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# Secondary structural investigations into homo-oligomers of δ-2,4-*cis* oxetane amino acids

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**Abstract**—Investigations into the secondary structural preferences of homo-oligomers of a new class of sugar amino acids, δ-2,4-*cis*-oxetane amino acids, are reported. The oligomers were seen to adopt a well-defined repeating β-turn structure in solution.


## 1. Introduction

The ability of sugar amino acids (SAA's) to act as peptidomimetics was first demonstrated by Paulsen[1] and subsequently there has been much interest in the synthesis of SAA's and investigation into their structural preferences.[2] The mechanisms of protein folding are not fully understood and the folding of a protein cannot be predicted from its amino acid sequence. The assembly of a molecule, therefore, which has a propensity to adopt a well-defined secondary structure, is not readily predictable.

Homo-oligomers of conformationally restricted[3,4] SAA's have been extensively studied and provide many examples of 'foldamers', molecules which display a predisposition towards the formation of well-defined compact secondary structures in relatively small molecules.[5,6] The structural preferences of homo-oligomers of β-*cis*-oxetane amino acids and δ-2,4-*trans*-oxetane amino acids have previously been investigated (Fig. 1). The D-arabinoate and 6-deoxy-L-altronate β-*cis*-oxetane amino acids **1** and **2** were seen to adopt helical structures in solution stabilised by 10-membered hydrogen-bonds.[7] In contrast, however, the majority of the δ-2,4-*trans*-oxetane amino acids did not show a predisposition to adopt a well-defined secondary structure in solution. There were two exceptions to this: the L-rhamnoate **3** and D-lyxonate **4**, both of which exhibited an ordered structure which was not stabilised by hydrogen-bonds but was seen to be a result of steric interactions enforced by the bulky *tert*-butyldimethylsilyl protecting groups.[8] Herein, we report investigations into the secondary structural preferences of homo-oligomers derived from δ-2,4-*cis*-oxetane amino acids **15** (Fig. 2), the synthesis of which was described in a preceding paper.[9]

The secondary structural preferences of many tetrahydrofuran (THF) SAA's have been investigated and helical and turn type structures have been observed in their homo-oligomers.[10] For example, homo-oligomers of a series of 2,5-*cis* and 2,5-*trans* THF SAA's **8**–**14** (Fig. 2) were studied and it was seen that the inversion of a single position of the carbohydrate ring had a profound effect on the secondary structural preferences of the oligomers.[11] The 2,5-*cis* relationship was seen to be essential for β-turn formation and both changes in protecting groups **10** and **11** and deoxygenation of C-3 **13** had little effect on the secondary structure.[12,13] However, both changes to the relative configuration of C-3 and C-4 with respect to C-2 and C-5 and also on moving to 2,5-*trans* systems had a marked effect on the observed structure. Taking the flexible 2,5-*trans* amino acid scaffold **8** and altering the relative configuration of C-3 and C-4 to rigidify the backbone by the use of an acetonide protecting group gave **9**, the octamer of which adopted a left-handed helical structure in solution.[14,15] In addition, in the 2,5-*cis* oligomers from **12** with all the substituents, on the same face, no H-bonding was observed. It could, therefore, be postulated that homo-oligomers of the 2,4-*cis* oxetane amino acid **15**, due to their structural similarities with the 2,5-*cis* THF SAA's, might be expected to adopt a repeating β-turn structure.

