaHCO_3$) provided the corresponding free amine, which proved to be very unstable. Therefore, **4** was coupled as such by utilizing an excess of triethylamine (TEA).



Scheme 1. (i) HBTU (1 equiv.), DBU (1 equiv.), dry CH_3CN, room temp. 40 min; (ii) H_2, Pd/C (10%), MeOH, room temp., 16 h; (iii) TFA (18 equiv.), dry CH_2Cl_2, room temp., 2 h; (iv) HATU (1.1 equiv.), Et_3N (3 equiv.), dry CH_3CN, 40 min, room temp.

Moieties **3** and **4** were coupled with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and TEA in dry acetonitrile under an inert atmosphere to provide dimer **5** in satisfactory yield. By deprotection of the carbobenzoxy group with H_2 in methanol in the presence of Pd/C (5%), corresponding acid **6** was obtained in quantitative yield. The coupling step was repeated to get **7** in good yield as well. Repetition of these two steps finally led to Boc-[(*S*)-β^3-hPhg-D-Oxd]$_6$-OH (**14**). All compounds are stable at room temperature and soluble in acetonitrile, acetone, methanol, and DMSO.

Conformational Analysis

Information on the conformation of the described oligomers in solution was obtained by FT-IR, ^{1}H NMR spectroscopic, and CD techniques in structure-supporting solvents (dichloromethane, deuteriochloroform, and methanol) as well as DMSO.

The FT-IR absorption spectra of benzyl esters **2**, **5**, **7**, **9**, **11**, and **13** were obtained from 3 mM solutions in dichloromethane. At this concentration, self-aggregation is usually unimportant.[8] Figure 2 shows the FT-IR absorption spectra (NH stretching region) for all the synthesized compounds. They help to detect nonhydrogen-bonded amide NH bands (above 3400 cm^{-1}) and hydrogen-bonded amide proton bands (below 3400 cm^{-1}). These preliminary results suggest that the longer oligomers of this series form strong hydrogen bonds, as was observed for the oligomers of the L-Ala-D-Oxd series.[9]

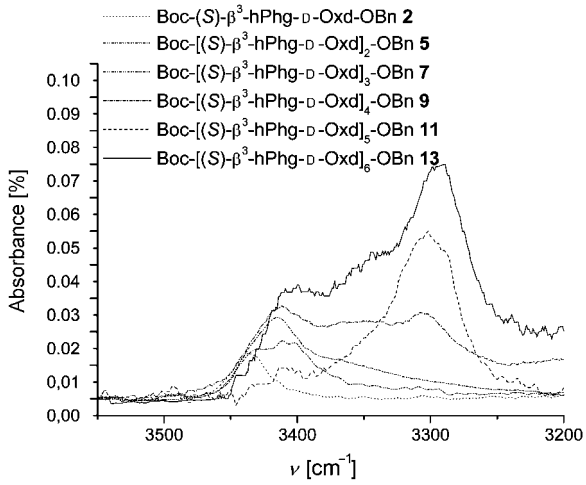


Figure 2. FT-IR absorption spectra in the NH stretching region for 3 mM samples of oligomers **2**, **5**, **7**, **9**, **11**, and **13** in pure CH_2Cl_2 at room temperature.

Monomer **2** has only one absorption band at 3439 cm^{-1} due to a nonhydrogen-bonded amide NH. Obviously, the sequence length is not sufficient for an effective hydrogen bond. Contrary to this, the maximum of the corresponding absorption band shifts slowly towards 3289 cm^{-1} in hexamer **13**, which thus demonstrates that the NH hydrogens are now chelated and form possibly an ordered secondary structure, such as a helix. It is worth mentioning that trimer **7** shows an absorption band with a broad maximum located between 3416 and 3344 cm^{-1}. This suggests that even in this oligomer, an ordered structure is favored, although still in an equilibrium with nonordered structures.

For further validation of these results, the oligomers were analyzed by ^{1}H NMR spectroscopy. We have already demonstrated that the formation of nonconventional, weak CH···O=C intramolecular H-bonds can simply be spotted by checking the α-proton chemical shift because the carbonyl proximity leads to a remarkable deshielding of the proton chemical shift.[10] This effect was also observed in β-amino acid derivatives like the homooligomers of (4*R*)-(2-oxo-1,3-oxazolidin-4-yl)acetic acid (D-Oxac).[11]

The same trend can be seen when analyzing the ^{1}H NMR chemical shifts of the methylene hydrogens of the β^3-homophenylglycine moiety in these compounds. Indeed, these hydrogens are always more deshielded by about 0.3–0.4 ppm in comparison to the chemical shift of Boc–β^3-homophenylglycine,[12] which thus shows that they suffer the effect of an oxazolidin-2-one carbonyl group in the vicinity of the $C_\alpha H$ proton in such a way that the imide–CO–N bond ex-

ternal to the ring system is forced into the *trans* conformation. A strictly comparable trend was observed for the C-deprotected series, which is not shown here.

Furthermore, the occurrence of intramolecular C=O···H–N hydrogen bonds in trimer **7** has been detected by an investigation of the [D_6]DMSO dependence of the NH proton chemical shifts (Figure 3).[13] DMSO is a strong hydrogen-bond acceptor and, if it is bound to a free NH proton, a considerable downfield shift of the proton signal can be expected.

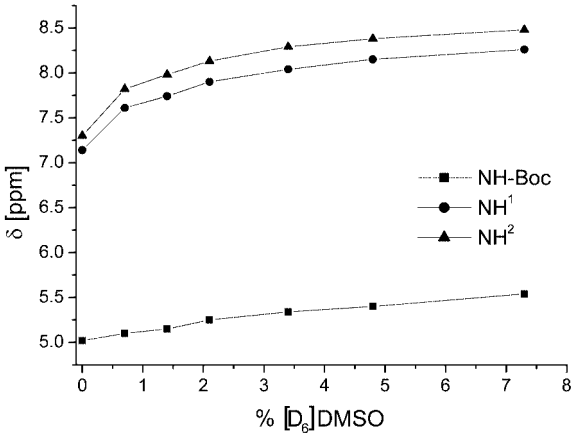


Figure 3. Variation of the NH proton chemical shifts [ppm] of **7** as a function of increasing percentages of [D_6]DMSO added to the $CDCl_3$ solution (v/v) (concentration: 1 mM).

