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De novo design of non-hydrogen-bonded helical pseudopeptides composed of oxanipecotic acid oligomers†

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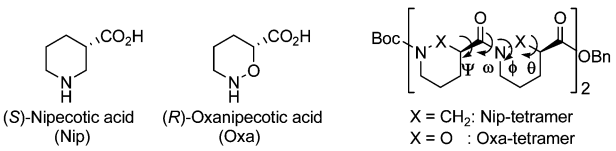
***Ab initio* calculation and circular dichroism experiments reveal that Oxa-oligomers adopted pronounced non-hydrogen-bonded helical structures.**

Helical (pseudo)peptides and synthetic polymers have been designed and characterized for understanding the molecular basis of helical conformations as well as for potential applications as new materials.[1] Recently, Gellman and coworkers suggested that nipecotic acid oligomers (Nip-oligomers) adopted non-hydrogen-bonded helical structures such as the polyproline II (PPII) helix.[2] Realizing that the helicity of Nip-oligomers may result from the constrained θ and ϕ dihedral angles in nipecotic acid, it was reasoned that if we control the four torsional angles (θ, ϕ, ω and ψ) of the backbones, we could construct pseudopeptides adopting non-hydrogen-bonded helical structures with more pronounced helicity. In this respect, Nip-oligomers are not fully optimized helical pseudopeptides, evidenced by equal distribution of *cis*- and *trans*-conformations of the amide bond (ω) due to the symmetric chemical environment adjacent to the nitrogen atom in the piperidine ring.[3] It was postulated that if nipecotic acid analogues with asymmetric chemical environments in the ring were employed to construct non-hydrogen-bonded helical pseudopeptides, their helicity could be greatly enhanced by biased conformation of the amide bond (ω) and the C_α–C_{sp^2} bond (ψ).



Oxanipecotic acid, the α-aminooxy acid analogue of nipecotic acid, possesses CH_2 and oxygen adjacent to the nitrogen atom in the ring.[4] Its asymmetric chemical environment around the nitrogen atom would be advantageous in forming helical conformations of oxanipecotic acid oligomers (Oxa-oligomers).

To prove our assumption and design novel pseudopeptides with great helicity, we characterized *a priori* energy landscapes of dimethylated (*S*)-Nip- and (*R*)-Oxa-tetramers (MeO_2C–Nip_4–OMe and MeO_2C–Oxa_4–OMe, respectively) by mapping potential energy surfaces (PES) along the θ, ϕ, ω and ψ angles at the B3LYP/6-31G(*d*) level using GAUSSIAN 98.[5] Owing to the geometric constraints of piperidine and tetrahydro-1,2-oxazine in nipecotic acid and oxanipecotic acid, respectively, one low energy conformer along θ and ϕ with di-equatorial conformations was optimized (θ = 173°, ϕ = −140° for Oxa and θ = −179°, ϕ = −123° for Nip).[6] For the dihedral angle of the amide bond (ω), Ac–Nip–OMe exhibited similar stabilities of *cis* and *trans* conformations, whereas Ac–Oxa–OMe adopted a more stable *cis* conformation than *trans* conformation by ΔG^{298} = ~5.7 kcal mol^{-1}.[7,8] This suggested that Oxa-oligomers formed exclusively *cis* conformation.

From the fully relaxed PES along ψ for simplified (*S*)-Nip- and (*R*)-Oxa-dimers, we found three stable conformations (L1, L2, R1) for each dimer (Fig. 1).[8] The Nip-dimer showed similar stabilities of L1 and L2 but R1 was 5.9 kcal mol^{-1} higher in energy than L1 and L2 due to the repulsive interaction of βCH_2 groups between adjacent rings. For the Oxa-dimer, L2 and R1 had similar energies whereas L1 was ~1 kcal mol^{-1} higher in energy than L2 and R1 due to the electrostatic repulsion between the carbonyl group and the oxygen atom.

Given that Nip-/Oxa-tetramers contain three ψ dihedral angles, combinations of L1, L2 and R1 produce 27 possible conformers for each tetramer. The mixed combinations of left-handed (L1 and L2) and right-handed (R1) conformations leading to sterically hindered structures were predicted to have higher energies and were disregarded in this work. Therefore, we focused on nine conformers composed of either left-handed (L1, L2) or right-handed (R1) conformations.

