

# Cyclic $\alpha,\beta$ -Tetrapeptides: Sequence-Dependent Cyclization and Conformational Preference

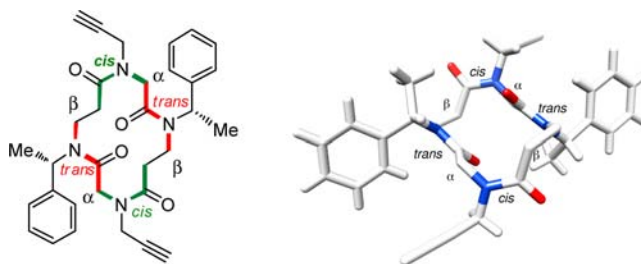
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## ABSTRACT



The presence of at least one *N*-C $\alpha$  branched side chain is crucial for successful cyclization of  $\alpha,\beta$ -tetrapeptides. The *ctct* amide sequence revealed in the crystal structure of the 14-membered cyclotetrapeptide **8** is also the most populated conformation in solution and is reminiscent of the predominant amide arrangement of the 12-membered cyclic tetrapeptides (CTPs).

Cyclic peptides represent an intriguing class of natural and nonnatural products regarding their conformations and broad ranging biological activities.<sup>1</sup> In particular, naturally occurring CTPs act as histone deacetylase and tyrosinase inhibitors with anticancer and antimicrobial activities.<sup>2</sup> Small cyclic peptides including tetramers represent

ideal scaffolds to constrain a peptide in its bioactive conformation, typically a  $\beta$ -turn.<sup>3</sup> However, the formation of constrained cyclic peptides is often challenging since the transoid form of the main-chain amides results in extended conformations which are detrimental to peptide ring closure.<sup>4</sup> Head-to-tail cyclization of short-chain peptides can be promoted by incorporation of turn-inducing residues such as D-amino acids, *gem*-disubstituted amino acids, proline residues, or *N*-alkylated amino acids.<sup>5</sup> However, these backbone modifications considerably limit the diversity of the final cyclotetrapeptides. To overcome this problem, specific synthetic strategies are in constant development.<sup>6</sup> Another approach is to use more likely accessible cyclic pseudopeptides. Among them, cyclopeptides (i.e., cyclic

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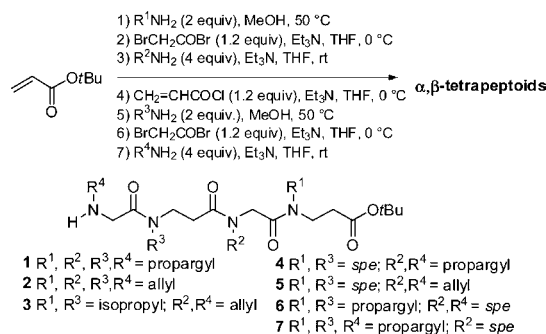
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*N*-substituted glycine oligomers) represent promising cyclopeptide surrogates since their sequence is highly tunable by the so-called submonomer synthesis<sup>7</sup> and their macrocyclization has been shown to proceed more easily compared to peptides, even for constrained rings.<sup>8</sup> The cyclization efficiency is mainly due to the easy *cis*–*trans* isomerization of the backbone *N,N*-disubstituted amides. An initial study on the cyclization of  $\alpha$ -peptoids was reported by the Kirshenbaum group in 2007.<sup>9</sup> Cyclization of oligomers from pentamer to 20-mer lengths occurred efficiently using PyBOP, but ring closure of the tetramer proceeded with only a 12% yield. A constrained 12-membered cyclopeptoid was however efficiently obtained using PyBOP (65% yield) by De Riccardis et al., allowing the first X-ray analysis of a cyclotetrapeptoid. The crystal structure unveiled a *cis-trans-cis-trans* (*ctct*) tetralactam core geometry.<sup>10</sup> Cyclization of  $\beta$ -peptoids (*N*-substituted  $\beta$ -alanine oligomers) has been investigated by our group.<sup>11</sup> The efficient cyclization of a tetramer bearing propargyl side chains gave rise to a 16-membered ring that adopted an all-*cis* arrangement in the crystal structure. Recently, we have introduced a novel peptoid backbone composed of  $\alpha$ - and  $\beta$ -peptoid monomers in alternation.<sup>12</sup> Employing HATU-optimized conditions, we successfully prepared a cyclic  $\alpha,\beta$ -tetrapeptoid carrying benzyloxyethyl side chains on the  $\alpha$ -residues and (*S*)-1-phenylethyl side chains (*spe*) on the  $\beta$ -residues in 82% yield for the macrocyclization.<sup>12a</sup> However, during our ongoing project aimed at developing cyclic templates for multivalent ligand display,<sup>13</sup> we encountered difficulties in cyclizing  $\alpha,\beta$ -tetramers, meant to yield rare 14-membered cyclopseudopeptides.<sup>14</sup> Herein, we present a study relating to the cyclization of  $\alpha,\beta$ -tetrapeptoids with different sequence patterns and the conformational behavior of these 14-membered rings in solid state and solution.