The results of this titration are in good agreement with the results obtained by FTIR spectroscopy. The NH protons of Boc-(L-Ala-L-Oxd)$_3$-OBn (**7**) are somehow sensitive to DMSO, which confirms the tendency of **7** to form a hydrogen bond driven secondary structure. However, this secondary structure cannot yet be well established in this short sequence. Unfortunately, it was impossible to perform the titration of longer oligomers **11** and **13** as a result of their low solubility in $CDCl_3$. Only in a mixture of $CDCl_3$ and [D_6]DMSO (minimum 5%), could ^{1}H NMR spectra be obtained, but with a very poor resolution. We could only record ^{1}H NMR spectra exhibiting complex signals that can be attributed to the NH hydrogens at 8.5–8.8 ppm. On addition of further portions of [D_6]DMSO, this complex pattern is shifted by less than 0.3 ppm downfield, which suggests that these signals belong to chelated hydrogens. For a better evaluation of the presence of N–H···O=C hydrogen bonds, we recorded some ^{1}H NMR spectra of **13** in [D_6]DMSO (3 mM solution) at different temperatures (Figure 4). In the solvent $CDCl_3$, small temperature coefficients of $\leq$ 3 ppb/K indicate the presence of hydrogen-bonded amide protons,[14] whereas protons that participate in an equilibrium between hydrogen-bonded and nonhydrogen-bonded states show larger temperature coefficients. In [D_6]-DMSO, the criterion for the temperature coefficients is a bit higher. Thus, the values for hydrogen-bonded amide protons are 4 ppb/K or smaller.[15]

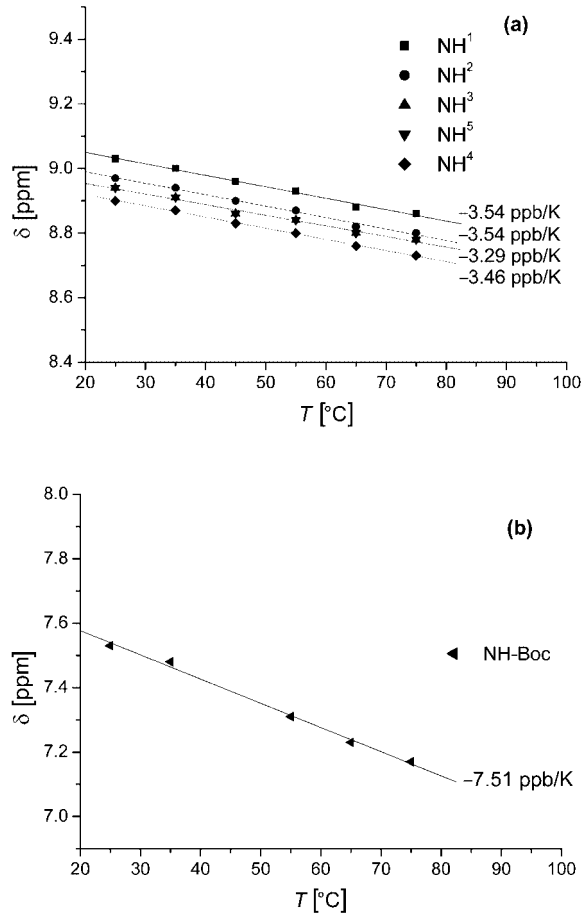


Figure 4. Variation of NH proton chemical shifts [ppm] of the five amide protons and the Boc-NH proton of **13** as a function of the temperature for 3 mM samples measured in [D_6]DMSO: (a) amide NH; (b) Boc-NH.

Whereas the five recorded amide protons have small temperature coefficients consistent with those for hydrogen-bonded NH protons, the Boc-NH has a larger temperature coefficient, which suggests that this proton is not involved in a hydrogen bond. This might be caused by its position at the beginning of the chain. Finally, NOESY experiments were recorded on the same solution of **13** to obtain more structural information. Figure 5a and Figure 5b show cross peaks between the NH amide hydrogens (8.50–9.00 ppm) and the NH carbamate hydrogen. Giving as assumption that the NH→NH cross peaks may be ascribed to $N_iH \rightarrow N_{i+1}H$ interaction, we could assign the chemical shift to the NH hydrogens. The presence of these cross peaks indicate the formation of a helix.[16] Furthermore, interesting NH→H_c, NH→H_d, and NH→Me cross peaks can be detected (Figure 5c and Figure 5d; for signal assignment Figure 6) but unfortunately these signals overlap.

Some support of the formation of an ordered secondary structure in the longer oligomers comes from the CD spectra of free acids **3**, **6**, **8**, **10**, **12**, and **14** in MeOH solution (Figure 7). Although this technique is intrinsically a low resolution method,[17] it can provide useful information on the presence of secondary structures.[18]

