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Oligomers of Enantiopure Bicyclic γ/δ-Amino Acids (BTAa). 1. Synthesis and Conformational Analysis of 3-Aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic Acid Oligomers (PolyBTG)

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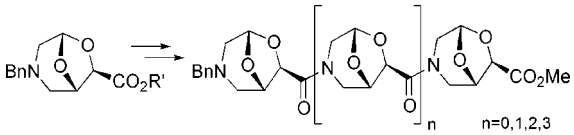
ABSTRACT



A series of dimeric through pentameric oligomers of a bicyclic γ/δ-amino acid (BTG) were synthesized using peptide coupling methods in solution with PyBroP or HATU. The analysis of ^{1}H NMR and CD spectra suggests that these oligomers could have a partially ordered structure in alcohol solutions.

Several homooligomers of noncoded α,[1] β,[2] γ,[3] and δ[4] amino acids have been synthesized in recent years, and their conformational proprieties have been extensively studied. It has been demonstrated that these oligomers (named "foldamers" by Gellman)[5] can adopt a variety of secondary structures, including helices, sheets, and turns, depending either on the number of units and the amino acid structure (side chain substitution, configuration of the stereocenters, etc.) or the external conditions (solvent, temperature, solid state, etc.). Furthermore, the possibility that β-peptides could adopt a tertiary structure has been recently suggested.[6] The great interest in the synthesis of these peptides has been also stimulated by the observation that, similar to the proteins and RNA, these oligomers can catalyze a wide range of processes. For example, the synthetic application of polypeptides, with adopted folded structures, as catalyst in transesterification reactions has recently been reported.[7]

(1) For example: Yang, D.; Qu, J.; Li, B.; Ng, F.-F.; Wang, X.-C.; Cheung, K.-K.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **1999**, *121*, 589−590.

(2) (a) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. *Helv. Chim. Acta* **1998**, *81*, 932−976 and references therein. (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 7574−7581 and references therein.

(3) (a) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983−1002. (b) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569−8570. (c) Hanessian, S.; Luo, X.; Schaum, R. *Tetrahedron Lett.* **1999**, *40*, 4925−4929.

(4) (a) Szabo, L.; Smith, B. L.; McReynolds, K. D.; Parril, A. L.; Morris, E. R.; Gervay, J. *J. Org. Chem.* **1998**, *63*, 1074−1078. (b) Smith, M. D.; Claridge, T. D. Tranter, G. E.; Sansom, M. S. P.; W.; Fleet, G. W. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2041−2042. (c) Long, D. D.; Hungerford, N. L.; Smith, M. D.; Brittain, D. E. A.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2195−2198. (d) Claridge, T. D. W.; Long, D. D.; Hungerford, N. L.; Aplin, R. T.; Smith, M. D.; Marquess, D. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 2199−2202. (e) Schwalbe, H.; Wermuth, J.; Richter, C.; Szalma, S.; Eschenmoser, A.; Quinkert, G. *Helv. Chim. Acta* **2000**, *83*, 1079−1107.

(5) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180.

(6) Appella, D. H.; Christianson, L. A.; Karle, L. I.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206−6212.

(7) Rossi, P.; Felluga, F.; Tecilla, P.; Formaggio, F.; Crisma, M.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **1999**, *121*, 6948−6948 and references therein.

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Thus, the design and synthesis of new oligomers which possess the specific structural properties of the natural biopolymers such as catalysis and molecular recognition is of current interest for producing artificial enzymes and receptors.

Herein, we describe the synthesis and a preliminary conformational study of new γ/δ-peptide oligomers (polyBTG), constructed from the enantiopure (1*R*,7*R*)-3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid (BTG). This compound, recently prepared by us,[8] belongs to a new series of amino acids (BTAa)[9] containing the 3-aza-6,8-dioxabicyclo-[3.2.1]octane-7-carboxylic acid skeleton. The bicyclic lactams [BTAa(O)] can be easily synthesized from L- or D-α-amino aldehyde derivatives (in turn prepared from α-amino acids) and (*R*,*R*), (*S*,*S*), or (*R*,*S*) tartaric acid mono methyl esters through amide bond formation and carbonyl ketalization. The amide group is then selectively reduced to give the final amino acids BTAa (Figure 1).