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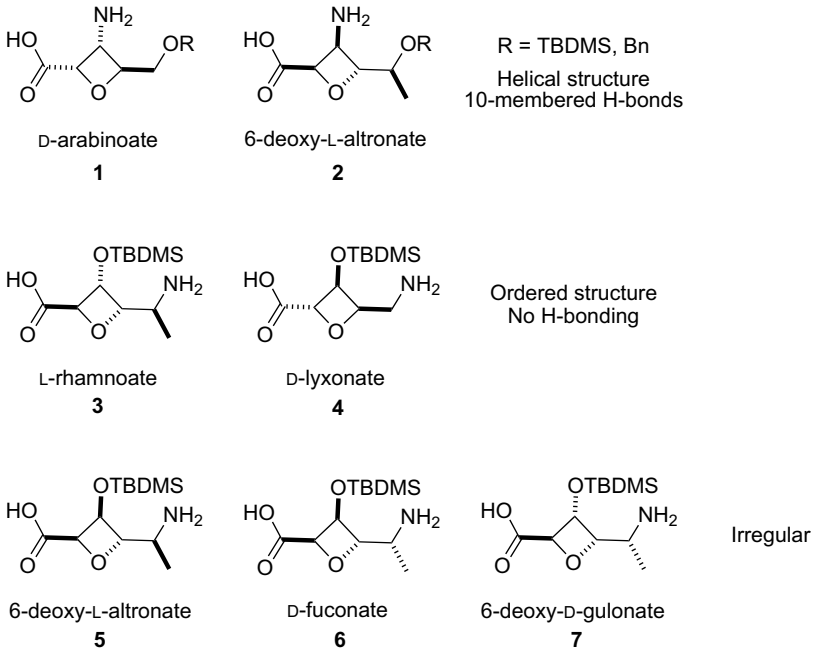


**Figure 1.** Structures adopted by homo-oligomers of oxetane amino acids previously studied.

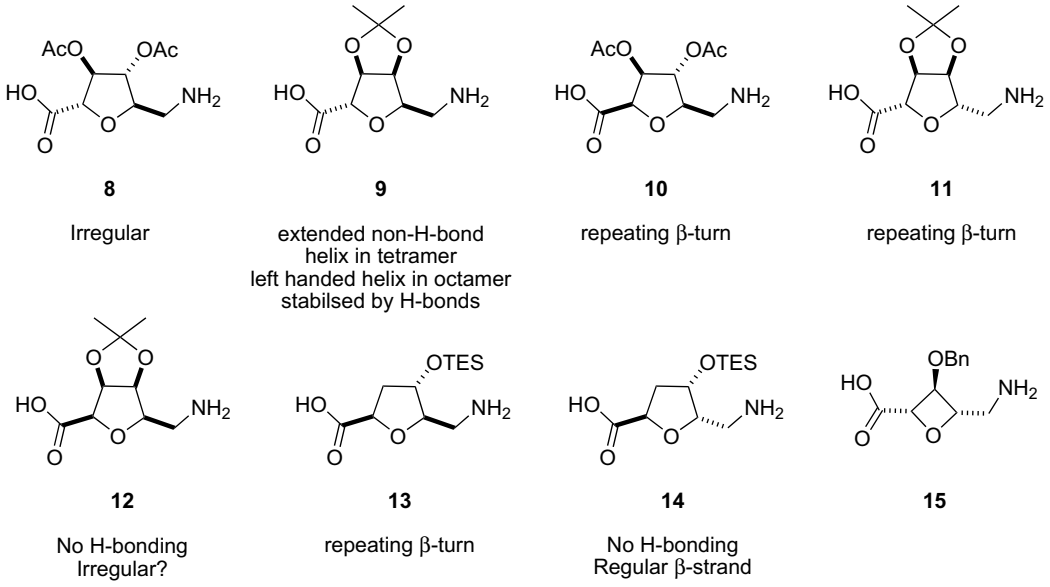


**Figure 2.** Structures adopted by some tetrahydrofuran δ-SAA oligomers.

## 2. Materials and methods

The characterisation of the solution conformations of tetramer **17** and hexamer **18** has been performed with $^1$H NMR and IR spectroscopy. NMR experiments were performed at 500 MHz in both $CDCl_3$ and $C_6D_6$ in an attempt to remove ambiguities arising from coincidental resonance overlap, with chloroform generally providing the more favourable dispersion. A variety of 2D experiments were employed to establish resonance assignments and to probe the solution conformations via NOEs. TOCSY and HSQC spectra established proton assignments within each sugar residue and ROESY experiments (performed as the Tr-ROESY technique[16] to suppress TOCSY interference, $\tau_m = 200$ ms) provided sequential proton assignments for each oligomer and established longer-range spatial proximities.