The synthesis of  $\alpha,\beta$ -alternating peptoids combines the solution-phase submonomer syntheses of  $\alpha$ - and  $\beta$ -peptoids (Scheme 1). Linear  $\alpha,\beta$ -tetrapeptoid precursors with pendant allyl, propargyl, and isopropyl groups were prepared following a solution-phase submonomer method previously optimized for gram-scale preparation of pure peptoids using volatile amines.<sup>15</sup> Accordingly, *N*-allyl, *N*-propargyl, and mixed *N*-isopropyl, *N*-allyl tetrapeptoids **1**, **2**, and **3** were prepared in seven steps with a single final purification by flash chromatography in 45%, 42%, and 36% yield, respectively. Intermediate purification was, however, required when installing *spe* side chains, and with this modification linear compounds **4** to **7** were obtained with overall yields ranging from 32% to 49% (see Supporting Information (SI) for details).

**Scheme 1.** Synthesis of Linear  $\alpha,\beta$ -Tetrapeptoids



Our initial aim was to synthesize cyclic  $\alpha,\beta$ -tetrapeptoids bearing four propargyl or allyl side chains ready for the ligation of carbohydrate ligands. However, the first attempt at cyclizing **1** using an HATU-mediated procedure<sup>11</sup> after TFA deprotection of the *t*Bu ester was unsuccessful. Only a small amount of the expected cyclotetrapeptoid was formed. Other conditions that have proved efficient in peptoid ring closure such as DPPA, PyBOP, and EDCI/HOBt were likewise tested on **1** and **2**, but no or little macrocyclization occurred and we instead isolated the derived activated species. We then attempted to cyclize **1** using HATU at 50 °C, using conventional heating or microwave activation (MW).<sup>16</sup> With these conditions, macrocyclization occurred but mass spectrometry analysis revealed the presence of a mixture of the expected cyclo-tetrapeptoid (< 10%) and the dimeric form, i.e. the  $\alpha,\beta$ -cyclooctapeptoid (21% and 27% yield for oil bath and MW heating, respectively). Higher dilution of the reaction mixture did not improve the yield of monomeric form.

Keeping in mind that the formation of cyclic  $\alpha,\beta$ -tetrapeptoids can be highly efficient,<sup>12a</sup> we decided to examine the sequence requirements for efficient cyclization, in particular by introducing the chiral  $\alpha$ -branched *spe* side chain. The latter is known to slightly promote the *cis*