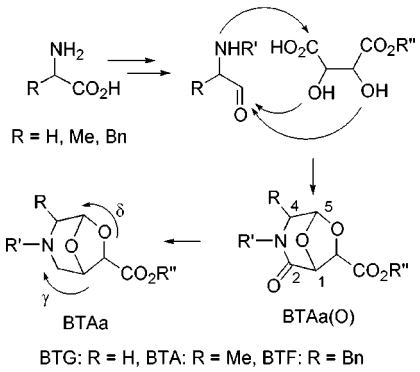


Figure 1.

These BTAa can be described as conformationally rigidified γ- or δ-amino acids according to the Seebach[10] and Gellman[11] subdivisions (see Figure 1).

A large panel of these new γ/δ-amino acids, different either in the type of substitution or in the configuration of the stereocenters, have been prepared by simply changing the starting α-amino acids and tartaric acids. Owing to the unique features of the new BTAa molecular scaffold—which has a rigid skeleton, several points of substitution and coordination, a proline-like secondary amino function, a carboxylic group which can be oriented in *exo* or *endo* position—we were intrigued by the possibility of producing BTAa homooligomers and studying their structural properties.

(8) Guarna, A.; Guidi, A.; Machetti, F.; Menchi, G.; Occhiato, E. G.; Scarpi, D.; Sisi, S.; Trabocchi, A. *J. Org. Chem.* **1999**, *64*, 7347−7364.

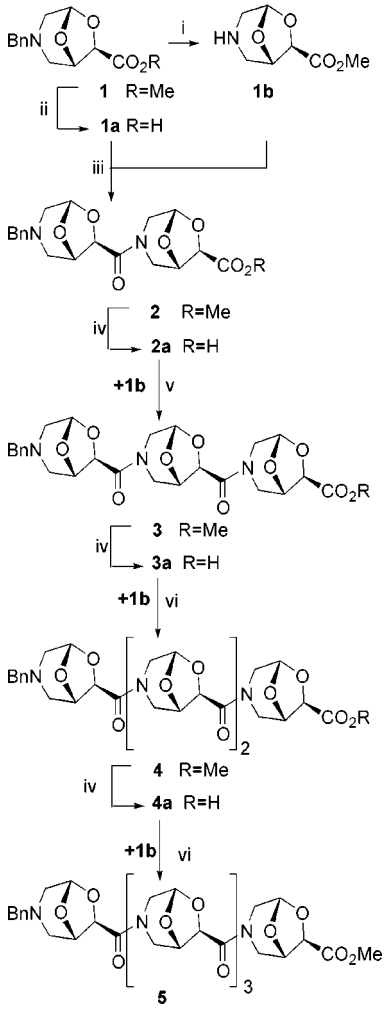
(9) We named these compounds BTAa (i.e., *B*icycles from *T*artaric *A*cid and *A*mino acid) using the single letter code of the α-amino acids from which the various type of BTAa's are derived (see ref 8).

(10) Seebach, D.; Overhand, M.; Künle, F. N. M.; Martinoni, B.; Obere, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913−941. See also: Ondetti, M. A.; Pluscec, J.; Weaver, E. R.; Williams, N.; Sabo, E. F.; Kocy, O. *Chemistry and Biology of Peptides*; Ann Arbor Science Publishers: Ann Arbor, 1972; p 525.

(11) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054−1062.

Thus, starting from the monomer Bn−BTG−OMe (**1**), a strategy for oligomerization has been developed leading to the synthesis of a dimer (Bn−(BTG)$_2$−OMe, **2**), a trimer (Bn−(BTG)$_3$−OMe, **3**), a tetramer (Bn−(BTG)$_4$−OMe, **4**), and a pentamer (Bn−(BTG)$_5$−OMe, **5**) (Scheme 1).