Fig. 2 shows three representative conformations for (*S*)-Nip- and (*R*)-Oxa-tetramers (L2–L2–L2, L1–L1–L1, R1–R1–R1) fully optimized from their predetermined θ, ϕ, ω and ψ initial angles to form helical structures.[8] Both tetramers with R1–R1–R1 conformation displayed high energies owing to unfavorable folded structures. For the Oxa-tetramer, the L2–L2–L2 conformer with highly helical structure (radius of ~2.3 Å, axial translation of ~5.2 Å, ~2.7 residues per turn) was lowest in energy, and substitution of L2 for L1 resulted in an increase of energy by 1–2 kcal mol^{-1}. In contrast, the Nip-tetramer displayed eight conformers with similar energies within 1.5 kcal mol^{-1}. Furthermore, additional conformational diversity of the Nip-tetramer by *trans* conformation of the amide bond (ω) was also expected. Overall, the Oxa-oligomers tend to have predominant populations of highly helical left-handed conformers (L2–L2–L2) but the Nip-oligomers equilibrate between several conformations with similar energies. As a consequence,

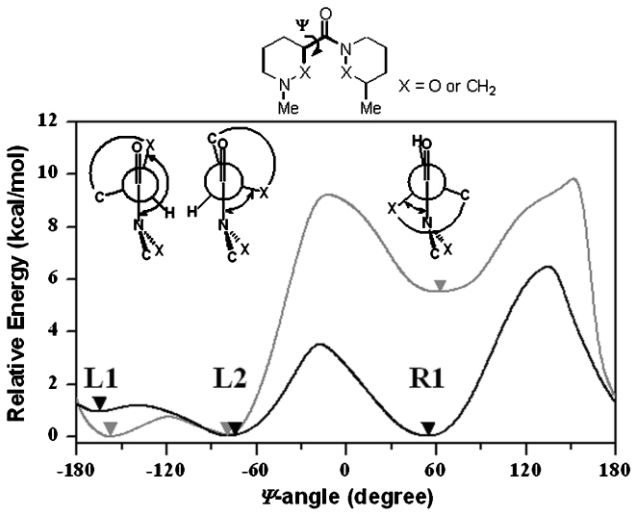


Fig. 1 *Ab initio* potential energy surfaces for Nip- and Oxa-dimers along ψ determined at B3LYP/6-31G(*d*). L1 and L2 represent left-handed conformations, and R1 right-handed conformation: ψ = −158°, −84°, 61° for Nip-dimer (gray line) and −165°, −79°, 54° for Oxa-dimer (black line).

† Electronic supplementary information (ESI) available: spectral data for synthesized Oxa-oligomers and *ab initio* data for Nip- and Oxa-compounds; 3D rotatable structures for Nip- and Oxa-tetramers. See http://www.rsc.org/suppdata/cc/b3/b301382k/

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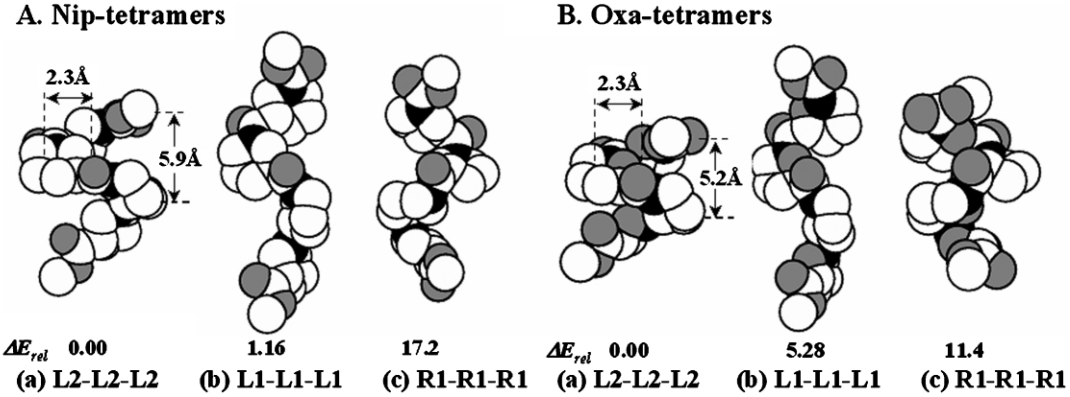

Fig. 2 Three representative structures for (*S*)-Nip- and (*R*)-Oxa-tetramers fully optimized at B3LYP/6-31G(*d*). All hydrogen atoms are omitted for clarity. ΔE_{rel} (kcal mol^{-1}) denotes relative electronic energy.

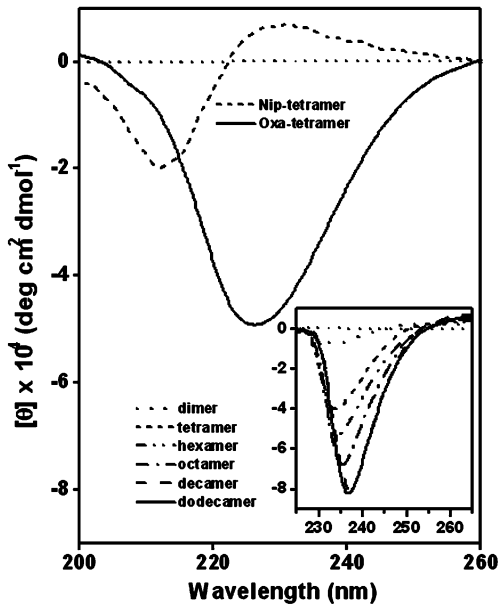

Fig. 3 CD spectra for (*S*)-Nip- and (*R*)-Oxa-tetramers in MeOH (main panel) and (*R*)-Oxa-oligomers in $CHCl_3$ (inset) at 0.5 mM concentrations at 25 °C.

the Oxa-oligomers are expected to adopt greater helical structures than the corresponding Nip-oligomers.