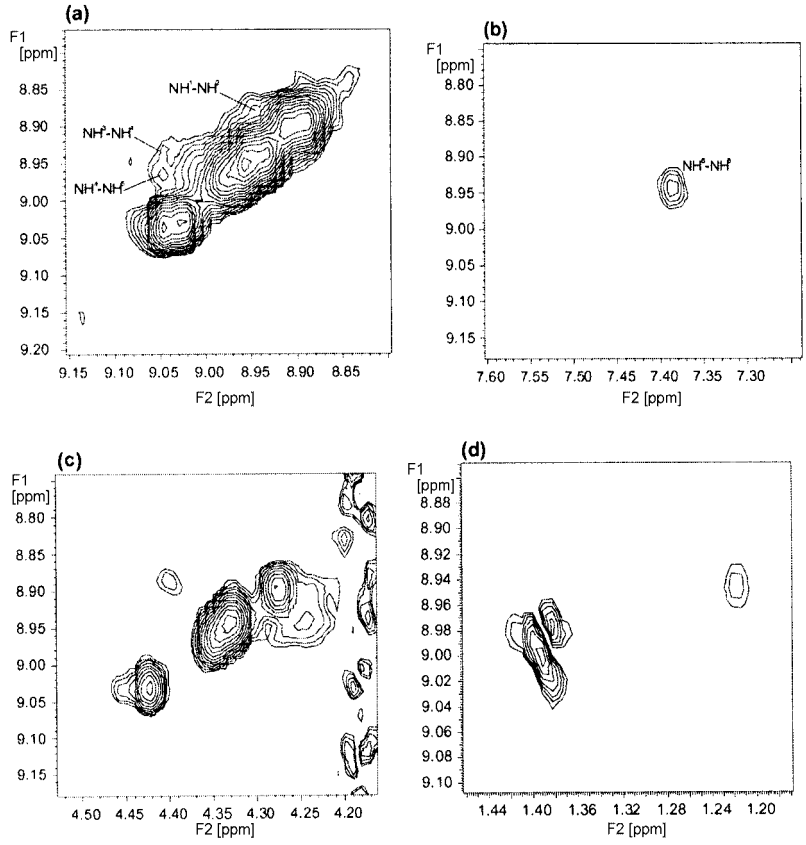


Figure 5. Significant NOE enhancements of **13** obtained by performing NOESY experiments on a 3 mM solution in [D_6]DMSO utilizing a mixing time of 0.400 s at 25 °C: (a) cross peaks between the NH→NH amide hydrogens (NH amide: 8.80–9.10 ppm); (b) cross peak between NH amide and NH carbamate hydrogen (NH carbamate: about 7.40 ppm); (c) NH→H_c and NH→H_d cross peaks (H_c and H_d: 4.20–4.50 ppm); (d) NH→Me cross peaks (Me: 1.20–1.45 ppm).

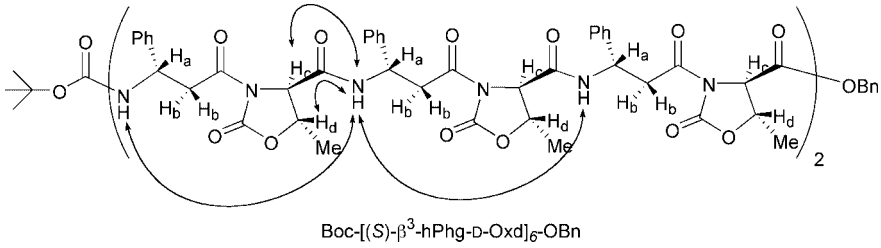


Figure 6. Results for the NOESY experiments on **13** shown in Figure 5.

Deeper inspection of the spectra shows a great difference between the normalized *per*-residue spectra of **3**, **12**, and **14**. The spectrum of **3** exhibits a minimum at 193 nm and a maximum at 202 nm. The minimum slowly moves towards 196 nm in the longer oligomers with increasing intensity. The maximum at 202 nm gradually disappears and is replaced by a shoulder at 202–206 nm. The CD spectrum of **14** is even different with a minimum at 197 nm having a much lower intensity and a new maximum at 220 nm. This variation suggests the formation of an ordered structure, although the CD spectra are not able to determine the actual nature of this structure. Recently, CD spectra of α,β-hybrid peptides were reported,[3b,3h,3i] but a clear correlation between structured helices and CD spectra, as it is known for native helices, could not be established.[19]

To get more insight into the nature of the hydrogen-bonded secondary structure indicated by the experimental investigations, quantum chemical calculations were performed on oligomers **7** and **13** by employing ab initio MO theory at the HF/6-31G* level (for computational details, see Experimental Section). This approximation level was successfully used in the prediction of the conformation of peptide foldamers in numerous cases.[4a–4c,4f–4h,20] Thus, it was possible to predict all helix types that can be expected in oligomers of regular α,β-hybrid peptides.[4h] A look at this catalogue of basic helices shows that several of them can a priori be excluded in our case as a result of the torsion angle ϕ of the α-amino acid constituent D-Oxd kept fixed at values of about 60°. Thus, only three helix types have to be taken into consideration. Two helices are with backward

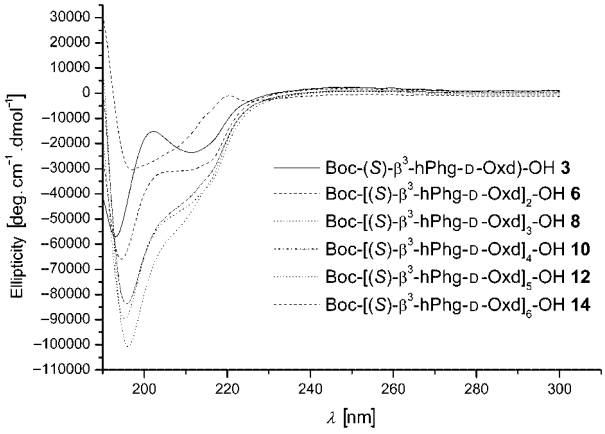


Figure 7. Normalized *per*-residue CD spectra of **3**, **6**, **8**, **10**, **12**, and **14** (1 mM concentration in MeOH solution).

directions of the hydrogen bonds along the sequence. In the one, H_{11}, 11-membered hydrogen-bonded cycles are formed, in the other, $H_{14/15}$, 14- and 15-membered hydrogen-bonded rings alternate, but keep their backward hydrogen bond directions. The third helix type, $H_{11/9}$, is a β- or mixed helix with the hydrogen bond directions alternating in the forward and backward directions to form 11- and 9-membered hydrogen-bonded pseudocycles. These three helix types of alternate α,β-hybrid peptides that were predicted by theory and also experimentally confirmed,[3] served as starting points for calculations on trimers (n = 3) and hexamers (n = 6) of our oligomers (Figure 1). In comparison to α,β-hybrid peptides consisting of ordinary α- and β-amino acids, our oligomers are only able to form every second hydrogen bond because of the oxazolidin-2-one constituent, that is, only every second 11-membered ring appears in H_{11}, and the 15-membered rings in $H_{14/15}$ and the 11-membered rings in $H_{11/9}$ are missing. Thus, the helices of our oligomers should be less stable than those in the ordinary α,β-hybrid peptides for a given sequence length. This could also be the reason for the experimentally found increasing tendency of secondary structure formation in the longer sequences. According to the calculations, a left-handed helix H_{11} is most stable. The structure is a bit distorted in the trimer, but rather perfect in the hexamer (Figure 8). The helix $H_{14/(15)}$ cannot be kept because of steric effects caused by the oxazolidin-2-one ring. Optimization of the $H_{14/(15)}$ starting structure tends to the formation of 11-membered hydrogen-bonded pseudocycles. A left-handed mixed helix $H_{(11)/9}$ with in fact only nine-membered hydrogen-bonded rings is principally possible (Figure 8). However, the hexamer $H_{(11)/9}$ is by 7.6 kcal mol^{-1} less stable than the H_{11} hexamer. Apart from a correct overall shape, the hydrogen bond lengths are too long. The energy difference between both helix types is reduced to 2.9 kcal mol^{-1} in an aqueous environment as shown by the estimation of the solvation energy on the basis of a polarizable continuum model (total energies of both helices are given in the Supporting Information; pdb files are available from the authors on request).