Scheme 1[a]



[a] Reagents and conditions: (i) H_2 (1 atm), 20% $Pd(OH)_2$/C, MeOH, 21 h, 100%; (ii) HCl 4 M, 21 h, 100%; (iii) PyBrOP, DIPEA, CH_2Cl_2, 97%; (iv) LiOH, MeOH−THF, 100%; (v) PyBrOP, DMF, DIPEA, 68%; (vi) HATU, DIPEA, DMF, 50%.

The orthogonally protected monomer Bn−BTG−OMe (**1**)-was synthesized as previously reported.[8] Briefly, the coupling of (*R*,*R*)-2,3-di-*O*-isopropylidentartaric acid mono methyl ester with 2-(*N*-benzylamino)acetaldehyde, followed by a treatment in refluxing toluene with H_2SO_4 adsorbed on SiO_2, gave (1*R*,5*S*,7*R*)-3-benzyl-2-oxo-6,8-dioxa-3-azabicyclo-[3.2.1]octane-7-*exo*-carboxylic acid methyl ester (Bn−BTG-(O)−OMe), which was selectively reduced with BH_3·Me_2S to give **1**. The deprotection of the amino group by hydrogenation over 20% $Pd(OH)_2$/C gave **1b** whereas treatment with 4 M HCl furnished **1a**. Amide bond formation between **1b** and **1a** to give dimer **2**[12] was accomplished using *N*,*N*′-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/

HOBt) or bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) as coupling reagents.

Dimer **2** was obtained in pure form after filtration of the reaction mixture, followed by FCC purification of the crude residue obtained after evaporation of the solvent. The highest yield (97%) was obtained using PyBrop. In both cases the aqueous workup had to be avoided because extraction of dimer **2** with organic solvents was particularly difficult and lowered the final yield.

The tripeptide **3** could be obtained through two different approaches: by elongating the oligomer from the *N*-terminal or the *C*-terminal side. The latter approach resulted in the best yield (68%) compared with a yield of 6% obtained by the other procedure. In both cases couplings were performed using PyBroP as activating reagent.

Hydrolysis of dimer **2** performed under basic condition (LiOH in THF−MeOH) gave better yields than acid hydrolysis, wherein the formation of decomposition products was observed by HPLC.

On the basis of the these results, the synthesis of tetramer **4** was performed by coupling of monomer **1b** and acid trimer **3a**, the latter obtained by hydrolysis of **3** with LiOH.

When the coupling was performed using PyBroP, the yields of compound **4** were very low (8%). Thus, the reaction was carried out using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophospate (HATU) as coupling reagent to afford **4** in 30% yield after chromatography. In this case the yield was lowered by the poor solubility of tetramer **4** in organic solvents which affected the chromatographic purification. However, the yield was improved up to 50% when the isolation of **4** from the reaction mixture was carried out by crystallization from MeOH. Alternative synthesis of tetramer through a coupling between Bn−BTG_2−OH and H−BTG_2−OMe gave lower yields using either PyBroP or HATU (8% and 11%, respectively).

The tetramer **4** was hydrolyzed to **4a** with LiOH, and the pentamer **5** was obtained in 50% yield through the coupling of **4a** with **1b** using HATU in DMF solution and purification by crystallization from MeOH.

The ^{1}H NMR spectra of dimer **2** in $CDCl_3$, DMSO-d_6, and CD_3OD showed two sets of signals of almost equal intensity. This observation suggests the presence of two rotamers related to *E*/*Z* conformations of the amide bond (Figure 2). These are easily distinguished by the anisotropic

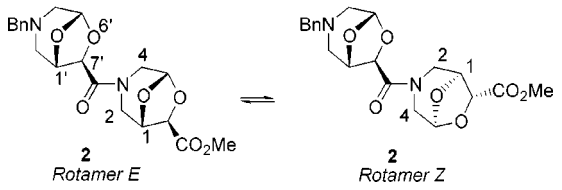


Figure 2.

effect of the carbonyl group[13] which causes a strong downfield shift (∼1 ppm with respect to monomer **1**) of the protons on C-2 in rotamers *E* and on protons on C-4 in rotamers *Z*. An energy barrier ($\Delta G^{\#}$) of 18.7 kcal/mol in DMSO-d_6 for the rotation of the amide bond in **2** was also determined by recording a series of ^{1}H NMR spectra with increasing temperature until the signals for the two rotamers were observed to coalesce.

