

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 921

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Omegatides: constrained analogs of peptide primary sequence†

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Received 5th October 2011, Accepted 21st November 2011

DOI: 10.1039/c2ob06692k

Certain motifs of two or three contiguous amino acids are associated with important and varied pharmacological activities.¹ Consequently, methods to make conformationally constrained compounds that *closely* reflect the primary sequence and structures of di- and tri-peptides are important. Of these, retroinverso-mimics,² peptoids,^{3,4} oligomers of β -amino acids,^{5,6} and ester-based analogs,⁷ tend to be *more flexible* than parent systems. Oligomers of *N*-methyl-,^{8,9} or α -methyl-,^{10,11} and cyclopropyl-^{12,13} amino acids are more rigid, but they contain acyclic amide bonds. Smith/Hirschmann devised routes to oligomers of γ -pyrrolidones,^{14–17} but their syntheses are labor intensive (*e.g.* 15 steps, 11% yield, involve separation of diastereomers by chromatography *etc.*) even for simple alkyl-side chains.^{15–17} Consequently, even though about 30 years have passed since genesis of the term “peptide-mimic” or “peptidomimetic”,¹⁸ there is a need for facile methods to construct oligomers of *contiguous constrained amino acid surrogates*. Arora *et al.* recently published an example of this based on oligo oxopiperazines;¹⁹ here we wish to add another.

This manuscript is about a design for contiguous constrained amino acid surrogates that have side chains to reflect the primary sequence di- and tri-peptides; we call this design “omegatides” (Fig. 1). It follows from our previous work on analogs containing

skipped tetramic acids.²⁰ These are oligomers based on tetramic acids building blocks wherein the Φ and ψ angles are locked, and rotation about the ω -bond is less constrained. This is opposite to the situation for peptides where the ω -vector is *more* constrained than Φ and ψ .

A solution phase strategy for the preparation of omegatides was developed (Scheme 1). It starts with 5-substituted 2,4-pyrrolidinediones (tetramic acids) **A** that can be prepared from amino acids on multigram scales *via* a one-pot procedure without chromatography.^{21–24} Tønder developed procedures to add an amino acid to analogous compounds (different side-chains to the ones shown), and to reduce the resulting vinylogous ureas;^{25,26} those procedures were applied here to give our starting materials **1** and **2**. Scheme 1 shows the steps leading up to these materials so that this graphic represents the true length of the synthesis. Compounds **2** are nucleophilic amines which can be cyclized to **3** using (triphenylphosphoranylidene)ketene.²⁷ Significant water solubilities were observed for compounds **3** and the “C-deprotected” forms **4**; this facilitated their isolation from triphenylmethylphosphonium trifluoroacetate in this synthesis (we found that excess ketene is hydrolyzed in the presence of water to this salt). Transformation of **4** into the trimers **7**, *via* the intermediates **5** and **6**, involves reiteration of steps already described. None of the *anti*-diastereomer was detected (¹H NMR) in the hydrogenation of **5** or of **1**.

Two methods were used to assess the conformational biases and constraints on these systems. The first was quenched molecular dynamics (QMD)^{28–31} to probe *thermodynamic accessibility* of conformational states. In this technique the molecule is energy minimized then subjected to a molecular dynamics run at high temperature (1000 K) for a short time (600 ps), conformational states are recorded every 1 ps, then these are minimized *via* molecular mechanics. The lowest energy structures below a user-defined cut-off are selected then clustered into families based on root mean squared deviation (RMSD) from user-defined atoms. Once these states have been identified, density functional theory (DFT) was used to investigate *kinetic barriers to interconversion* (see the ESI†).

Application of the QMD technique to **4a** showed an overwhelming preference for it to exist in two preferred conformations {594 of the 600 structures sampled existed as these two conformers to within an RMSD of 0.5 Å}. Within those two families, the lowest energy structure was found in the most populated family (474 structures). Members of this family present the two methyl side chains on the same side of the molecule, so we refer to this

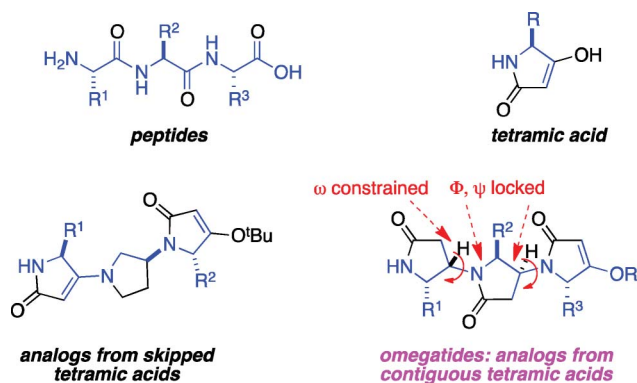
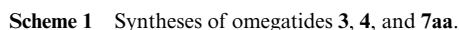