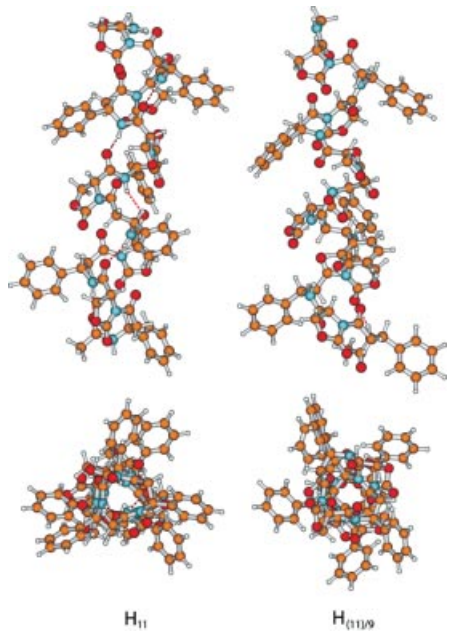


Figure 8. Most stable helix types H_{11} and $H_{(11)/9}$ in hexamers of Ac-[(*S*)-β^3-hPhg-D-Oxd]$_6$-NHCH$_3$ at the HF/6-31G* level of ab initio MO theory.

Conclusions

In this paper, we reported the synthesis and conformational analysis of a novel class of foldamers containing alternating (*S*)-β^3-homophenylglycine [(*S*)-β^3-hPhg] and D-4-carboxyoxazolidin-2-one (D-Oxd) residues. These pseudopeptides were synthesized in the liquid phase utilizing uronium salts (HATU or HBTU) as coupling agents. The experimental conformation analysis performed in solution by IR, ^{1}H NMR, and CD spectroscopy unambiguously proved that these oligomers fold into ordered structures with increasing sequence length. Theoretical calculations performed by employing ab initio MO theory suggest a helix with 11-membered hydrogen-bonded rings as the preferred secondary structure type. A left-handed mixed helix $H_{(11)/9}$ was also obtained as a conformer, but it is less stable than the H_{11} hexamer and the hydrogen bond lengths are too long, owing to steric effects caused by the oxazolidin-2-one rings. The novel structures enrich the field of peptidic foldamers and might be useful in the mimicry of native peptides.

Experimental Section

General: Routine NMR spectra were recorded with spectrometers at 400, 300, and 200 MHz (^{1}H NMR) and at 100, 75, and 50 MHz (^{13}C NMR). Chemical shifts are reported in δ values relative to the solvent peak of $CHCl_3$ set at δ = 7.27 ppm. High quality ^{1}H NMR spectra were recorded with a Varian Inova 600. The measurements were carried out in $CDCl_3$ and in [D_6]DMSO by using tetramethylsilane as an internal standard. Proton signals were assigned by COSY spectra. Data for conformational analysis were obtained from 2D NOESY spectra with typical mixing times of 0.4 s. High quality infrared spectra (64 scans) were obtained at 2 cm^{-1} resolution by using a 1 mm NaCl solution cell and a Nicolet 380 FT-IR

spectrometer. All spectra were obtained for 3 mM solutions in dry CH_2Cl_2 at 297 K. All compounds were dried in vacuo. Sample preparation was performed under a nitrogen atmosphere. The melting points of the compounds were determined in open capillaries. They are uncorrected. The CD spectra were obtained by employing a Jasco J-810 spectropolarimeter. Cylindrical fused quartz cells of 0.02 cm path length were used. The values are expressed in terms of the molar ellipticity $[\theta]_T$ deg cm^2 dmol^{-1}.

Boc-(*S*)-β^3-hPhg-D-Oxd-OBn (2): To a stirred solution of Boc-(*S*)-β^3-hPhg-OH (1.11 g, 4.2 mmol) in acetonitrile (150 mL) was added HBTU (1.59 g, 4.2 mmol) followed by D-Oxd-OBn (**1**, 1.0 g, 4.2 mmol) and finally DBU (1.25 mL, 8.4 mol). The mixture was stirred for 45 min, and acetonitrile was then removed under reduced pressure. The residue was dissolved in ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and 5% aqueous $NaHCO_3$ (1 × 30 mL), and the solution was then dried with sodium sulfate and concentrated in vacuo. Pure product **2** was obtained in 95% yield (0.89 g) as a white solid after silica gel chromatography (cyclohexane/ethyl acetate, 8:2). M.p. 132 °C. $[\alpha]_D$ = +12.5 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*Bu), 1.53 (d, *J* = 6.3 Hz, 3 H, Me), 3.11–3.28 (m, 1 H, C*H*H-CHPh), 3.61–3.84 (m, 1 H, CH*H*-CHPh), 4.42 (d, *J* = 4.2 Hz, 1 H, CHN), 4.55 (dq, *J* = 4.2, 6.3 Hz, 1 H, CHO), 5.19 (AB, *J* = 12.3 Hz, 2 H, OCH_2Ph), 5.30 (br. s, 2 H, NH + CH_2-C*H*Ph), 7.31–7.38 (m, 10 H, 2 × Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 28.3, 42.5, 51.1, 61.8, 67.8, 73.4, 79.7, 126.2, 127.6, 128.2, 128.7, 134.6, 140.9, 152.1, 155.1, 167.8, 170.3 ppm. IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3439, 1791, 1752, 1706 cm^{-1}. $C_{26}H_{30}N_2O_7$ (482.53): calcd. C 64.72, H 6.27, N 5.81; found C 64.69, H 6.30, N 5.86.