## 3. Results and discussion

The partial $^1$H NMR spectrum of dimer **16**, tetramer **17** and hexamer **18** (Fig. 3) serves to illustrate the significant resonance dispersion found for these homo-oligomers, a

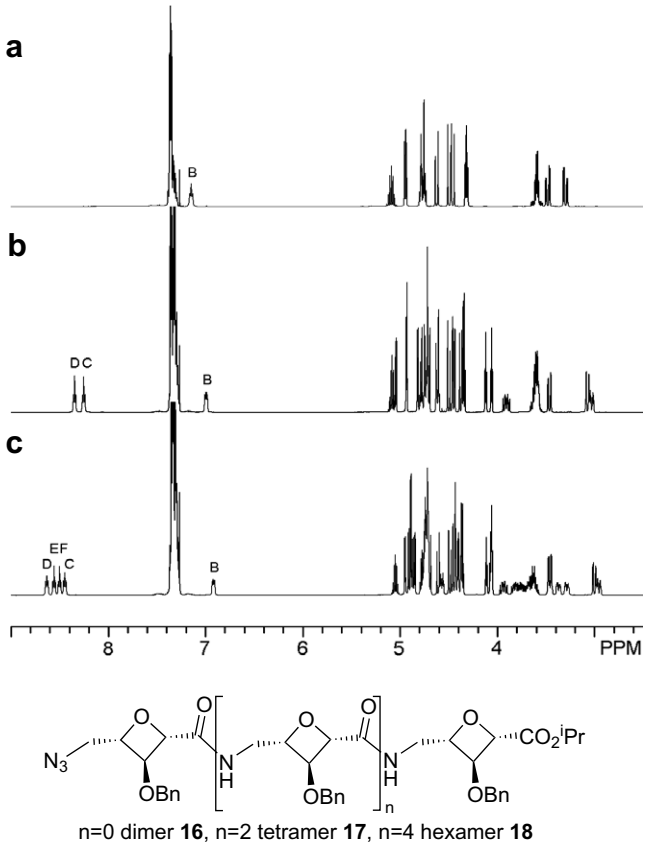


**Figure 3.** Partial $^{1}H$ spectra for (a) dimer **16** (400 MHz); (b) tetramer **17** (500 MHz); and (c) hexamer **18** (500 MHz).

feature suggestive of conformational preferences in the tetrameric and hexameric species. A particularly striking feature is the amide proton resonance dispersion, which clearly illustrates two distinct amide proton environments corresponding to the resonance shifts of ca. 7 ppm (similar to that of the dimer) and of >8 ppm. The low-frequency resonance is typically associated with amide protons that are solvent exposed whilst those to higher frequency are those involved in hydrogen-bonding interactions.[17] This behaviour has been confirmed for the hexamer in a DMSO titration experiment (Fig. 4) in which those protons that show greatest sensitivity to the DMSO additions are taken to be solvent exposed and not involved in internal hydro-

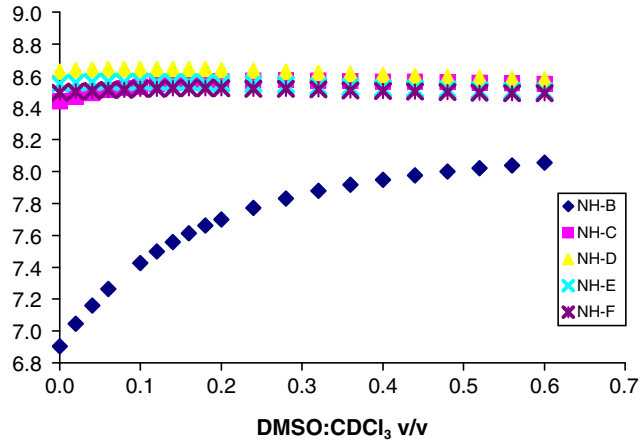


**Figure 4.** Solvent titration plot for hexamer **18** (DMSO-$d_6$ additions to an initial $CDCl_3$ solution).

gen-bonds. Thus, in both the tetramer and hexamer, only $NH^B$ appears unable to take part in such H-bonding associations in the most highly populated conformations. Dilution studies have shown the spectra to be invariant to solution concentrations, suggesting that the H-bonds present in these systems arise from *intra*-molecular interactions.