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conformation of peptoid amides and hence to favor helical structures.<sup>17</sup> We thus speculated that the *spe* side chain may also promote cyclization of short peptoids. Compounds **4** and **5** carrying two *spe* side chains on the  $\beta$ -peptoid residues and either a propargyl or an allyl group on the  $\alpha$ -peptoid residues were submitted to several cyclization conditions after acid C-terminus deprotection (Table 1). The DPPA conditions successfully used to access cyclic  $\beta$ -tetrapeptides<sup>11</sup> proved inefficient (entry 1). Uronium-based coupling reagents (HATU, TBTU) and the pentafluorophenol derivative FDPP provided the cyclic  $\alpha,\beta$ -tetrapeptides **8** and **9** in yields of ~30% (entries 2–4 and 6). The best results were, however, obtained using the coupling system EDCI/HOBt described for example for aza- $\beta^3$ -cyclotetrapeptide formation.<sup>18</sup> Thus, the cyclic  $\alpha,\beta$ -tetrapeptides **8** and **9** were isolated in 64% and 51% yields, respectively (entries 5, 8), and the presence of the cyclic dimer was not detected by mass spectrometry. We were then able to demonstrate that the *spe* side chain could be interchanged with the less bulky and nonaromatic isopropyl side chain without loss of cyclization efficiency (macrocycle **10**, entries 9 and 11 vs macrocycle **9**, entries 6 and 8). To increase yields when using HATU, MW activation was tested but unfortunately without success (entry 10). Next, to explore the importance of the *spe* location on the backbone, cyclizations of **4** and **6** were compared. The efficiency was slightly higher for the oligomer **6** when using EDCI/HOBt (67% vs 64%, entries 13 and 5) and was significantly increased in the case of HATU as the coupling reagent (57% vs 32%, entries 12 and 2). These results indicate that cyclization is promoted by the presence of an *spe* side chain on the  $\alpha$ -residues. We further demonstrated that only one *spe* side chain, located in the middle of the backbone, can ensure the formation of cyclic tetrapeptides as exemplified by the cyclization of **7** in 73% yield (entry 14). This study shows that at least one *N*-C $\alpha$  branched side chain such as *spe* or isopropyl is needed to allow cyclization of  $\alpha,\beta$ -tetrapeptides. The impact is greater when the bulky side chain is located on  $\alpha$ -residues, possibly because the  $\beta$ -peptoid residues are more flexible than  $\alpha$ -peptoid residues and their amide conformation is more difficult to control.<sup>19</sup>

We were pleased to obtain crystals suitable for X-ray analysis by slow evaporation of compound **8** in dry methanol. The 14-membered cyclotetrapeptide **8** adopts a  $\beta$ *cis*- $\alpha$ *trans*- $\beta$ *cis*- $\alpha$ *trans* (*ctct*, in the *N*-to-*C* direction) conformation in a zigzag arrangement which, exclusive of the *spe* lateral chains, is centrosymmetric (Figure 1). The few crystal structures of  $\alpha,\beta$ -CTPs described in the literature display a *tttt* conformation.<sup>14a–c</sup> It is interesting to note that the *ctct* arrangement is known to be predominant

**Table 1.** Cyclization of  $\alpha,\beta$ -Tetrapeptides

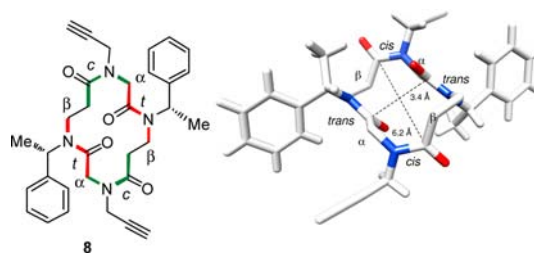
cyclic compounds:

**8** R<sup>1</sup>, R<sup>3</sup> = *spe*; R<sup>2</sup>, R<sup>4</sup> = propargyl      **11** R<sup>1</sup>, R<sup>3</sup> = propargyl; R<sup>2</sup>, R<sup>4</sup> = *spe*  
**9** R<sup>1</sup>, R<sup>3</sup> = *spe*; R<sup>2</sup>, R<sup>4</sup> = allyl              **12** R<sup>1</sup>, R<sup>3</sup> = propargyl; R<sup>2</sup> = *spe*  
**10** R<sup>1</sup>, R<sup>3</sup> = isopropyl; R<sup>2</sup>, R<sup>4</sup> = allyl