Boc-(*S*)-β^3-hPhg-D-Oxd-OH (3): To a solution of Boc-(*S*)-β^3-hPhg-D-Oxd-OBn **2** (2.86 mmol, 1.37 g) in methanol (185 mL), was added 10% palladium on charcoal (86 mg). The mixture was stirred under a hydrogen atmosphere for 24 h. The catalyst was then filtered through a celite pad, and the mixture was concentrated. Corresponding acid **3** was obtained pure in quantitative yield (1.10 g) without any further purification. M.p. 115 °C. $[\alpha]_D$ = +63.0 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.45 (s, 9 H, *t*Bu), 1.53 (d, *J* = 6.0 Hz, 3 H, Me), 3.12 (dd, *J* = 9.9, 14.1 Hz, 1 H, C*H*H-CHPh), 3.67 (dd, *J* = 3.0, 14.1 Hz, 1 H, CH*H*-CHPh), 4.42 (d, *J* = 3.9 Hz, 1 H, CHN), 4.71 (dq, *J* = 3.9, 6.0 Hz, 1 H, CHO), 5.16–5.32 (m, 1 H, CH_2-C*H*Ph), 7.31–7.42 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 21.3, 28.8, 43.9, 52.4, 63.1, 75.6, 80.4, 127.5, 128.4, 129.6, 143.2, 154.2, 157.7, 171.6 ppm. IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3435, 1790, 1750, 1710 cm^{-1}. $C_{19}H_{24}N_2O_7$ (392.16): calcd. C 58.16, H 6.16, N 7.14; found C 58.20, H 6.12, N 7.16.

TFAH-(*S*)-β^3-hPhg-D-Oxd-OBn (4): A solution of Boc-L-Ala-L-Oxd-OBn (**2a**, 1 mmol, 0.48 g) and TFA (18 mmol, 1.38 mL) in dry dichloromethane (10 mL) was stirred for 2 h at room temperature. The volatiles were then removed under reduced pressure, and the product was obtained pure in quantitative yield (0.49 g) without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 6.0 Hz, 3 H, Me), 3.72 (dd, *J* = 3.9, 18.6 Hz, 1 H, C*H*H-CHPh), 3.87 (d, *J* = 8.1, 18.6 Hz, 1 H, CH*H*-CHPh), 4.43 (br. s, 3 H, NH), 4.52–4.60 (m, 2 H, CHN + CHO), 4.77 (dd, *J* = 3.9, 8.1 Hz, 1 H, CH_2-C*H*Ph), 5.19 (AB, *J* = 12.0 Hz, 2 H, OCH_2Ph), 7.31–7.38 (m, 10 H, 2 × Ph) ppm.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_2$-OBn (5): To a stirred solution of Boc-(*S*)-β^3-hPhg-D-Oxd-OH (**3**) (1 mmol, 0.39 g) and HATU (1 mmol, 0.38 g) in dry acetonitrile (35 mL) under an inert atmosphere was added a mixture of H-L-Ala-L-Oxd-OBn·CF_3CO_2H (**4**, 1 mmol, 0.50 g) and Et_3N (3 mmol, 0.44 mL) in dry acetonitrile (35 mL) at room temperature. The solution was stirred for 40 min under an inert atmosphere. Acetonitrile was then removed under reduced pressure and replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and 5% aqueous $NaHCO_3$ (1 × 30 mL), and the solution was dried with sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate, 8:2) in 73% yield (0.55 g). M.p. 157 °C. $[\alpha]_D$ = –11.0 (*c* = 1.0, CH_3CN). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, *t*Bu), 1.46 (d, *J* = 5.1 Hz, 3 H, Me), 1.54 (d, *J* = 6.0 Hz, 3 H, Me), 3.21 (dd, *J* = 7.8, 13.8 Hz, 1 H, C*H*H-CHPh), 3.36 (dd, *J* = 9.9, 15.0 Hz, 1 H, C*H*H-CHPh), 3.53–3.64 (m, 2 H, 2 × CH*H*-CHPh), 4.27 (d, *J* = 4.2 Hz, 1 H, CHN), 4.50–4.56 (m, 2 H, CHN + CHO), 4.71 (dq, *J* = 4.5, 6.0 Hz, 1 H, CHO), 5.20 (br. s, 4 H, OCH_2Ph + NH + CH_2-C*H*Ph), 5.50–5.59 (m, 1 H, CH_2-C*H*Ph), 7.21–7.40 (m, 16 H, NH + 3 × Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 21.0, 28.3, 29.5, 38.6, 41.3, 42.7, 50.0, 51.5, 61.6, 62.1, 67.9, 73.6, 74.1, 126.2, 127.6, 127.8, 128.2, 128.7, 128.8, 134.6, 139.6, 141.0, 152.2, 152.5, 155.2, 167.1, 167.9, 170.3, 171.1 ppm. IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3430, 3412, 1788, 1754, 1725, 1707 cm^{-1}. $C_{40}H_{44}N_4O_{11}$ (756.80): calcd. C 63.48, H 5.86, N 7.40; found C 63.47, H 5.78, N 7.38.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_2$-OH (6): For the synthetic procedure from **5**, see the preparation of Boc-(*S*)-β^3-hPhg-D-Oxd-OH (**3**) given above. M.p. 75 °C. $[\alpha]_D$ = –11.7 (*c* = 1.0, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.42 (s, 9 H, *t*Bu), 1.51 (d, *J* = 6.0 Hz, 3 H, Me), 1.56 (d, *J* = 6.3 Hz, 3 H, Me), 3.05 (dd, *J* = 9.0, 14.4 Hz, 1 H, C*H*H-CHPh), 3.35 (dd, *J* = 11.1, 16.2 Hz, 1 H, CH*H*-CHPh), 3.56–3.66 (m, 2 H, 2 × CH*H*-CHPh), 4.43 (d, *J* = 3.9 Hz, 1 H, CHN), 4.53 (d, *J* = 3.9 Hz, 1 H, CHN), 4.59 (dq, *J* = 3.9, 6.3 Hz, 1 H, CHO), 4.69 (dq, *J* = 3.9, 6.0 Hz, 1 H, CHO), 5.18–5.22 (m, 1 H, CH_2-C*H*Ph), 5.57 (dd, *J* = 3.0, 11.1 Hz, 1 H, CH_2-C*H*Ph), 7.28–7.45 (m, 10 H, 2 × Ph) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 20.9, 21.3, 28.8, 30.5, 38.9, 43.0, 43.9, 48.2, 52.3, 63.2, 64.0, 75.7, 76.2, 80.2, 127.4, 128.3, 128.6, 129.7, 141.8, 143.4, 154.2, 154.4, 157.6, 170.2, 171.5, 181.5 ppm. IR (nujol): $\tilde{\nu}$ = 3313, 1780, 1706 cm^{-1}. $C_{33}H_{38}N_4O_{11}$ (666.68): calcd. C 59.45, H 5.75, N 8.40; found C 59.39, H 5.73, N 8.42.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_3$-OBn (7): For the synthetic procedure from **6** and **4**, see the preparation of Boc-[(*S*)-β^3-hPhg-D-Oxd]$_2$-OBn (**5**) given above. The product was obtained pure after silica gel chromatography (dichloromethane/ethyl acetate, 8:2) in 81% yield. M.p. 220 °C. $[\alpha]_D$ = –3.0 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, *t*Bu), 1.42 (d, *J* = 6.0 Hz, 3 H, Me), 1.50 (d, *J* = 6.0 Hz, 3 H, Me), 1.54 (d, *J* = 6.0 Hz, 3 H, Me), 3.15–3.67 (m, 6 H, 3 × CH_2-CHPh), 4.22 (br. s, 1 H, CHN), 4.37–4.72 (m, 5 H, 2 × CHN + 3 × CHO), 5.07 (br. s, 1 H, NH), 5.15–5.23 (m, 3 H, OCH_2Ph + CH_2-C*H*Ph), 5.45–5.50 (m, 1 H, CH_2-C*H*Ph), 5.50–5.60 (m, 1 H, CH_2-C*H*Ph), 6.94 (br. s, 1 H, NH), 7.17 (br. s, 1 H, NH), 7.25–7.39 (m, 20 H, 4 × Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 21.3, 28.5, 41.5, 42.8, 50.1, 50.7, 51.9, 62.0, 63.3, 68.2, 73.9, 74.8, 126.5, 128.1, 128.5, 129.0, 129.1, 134.8, 139.9, 152.5, 153.0, 155.6, 167.3, 168.1, 170.4, 171.6 ppm. IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3416, 3344, 1788, 1700 cm^{-1}. $C_{54}H_{58}N_6O_{15}$ (1031.07): calcd. C 62.90, H 5.67, N 8.15; found C 62.94, H 5.73, N 8.09.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_3$-OH (8): For the synthetic procedure from **7**, see the preparation of Boc-(*S*)-β^3-hPhg-D-Oxd-OH (**3**) given above. M.p. 177 °C. $[\alpha]_D$ = –27.0 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3CN): δ = 1.27 (d, *J* = 5.2 Hz, 3 H, Me), 1.32 (s, 9 H, *t*Bu), 1.43–1.48 (m, 6 H, 2 × Me), 2.80–3.18 (m, 2 H, CH_2-CHPh), 3.28–3.45 (m, 6 H, 3 × CH_2-CHPh), 4.16 (br. s, 1 H, CHN), 4.26–4.32 (m, 2 H, CHN + CHO), 4.37–4.0 (m, 1 H, CHN),