To validate the theoretical prediction, we examined the overall folded structures of (*S*)-Nip- and (*R*)-Oxa-tetramers by CD spectroscopy.[9] According to CD spectra in MeOH, the (*R*)-Oxa-tetramer showed a much stronger minimum, and the minimum band was red-shifted (~30 nm), compared with the (*S*)-Nip-tetramer (main panel in Fig. 3).[10] Interestingly, the (*R*)-Oxa-tetramer did not exhibit a maximum at longer wavelength, unlike the (*S*)-Nip-tetramer. The CD spectral pattern suggested that the (*R*)-Oxa-tetramer adopted a non-hydrogen-bonded left-handed helical structure more efficiently than the (*S*)-Nip-tetramer, consistent with the theoretical prediction.

To understand the red-shift of the CD minimum of the (*R*)-Oxa-tetramer compared to that of the (*S*)-Nip-tetramer, we performed molecular orbital analysis on Oxa- and Nip-dimers with L2 conformation as a model. The $\pi \rightarrow \pi^*$ transition energy for the Oxa-dimer was predicted to be smaller than that for the Nip-dimer by 10.5 kcal mol^{-1} as a consequence of lower LUMO energy for the Oxa-dimer.[11] This is close to the observed red-shift (corresponding to 12.2 kcal mol^{-1}), however, further studies should be done to support this preliminary result.

To further investigate the structural features of the (*R*)-Oxa-oligomers, we also measured their CD spectra in $CHCl_3$ at 25 °C (inset in Fig. 3).[12] It turned out that the absolute molar ellipticity for the CD minimum bands increased gradually with chain length up to decamer, whereas the corresponding bands of Nip-oligomers in MeOH changed little beyond tetramer.[2] It seems that the energetically favorable left-handed helical conformations for Oxa-oligomers result in a persistent increase in ellipticity up to decamer.

In conclusion, we have demonstrated that introduction of an asymmetric chemical environment into nipecotic acid to constrain all the torsional angles produces pseudopeptides with more pronounced helicity than the corresponding Nip-oligomers. In addition, we also showed that α-aminooxy peptides adopting seven-membered hydrogen-bonded conformations are able to adopt non-hydrogen-bonded helical structures in the case of oligomeric cyclic α-aminooxy acids.

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Notes and references

‡ Two authors contribute equally to this work.

1 T. Nakano and Y. Okamoto, *Chem. Rev.*, 2001, **101**, 4013; M. J. I. Andrews and A. B. Taber, *Tetrahedron*, 1999, **55**, 11711.
2 However, the molecular basis of the folded structures of Nip-oligomers remains unclear. See B. R. Huck, J. M. Langenhan and S. H. Gellman, *Org. Lett.*, 1999, **1**, 1717.
3 Y. J. Chung, L. A. Christianson, H. E. Stanger, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1998, **120**, 10555.
4 It is known that α-aminooxy peptides adopt a γ-turnlike conformation (N–O turn) irrespective of the nature of the acyclic α-aminooxy acid monomers. See D. Yang, B. Li, F-F. Ng, Y-L. Yan, J. Qu and Y-D. Wu, *J. Org. Chem.*, 2001, **66**, 7303 and references therein.
5 We found that oxyamide bonds in Oxa-oligomers are better described at B3LYP/6-31G(*d*) than HF/6-31G(*d*) based on the X-ray crystallographic data for α-aminooxy acids[4].
6 The NMR coupling constant of the α-proton and the calculated potential energy curve for the *N*-substituent of the Oxa-monomer indicated that the carbonyl groups on a ring were located at di-equatorial positions.
7 The ^{13}C NMR spectrum of Ac–Oxa–OMe in $CDCl_3$ displayed only one C_α resonance at 79.4 ppm, which corresponded to the *cis* conformer. We inferred that the predominant *cis* conformer could arise from electrostatic repulsion of the *trans* conformer between the ring oxygen and carbonyl oxygen as well as its steric hindrance between acetyl CH_3 and CH_2 in the ring.
8 See ESI.
9 According to the ROESY and NOESY 2D NMR spectra for Oxa-oligomers, no crosspeaks between protons of nonadjacent monomers were observed. Thus we determined the overall folded structures of oligomers using CD spectroscopy. Monomeric oxanipecotic acid was prepared by the known procedure. I. Shin, M-r. Lee, J. Lee, M. Jung, W. Lee and J. Yoon, *J. Org. Chem.*, 2000, **65**, 7667.
10 We obtained the same CD spectrum of Nip-tetramer as that of Gellman *et al.*[2].
11 The calculated HOMO-1 and LUMO energies at B3LYP/6-31G(*d*) for the Oxa-dimer were −144.5, 7.93 kcal mol^{-1}, and those for the Nip-dimers were −143.0, 19.9 kcal mol^{-1}, respectively.
12 The CD spectral measurement was performed in $CHCl_3$ in which all the oligomers were found to be well soluble.