entry	linear precursor	cyclization conditions <sup>a</sup>	cyclic compd	yield (%) <sup>b</sup>
1	<b>4</b>	DPPA/DIEA	<b>8</b>	—
2	<b>4</b>	HATU/DIEA	<b>8</b>	32
3	<b>4</b>	FDPP/DIEA	<b>8</b>	35
4	<b>4</b>	TBTU/Et <sub>3</sub> N/HOBt	<b>8</b>	27
5	<b>4</b>	EDCI/Et <sub>3</sub> N/HOBt	<b>8</b>	<b>64</b>
6	<b>5</b>	HATU/DIEA	<b>9</b>	33
7	<b>5</b>	PyBOP/DIEA	<b>9</b>	47
8	<b>5</b>	EDCI/Et <sub>3</sub> N/HOBt	<b>9</b>	<b>51</b>
9	<b>3</b>	HATU/DIEA	<b>10</b>	28
10	<b>3</b>	HATU/DIEA/ $\mu$ waves	<b>10</b>	19
11	<b>3</b>	EDCI/Et <sub>3</sub> N/HOBt	<b>10</b>	<b>50</b>
12	<b>6</b>	HATU/DIEA	<b>11</b>	57
13	<b>6</b>	EDCI/Et <sub>3</sub> N/HOBt	<b>11</b>	<b>67</b>
14	<b>7</b>	EDCI/Et <sub>3</sub> N/HOBt	<b>12</b>	<b>73</b>

<sup>a</sup> Conditions for HATU: HATU (1.2 equiv), DIEA (5 equiv), CH<sub>2</sub>Cl<sub>2</sub>/DMF 4:1 (5 mM), rt, 72 h; conditions for EDCI: EDCI (6 equiv), Et<sub>3</sub>N (6 equiv), HOBt (6 equiv), CH<sub>2</sub>Cl<sub>2</sub> (5 mM), rt, 72 h; see SI for the other cyclization conditions. <sup>b</sup> Isolated yields.

in 12-membered  $\alpha$ -CTPs.<sup>20</sup> Indeed, analysis of the  $\alpha$ -CTP structures deposited in the Cambridge Structural Database (version 5.34) revealed that 16 over 21 rings crystallized with the *ctct* conformation. The sole crystal structure of  $\alpha$ -tetracyclopeptoid also features a *ctct* conformation.<sup>10</sup> In brief, the analysis of compound **8** in the solid state suggests that the 14-membered cyclic  $\alpha,\beta$ -tetrapeptides may adopt the *ctct* amide arrangement that predominates for the 12-membered  $\alpha$ -CTP and peptoids.



**Figure 1.** X-ray crystal structure of cyclic  $\alpha,\beta$ -tetrapeptide **8**. (Left) Structure of **8** showing the  $\beta$ *cis*- $\alpha$ *trans*- $\beta$ *cis*- $\alpha$ *trans* conformation (*cis* amides in green; *trans* amides in red). (right) Side view of the crystal structure (H-atoms of the backbone are omitted for clarity).

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Using proton NMR experiments, the relative ratio of *cis* and *trans* amides bearing an *spe* side chain can be easily measured by integration of the benzylic signals.<sup>17b</sup> It was thus anticipated that 1D NMR studies of heterooligomers bearing *spe* side chains on either the  $\alpha$  or  $\beta$  residues would give crucial information on the geometry of the different amides constituting the tetracyclic core of the molecules. As mentioned above, the *spe* side chain is well-known to slightly promote the *cis* geometry of peptoid amides as observed for the linear precursor **6** or **7** exhibiting a *cis/trans* ratio of  $\sim 55:45$  (Table 2). Consistent with the literature,<sup>19b</sup> slight excesses of *trans* amides were observed for linear peptoids **4** and **5** where the *spe* side chains are located on the  $\beta$ -residues. The *cis/trans* ratio for the cyclopeptoid **8** was measured in different solvents. A *cis/trans* ratio of 16:84 was determined in CDCl<sub>3</sub> (Table 2), and an average of 30:70, in other solvents (CD<sub>3</sub>OD, CD<sub>3</sub>CN, and acetone-*d*<sup>6</sup>). The *cis/trans* ratios for cyclopeptoid **9** exhibited the same tendency. This high proportion of *trans* conformation at  $\beta$ -residues is in accordance with the solid-state conformation (Figure 1). When the *spe* side chains were placed on  $\alpha$ -peptoid residues (**11** and **12**), the *cis/trans* ratios revealed a large proportion of *cis* conformer (Table 2) again in accordance with the backbone conformation in the X-ray crystal structure. Overall, this NMR study seems to indicate that the  $\beta$ *cis*- $\alpha$ *trans*- $\beta$ *cis*- $\alpha$ *trans* conformation observed in the crystal structure is also the predominant conformation in solution, independently of the side chain sequences.