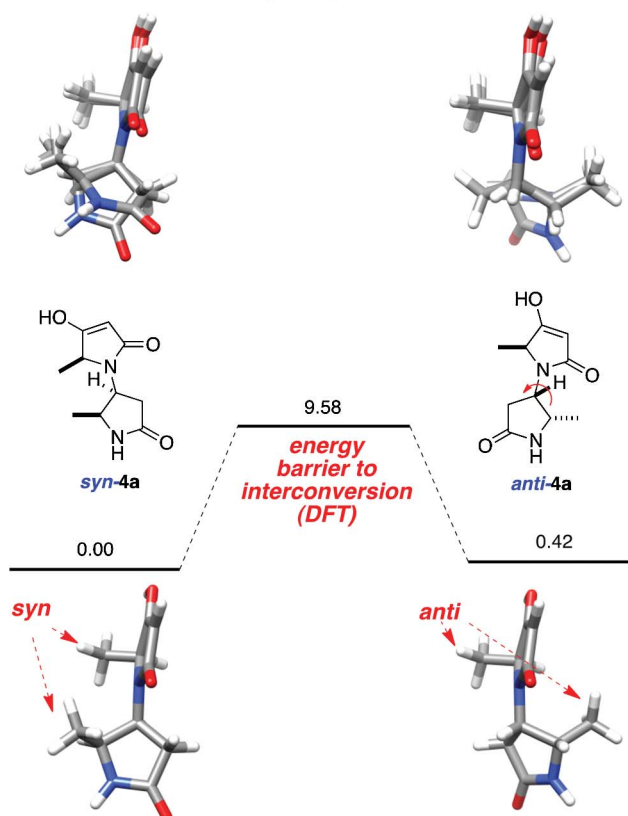
Fig. 1 Peptides, tetramic acids, previous work (skipped tetramic acid analogs), and omegatides.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for the new compounds reported. CCDC reference numbers 854831–854833. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06692k



DFT calculations on **4a** indicated the energy difference between the *syn* (preferred) and *anti* conformers was only 0.42 kcal mol⁻¹ and the energy barrier that must be surmounted to interconvert them was only 9.58 kcal mol⁻¹. Thus theory predicts that these two conformers should be rapidly interconverting on the NMR time-scale; this was consistent with the ¹H NMR of these materials in several solvents for which only one set of signals is observed at



25 °C. No dihedral angle in omegatides exactly corresponds to ω in peptides, but the CHCH–NCH angle is closely related. This has a value of -110° in **syn-4a**, while for **anti-4a** it was 101° (using the data from DFT).

Different envelope conformations of the five-membered rings mean that the ϕ, ψ -angles in omegatides can vary slightly, but only within quite narrow ranges. Fig. 3 shows a Ramachandran plot for the 600 conformers selected in the OMD experiment for

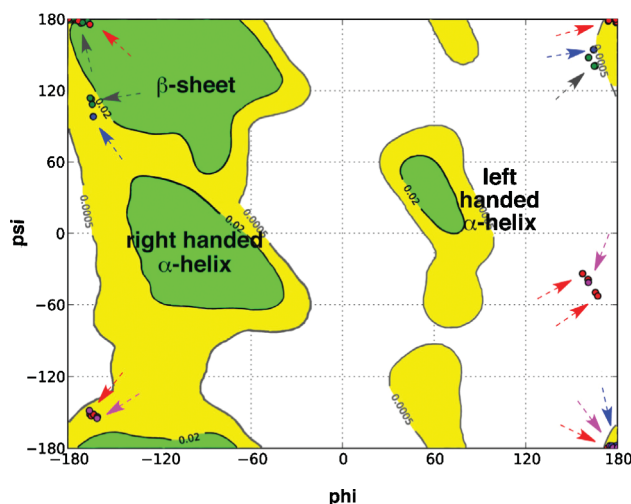


Fig. 3 Ramachandran plot for diastereomers of **4a**. Red (LL), blue (DD), pink (LD), green highlighted with black arrow (DL).

compound **4a**. This dot plot shows the ϕ, ψ -angles sampled for the L,L- (and, incidentally, the D,L-) isomer correspond to dihedrals found in β -sheet secondary structures; it also shows the degree of variance of ϕ, ψ -angles is much less than in peptides.

A single crystal study of the triomegatide **7** revealed ϕ and ψ dihedrals in the solid state, which are similar to those predicted by DFT calculations. In the solid state, **7** crystallized in an *anti,anti*-conformation using the nomenclature defined in Fig. 4.

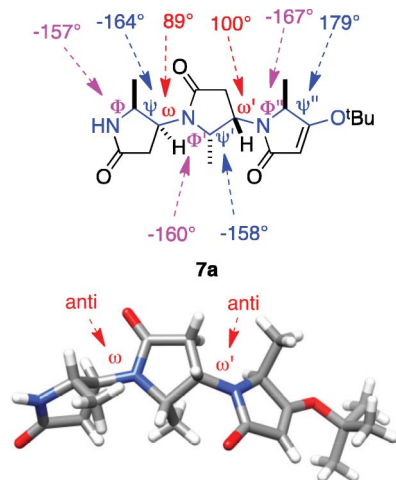
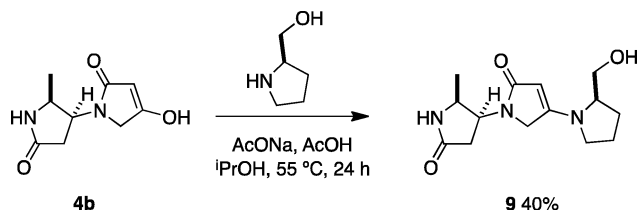


Fig. 4 Analysis of X-ray crystal structure for **7**.