4.46–4.51 (m, 1 H, CHO), 4.62–4.68 (m, 1 H, CHO), 5.02 (br. s, 1 H, CH_2-C*H*Ph), 5.31–5.46 (m, 2 H, 2×CH_2-C*H*Ph), 5.85 (br. s, 1 H, NH), 7.24–7.37 (m, 15 H, 3×Ph), 7.42–7.50 (m, 2 H, NH) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 19.9, 20.0, 20.4, 27.8, 41.7, 41.9, 42.3, 49.4, 49.5, 51.1, 61.5, 62.7, 62.9, 74.1, 74.8, 75.0, 126.4, 126.5, 127.5, 127.8, 127.9, 128.7, 128.9, 129.0, 141.1, 141.3, 142.6, 152.7, 153.1, 153.2, 155.4, 167.6, 167.7, 169.4, 170.0, 170.2, 170.3 ppm. IR (nujol): ṽ = 3343, 1782, 1764, 1676 cm^{-1}. $C_{47}H_{52}N_6O_{15}$ (940.95): calcd. C 59.99, H 5.57, N 8.93; found C 59.95, H 5.60, N 8.90.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_4$-OBn (9): For the synthetic procedure from **8** and **4**, see the preparation of Boc-[(*S*)-β^3-hPhg-D-Oxd]$_2$-OBn (**5**) given above. The product was obtained pure after silica gel chromatography (dichloromethane/ethyl acetate, 8:2) in 80% yield. M.p. 237 °C (dec.). $[\alpha]_D$ = –26.5 (*c* = 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 1.33 (d, *J* = 7.2 Hz, 3 H, Me), 1.34 (s, 9 H, *t*Bu), 1.37 (d, *J* = 6.0 Hz, 3 H, Me), 1.51 (d, *J* = 6.0 Hz, 3 H, Me), 1.55 (d, *J* = 6.0 Hz, 3 H, Me), 2.82–2.93 (m, 1 H, C*H*H-CHPh), 2.93–3.50 (m, 1 H, CH*H*-CHPh), 3.16 (dd, *J* = 10.8, 18.4 Hz, 1 H, C*H*H-CHPh), 3.20 (dd, *J* = 11.2, 18.8 Hz, 1 H, C*H*H-CHPh), 3.28 (dd, *J* = 10.4, 15.2 Hz, 1 H, C*H*H-CHPh), 3.56–3.68 (m, 3 H, 3×CH*H*-CHPh), 4.40 (d, *J* = 3.6 Hz, 1 H, CHN), 4.43–4.47 (m, 3 H, CHN + 2×CHO), 4.52 (d, *J* = 4.4 Hz, CHN 1 H), 4.60–4.63 (m, 2 H, CHN + CHO), 4.78 (dq, *J* = 4.0, 6.4 Hz, 1 H, CHO), 5.23 (br. s, 1 H, CH_2-C*H*Ph), 5.27 (AB, *J* = 12.4 Hz, 2 H, OCH_2Ph), 5.51–5.67 (m, 3 H, 3×CH_2-C*H*Ph), 6.54 (d, *J* = 6.8 Hz, 1 H, NH), 7.21–7.48 (m, 25 H, 5×Ph), 8.09 (d, *J* = 8.8 Hz, 1 H, NH), 8.22 (d, *J* = 8.8 Hz, 1 H, NH), 8.26 (d, *J* = 8.8 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 19.2, 19.5, 27.0, 37.1, 37.3, 41.2, 48.3, 60.8, 62.1, 66.6, 72.9, 74.0, 125.5, 125.6, 125.7, 126.3, 126.6, 126.7, 126.8, 127.3, 127.6, 127.8, 127.9, 151.5, 162.7, 166.8, 166.9, 167.4, 169.1 ppm. IR (CH_2Cl_2, 0.6 mM): ṽ = 3414, 3306, 1789, 1700 cm^{-1}. $C_{68}H_{72}N_8O_{19}$ (1305.34): calcd. C 62.57, H 5.56, N 8.58; found C 62.53, H 5.58, N 8.53.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_4$-OH (10): For the synthetic procedure from **9**, see the preparation of Boc-(*S*)-β^3-hPhg-D-Oxd-OH (**3**) given above. M.p. 250 °C (dec.). $[\alpha]_D$ = –34.1 (*c* = 0.2, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.23 (d, *J* = 5.2 Hz, 3 H, Me), 1.30 (d, *J* = 6.4 Hz, 3 H, Me), 1.41 (s, 9 H, *t*Bu), 1.65 (d, *J* = 6.0 Hz, 6 H, 2×Me), 3.00–3.14 (m, 1 H, C*H*H-CHPh), 3.32–3.75 (m, 7 H, CH*H*-CHPh + 3×CH_2-CHPh), 4.24–4.38 (m, 3 H, CHN + 2×CHO), 4.45 (d, *J* = 5.2 Hz, 1 H, CHN), 4.56 (d, *J* = 4.8 Hz, 1 H, CHN), 4.66–4.71 (m, 1 H, CHO), 4.78–4.83 (m, 1 H, CHO), 5.23 (br. s, 1 H, CH_2-C*H*Ph), 5.51–5.59 (m, 3 H, 3×CH_2-C*H*Ph), 7.73–7.97 (m, 20 H, 4×Ph), 7.42–7.50 (m, 2 H, NH) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 19.9, 20.0, 20.4, 27.8, 41.7, 41.9, 42.3, 49.4, 49.5, 51.1, 61.5, 62.7, 62.9, 74.1, 74.8, 75.0, 126.4, 126.5, 127.5, 127.8, 127.9, 128.7, 128.9, 129.0, 141.1, 141.3, 142.6, 152.7, 153.1, 153.2, 155.4, 167.6, 167.7, 169.4, 170.0, 170.2, 170.3 ppm. IR (nujol): ṽ = 3314, 1780, 1701, 1664 cm^{-1}. $C_{61}H_{66}N_8O_{19}$ (1215.22): calcd. C 60.29, H 5.47, N 9.22; found C 60.32, H 5.43, N 9.20.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_5$-OBn (11): For the synthetic procedure from **10** and **4**, see the preparation of Boc-[(*S*)-β^3-hPhg-D-Oxd]$_2$-OBn (**5**) above. The product was obtained pure after silica gel chromatography (toluene/acetonitrile, 6:4) in 70% yield. M.p. 260 °C (dec.). $[\alpha]_D$ = –45.0 (*c* = 0.6, CH_2Cl_2). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 1.31–1.38 (m, 18 H, 3×Me + *t*Bu), 1.51 (d, *J* = 6.0 Hz, 3 H, Me), 1.55 (d, *J* = 6.4 Hz, 3 H, Me), 2.81–3.08 (m, 2 H, CH_2-CHPh), 3.11–3.29 (m, 4 H, 4×CH*H*-CHPh), 3.54–3.69 (m, 4 H, 4×CH*H*-CHPh), 4.40–4.46 (m, 6 H, 3×CHN + 3×CHO), 4.52–4.61 (m, 3 H, 2×CHN + CHO), 4.79 (dq, *J* = 4.4, 6.0 Hz, 1 H, CHO), 5.22 (br. s, 1 H, CH_2-C*H*Ph), 5.27 (AB, *J* = 12.8 Hz, 2 H, OCH_2Ph), 5.48–5.66 (m, 4 H, 4×CH_2-C*H*Ph), 6.79 (d, *J* = 6.0 Hz, 1 H, NH), 7.20–7.49 (m, 30 H, 6×Ph), 8.49 (d, *J* = 8.8 Hz, 1 H, NH), 8.62 (d, *J* = 8.8 Hz, 1 H, NH), 8.70 (d, *J* = 8.8 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 17.7, 17.8, 17.9, 25.5, 39.8, 40.0, 46.6, 59.2, 60.1, 60.2, 60.3, 65.0, 71.2, 72.5, 124.0, 124.1, 124.6, 124.8, 125.0, 125.1, 125.7, 125.9, 126.0, 126.1, 126.2, 133.2, 138.8, 139.1, 149.9, 150.6, 165.2, 165.3, 167.3, 167.4, 167.6 ppm. IR (CH_2Cl_2, 0.2 mM): ṽ = 3306, 1779, 1712, 1665 cm^{-1}. $C_{82}H_{86}N_{10}O_{23}$ (1579.61): calcd. C 62.35, H 5.49, N 8.87; found C 62.30, H 5.47, N 8.85.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_5$-OH (12): For the synthetic procedure from **11**, see the preparation of Boc-(*S*)-β^3-hPhg-D-Oxd-OH (**3**) above. M.p. 274 °C (dec.). $[\alpha]_D$ = –39.0 (*c* = 0.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.23 (d, *J* = 5.2 Hz, 3 H, Me), 1.30 (d, *J* = 6.4 Hz, 3 H, Me), 1.41 (s, 9 H, *t*Bu), 1.65 (d, *J* = 6.0 Hz, 6 H, 2×Me), 3.00–3.14 (m, 1 H, C*H*H-CHPh), 3.32–3.75 (m, 7 H, CH*H*-CHPh + 3×CH_2-CHPh), 4.24–4.38 (m, 3 H, CHN + 2×CHO), 4.45 (d, *J* = 5.2 Hz, 1 H, CHN), 4.56 (d, *J* = 4.8 Hz, 1 H, CHN), 4.66–4.71 (m, 1 H, CHO), 4.78–4.83 (m, 1 H, CHO), 5.23 (br. s, 1 H, CH_2-C*H*Ph), 5.51–5.59 (m, 3 H, 3×CH_2-C*H*Ph), 7.73–7.97 (m, 20 H, 4×Ph), 7.42–7.50 (m, 2 H, NH) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 19.5, 23.0, 23.5, 25.8, 27.6, 63.2, 70.1, 75.0, 126.1, 128.7, 139.8, 149.7, 155.4, 166.3, 170.3 ppm. IR (nujol): ṽ = 3314, 1780, 1701, 1664 cm^{-1}. $C_{75}H_{80}N_{10}O_{23}$ (1489.49): calcd. C 60.44, H 5.40, N 9.42; found C 60.41, H 5.38, N 9.37.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_6$-OBn (13): For the synthetic procedure from (**12**) and (**4**), see the preparation of Boc-[(*S*)-β^3-hPhg-D-Oxd]$_2$-OBn (**5**) above. The product was obtained pure after crystallization from methanol/diethyl ether in 65% yield. M.p. 265 °C (dec.). $[\alpha]_D$ = –133.0 (*c* = 0.1, acetone). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.15 (d, *J* = 6.0 Hz, 3 H, Me), 1.21 (d, *J* = 6.4 Hz, 6 H, 2×Me), 1.25 (d, *J* = 6.0 Hz, 3 H, Me), 1.37 (s, 9 H, *t*Bu), 1.44 (d, *J* = 6.4 Hz, 3 H, Me), 1.48 (d, *J* = 6.4 Hz, 3 H, Me), 3.08–3.22 (m, 6 H, 6×CH*H*-CHPh), 3.32–3.52 (m, 6 H, 6×CH*H*-CHPh), 3.96–4.14 (m, 8 H, 4×CHN + 4×CHO), 4.15–4.26 (m, 2 H, CHN + CHO), 4.39 (d, *J* = 4.4 Hz, 1 H, CHN), 4.62 (dq, *J* = 4.4, 6.4 Hz, 1 H, CHO), 4.76–4.85 (m, 1 H, CH_2-C*H*Ph), 5.00 (AB, *J* = 12.8 Hz, 2 H, OCH_2Ph), 5.08–5.24 (m, 5 H, 5×CH_2-C*H*Ph), 7.21–7.40 (m, 35 H, 7×Ph), 7.53 (br. s, 1 H, NH), 8.90 (d, *J* = 8.4 Hz, 1 H, NH), 8.94 (d, *J* = 8.4 Hz, 2 H, 2×NH), 8.97 (d, *J* = 8.4 Hz, 1 H, NH), 9.03 (d, *J* = 8.4 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 (multiple signals), 28.9, 42.7 (multiple signals), 49.0 (multiple signals), 51.9, 62.7 (multiple signals), 75.3, 126.9 (multiple signals), 129.2 (multiple signals), 142.0 (multiple signals), 153.4 (multiple signals), 167.7 (multiple signals), 170.1 (multiple signals) ppm. IR (CH_2Cl_2, 0.2 mM): ṽ = 3405, 3289, 1709, 1670 cm^{-1}. $C_{96}H_{100}N_{12}O_{27}$ (1853.88): calcd. C 62.20, H 5.44, N 9.07; found C 62.25, H 5.38, N 9.09.