**Table 2.** *Cis/trans* Ratios for Amides Bearing an *spe* Side Chain

linear peptoids	<i>cis/trans</i> ratio <sup>a</sup>	cyclic peptoids	<i>cis/trans</i> ratio <sup>a</sup>
<b>4</b>	43:57	<b>8</b>	16:84
<b>5</b>	47:53 <sup>b</sup>	<b>9</b>	36:64 <sup>b</sup>
<b>6</b>	55:45	<b>11</b>	74:26
<b>7</b>	53:47	<b>12</b>	79:21 <sup>b</sup>

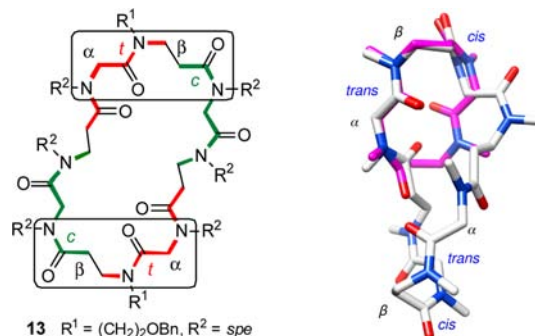
<sup>a</sup>Determined by <sup>1</sup>H NMR in CDCl<sub>3</sub>. <sup>b</sup>Determined by HSQC in CDCl<sub>3</sub>.

Conformational analysis of macrocycle **8** through a simulated annealing approach provided candidate structures for the 10 possible *cis/trans* states: *cccc*, *ctcc*, *cctc*, *cctt*, *ctct*, *tctc*, *cttc*, *tttc*, *cttt*, *tttt*. These different conformations were classified into 20 subgroups, and the geometry of the lowest energy conformation of each subgroup was optimized at the DFT (B3LYP/6-31G(d,p)) level (see SI for details). The structure of the lowest energy was found to

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be a  $\beta$ *cis*- $\alpha$ *trans*- $\beta$ *cis*- $\alpha$ *trans* arrangement whose conformation matches perfectly with the conformation of **8** in the solid state (superposition shown in the SI). Unlike previous findings on  $\beta$ -tetracyclopeptoids,<sup>11</sup> the solution and solid-state conformations of **8** are identical.

The comparison of the crystal structures of tetramer **8** and cyclic  $\alpha,\beta$ -octamer **13** recently published by us<sup>21</sup> reveals striking similarities. Indeed, both structures have the presence of two  $\alpha$ *trans*- $\beta$ *cis* segments in a turn-like conformation in common (Figure 2). The fact that this specific conformation is also present in an unconstrained cyclic octamer, having a different side chain sequence than tetramer **8**, suggests that the observed turn may represent a privileged conformation of the  $\alpha,\beta$ -peptoid family. This observation might pave the way toward novel peptoid secondary structures based on the  $\alpha,\beta$ -peptoid backbone and alternating *cis* and *trans* main-chain amides.<sup>22</sup>



**Figure 2.** Superimposition of the X-ray structures of the cyclic  $\alpha,\beta$ -tetrapeptoid **8** (in magenta) and the cyclic  $\alpha,\beta$ -octapeptoid **13** (for clarity, H-atoms and side chains are omitted).

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**Supporting Information Available.** Full experimental procedures; characterization of new compounds; HPLC data for **8–12**; <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds; molecular modeling on cyclopeptoid **8**; crystallographic data for **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.