Both the shift dispersion and titration data bear a remarkable similarity with those reported for the closely related [THF] oligomers;[11,12] these data alone offer a strong indication that the solution conformations of these oxetanes will be similar to those identified for the THF systems. Thus, the THF oligomers have been described as having a repeating β-turn like structure in which the amide proton of residue *i* hydrogen-bonds with the carbonyl group of residue *i*-2, thus forming a 10-membered H-bonded ring. The NOEs observed for the oxetane oligomers **17** and **18** (tetramer and hexamer) are again consistent with such a turn formation (Fig. 5) and again demonstrate the characteristically very strong NOE from the NH to *only one* of the geminal H5 protons of the previous residue (prochirality unassigned).

In a secondary structure in which this turn repeats along the sequence, all amide NH protons will have an earlier carbonyl group, with which they can H-bond, except that of $NH^B$, which is consistent with the above results.

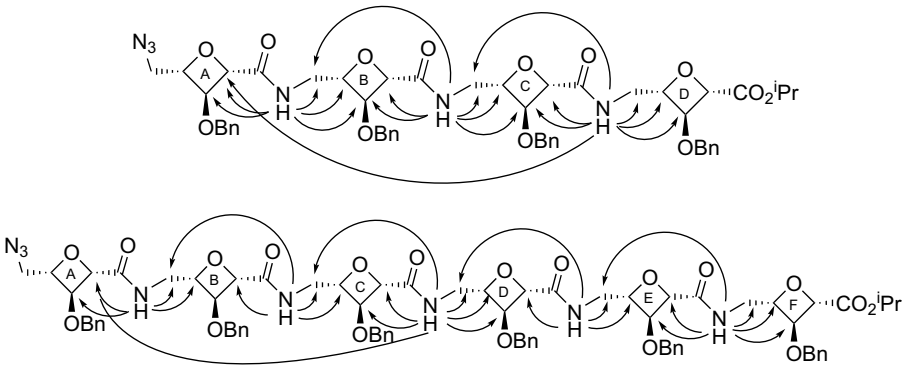


**Figure 5.** The characteristic NOEs observed in tetramer **17** and hexamer **18**.

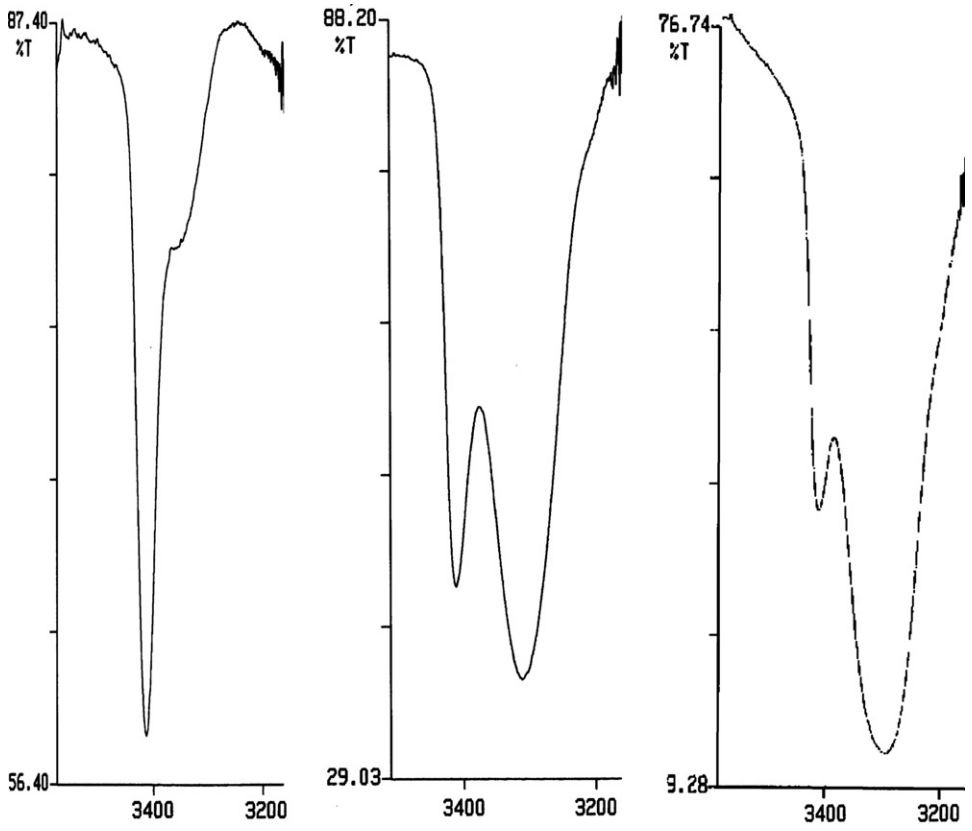


**Figure 6.** Partial IR spectra ($CHCl_3$) showing the amide N–H stretch region for (a) dimer **16**; (b) tetramer **17**; and (c) hexamer **18**.

Similarly, in the dimer the single amide proton lacks an H-bonding carbonyl required for this turn formation, and displays an amide shift similar to that of $NH^B$ in both tetramer and hexamer. H-bond involvement for all but one amide proton is also suggested by the solution IR data, in which the broader, lower-frequency band of an H-bonded amide increases proportionally with the length of the oligomers, relative to the sharper, higher-frequency band of the non-H-bonded amide (Fig. 6), again as observed in the related THF systems.[11,12]