Boc-[(*S*)-β^3-hPhg-D-Oxd]$_6$-OH (14): For the synthetic procedure from **13**, see the preparation of Boc-(*S*)-β^3-hPhg-D-Oxd-OH (**3**) above. M.p. 260 °C (dec.). $[\alpha]_D$ = +83.3 (*c* = 0.1, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.29–1.55 (m, 27 H, 6×Me + *t*Bu), 3.20–3.63 (m, 12 H, 6×CH_2-CHPh), 4.16–4.39 (m, 8 H, 4×CHN + 4×CHO), 4.44–4.50 (m, 3 H, 2×CHN + CHO), 4.76–4.82 (m, 1 H, CHO), 5.04–5.20 (m, 1 H, CH_2-C*H*Ph), 4.56–4.71 (m, 3 H, 5×CH_2-C*H*Ph), 5.41–5.58 (m, 3 H, 5×CH_2-C*H*Ph), 7.21–7.49 (m, 30 H, 6×Ph) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 (multiple signals), 29.0, 42.7 (multiple signals), 49.0 (multiple signals), 62.7 (multiple signals), 75.3, 126.9 (multiple signals), 127.9 (multiple signals), 129.1, 142.0 (multiple signals), 153.4 (multiple signals), 167.7 (multiple signals), 170.1 (multiple signals) ppm. IR

(nujol): $\tilde{\nu}$ = 3292, 1778, 1706, 1666 cm^{-1}. $C_{89}H_{94}N_{12}O_{27}$ (1763.76): calcd. C 60.61, H 5.37, N 9.53; found C 60.64, H 5.38, N 9.52.

Theoretical Calculations: Starting point for the calculations on trimers and hexamers of Boc-[(*S*)-β^3-hPhg-D-Oxd]$_n$-OH were conformations of the selected helix types with the ideal backbone torsion angles of α,β-hybrid peptide helices found in ref.[4h] The N-terminal Boc group was replaced by an acetyl group. The C-terminus was an *N*-methylamide group. The methyl substituents of the D-Oxd constituents were omitted in the calculations. The geometry of all starting conformations was completely optimized at the HF/6-31G* level of ab initio MO theory. The solvation influence was estimated for an aqueous environment on the basis of the IEF-PCM formalism in the Gaussian03 program package, which was employed for all calculations (see Supporting Information).

Supporting Information (see footnote on the first page of this article): Total energies of the various helix types and ^{1}H NMR and NOESY spectra for Boc-[(*S*)-β^3-hPhg-D-Oxd]$_6$-OBn.

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