Recently, we hypothesized that overlap of $C\alpha$ – $C\beta$ bond vectors is pivotal for comparing structures of peptidomimetics with ideal secondary structures.^{32,33} We did not design omegatides to be secondary structure mimics, but were curious about how they might match. Systematic overlay of the preferred conformations of **8** (a close analog of **7**, but lacking the *t*Bu group) on to both contiguous and non-contiguous side chains of preferred secondary structures revealed a preferred match corresponding to overlay of a *syn,anti-8a* conformer on three side chains of a β -strand motif (Fig. 5a). The RMSD for this match was 0.72 Å which, in our experience for a system based on three side-chains, is only a moderate fit. However, modeling showed the L,D,L-form of **8b** overlays with an RMSD of 0.43 Å (Fig. 5b).

Structural constraints do not allow proline to be incorporated as an *internal* residue into omegatides, but it could be added at the *N*- and *C*-termini. To illustrate the latter possibility and an easy way to mimic a *C*-terminal serine, prolinol was added to the precursor **4b** to give the Ala-Gly-Ser mimic **9**.



This work illustrates first stage preparations of peptidomimetics formed from contiguous restrained amino acid surrogates. It complements other studies in this laboratory on peptidomimetics from *alternating* tetramic acid-based lactams and pyrrolidones where the limited but extended conformational flexibility of these systems enables mimicry of several common secondary structure

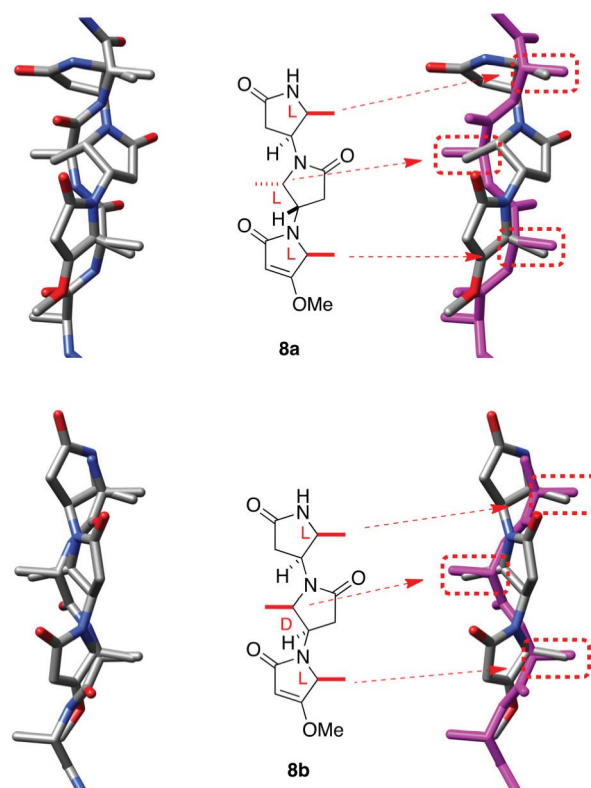


Fig. 5 Overlay of a preferred conformation of **8** on an ideal β -strand. Both diagrams are the same, except the strand is shown in pink on the right, and **8b** is an epimer of **8a**. The conformer overlaid is 1.29 kcal mol^{−1} above the lowest energy structure obtained in the QMD experiment for **8a** and 0.67 kcal mol^{−1} for **8b**.

elements.²⁰ Omegatides based on *contiguous* tetramic acid-derived residues, as described here, are different insofar as they provide rigid analogs of very particular conformations of di- and tri-peptides.³⁴

Further research is necessary to refine the synthetic procedures to prepare omegatides. In particular, the ketene cyclization of materials **6** where the R^1 side-chains are larger than methyl seems to be sensitive to steric effects, and preparation of analogs with other functionalized side-chains must be addressed. These investigations are potentially worthwhile because the featured compounds should be both proteolytically stable, and more bioavailable than peptides. Further, it is encouraging for applications in medicinal chemistry that compounds like **3** and **4** have some water solubilities. Most importantly, omegatides can only exist in a limited range of conformations, so rational syntheses of second generation analogs based on these preferred states in bioactive hit compounds is feasible; peptides and peptoids are far less amenable to this because there are more possible bioactive conformations for hit compounds having these structures.

Acknowledgements

Financial support for this project was provided by the National Institutes of Health (MH070040, GM076261), and the Robert A. Welch Foundation (A-1121). TAMU/LBMS-Applications Laboratory provided mass spectrometric support. The NMR

instrumentation at Texas A&M University was supported by a grant from the National Science Foundation (DBI-9970232) and the Texas A&M University System.

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