The body of data collected for the oxetane systems is therefore consistent with the preferred conformation arising from an internal 10-membered H-bonded motif reminiscent of a conventional α-amino acid peptide β-turn. The data further suggest that the secondary structure contains a repeat of this turn along the sequence (Fig. 7), as reported for the related THF systems and similar to that observed crystallographically for oligomeric peptides containing alternating L-proline and α-amino-isobutyric acid units.[18,19] In such a conformation, the large benzyl protecting groups sit on the opposite faces to the hydrogen-bonds and on the outer face of the central 'core' of the molecules so that they do not disrupt turn formation (such disruption has been previously observed in an acetonide protected [THF] system[20]). Additional twisting or bending of this structure is suggested by weak NOEs between $NH^D$ and the H-2 and H-3 protons of ring A in both the tetramer and hexamer. It seems likely that these relate to the unconstrained A ring folding back under the molecule, a feature that is perhaps related to the presence of the large benzyl protecting groups on the oxetane rings. Alternatively, these weak NOEs may arise from a minor conformation in which the molecule turns back on itself and places rings A and D in proximity. In either case, such a conformational flexibility is unsurprising in these short oligomers.

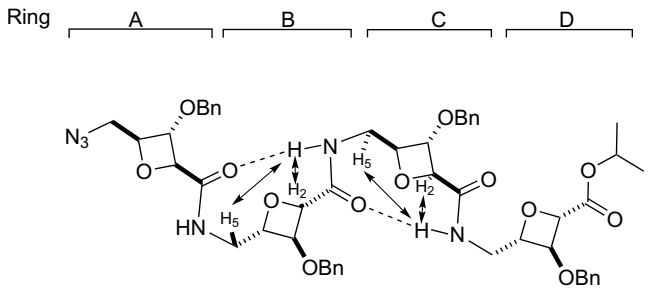


**Figure 7.** The repeating β-turn structure proposed, shown for tetramer **17**.

## 4. Conclusion

In conclusion, we have demonstrated that, in contrast to the non-H-bonded δ-2,4-*trans*-oxetane amino acid oligomers, the δ-2,4-*cis*-oxetane amino acid oligomers adopt well-defined secondary structures in solution in which the major conformation is dictated by internal 10-membered hydrogen-bonded rings. This β-turn motif is repeated along both the tetramer and hexamer. Such conformations are

similar to those reported for the δ-2,5-*cis*-THF homo-oligomers and it appears that a reduction of the sugar ring size by one carbon unit from a 5- to 4-membered ring does not significantly alter the secondary structures observed in solution.

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