Because of the high complexity of the ^{1}H NMR spectra for the longer oligomers, we were unable to gain information on the possible preferred conformation in solution by this means. Instead we found it more useful to record their CD spectra.[14]

Circular dichroism (CD) spectra of monomer **1**, dimer **2**, trimer **3**, tetramer **4**, and pentamer **5** were performed in MeOH (Figure 3, top) and TFE solutions (Figure 3, bottom).

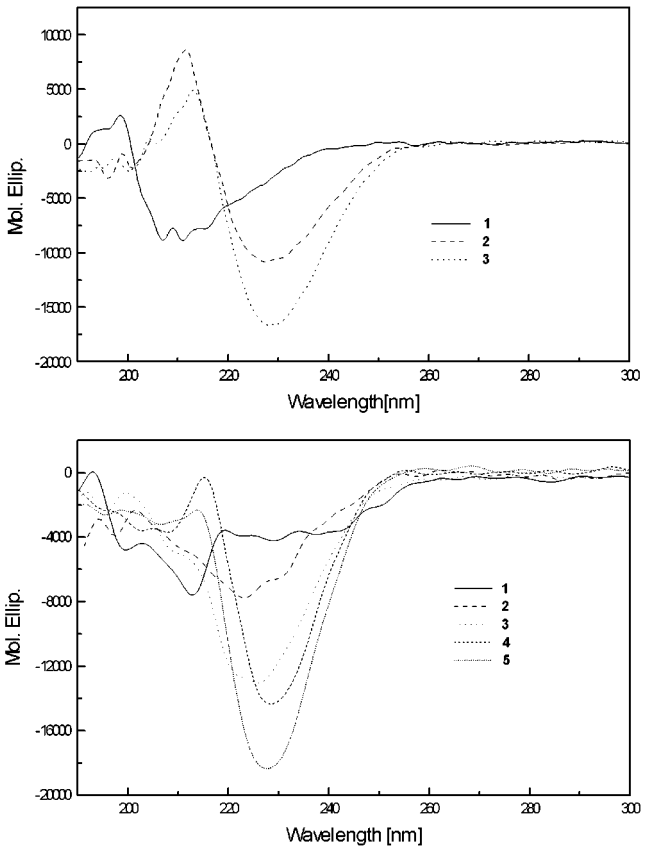


Figure 3. (Top) CD spectra of oligo-BTG in MeOH (100 μM): monomer **1**, dimer **2** trimer **3**. (Bottom) CD spectra of oligo-BTG in TFE (100 μM): monomer **1**, dimer **2**, trimer **3**, tetramer **4**, pentamer **5**.

Because of the low solubility of **4** and **5** in methanol, their CD spectra were recorded only in TFE. As expected, the oligomers gave a CD spectrum, both in MeOH and TFE, distinctly different from those of monomer **1**, due to the presence of amide bond(s) which determines a positive band and the crossover to negative values in MeOH (Figure 3,

(12) All new compounds were fully characterized by spectroscopic and analytical means.

top) and the negative bands in TFE (Figure 3, bottom). Each oligomer displays a negative Cotton effect at ca. 225−230 nm both in MeOH and TFE, with the intensity of the negative maximum increasing with oligomer length.

Also the positive band, at ca. 210−215 nm, in the MeOH spectra increases with the length of the chain, indicating an additive contribute of each unit to the ellipticity value. The presence of two bands in dimer **2** in TFE is noteworthy (a maximum at 223 nm and a shoulder at 228 nm), while for higher oligomers only one band is present (Figure 3). If we normalize the data also for the number of amide groups, which facilities the comparison among oligomers of different length, we observe that the spectra for tetramer and pentamer oligomers are nearly identical (Figure 4). Although not exhaustive, the analysis of the CD spectra of compounds **2**−**5** suggests that the formation of a secondary structure in the oligomers is possible. It is known in fact that the presence of a band whose intensity increases with the oligomer chain length is indicative of a secondary arrangement in solution. Furthermore, the normalized length-dependent trend for poly-BTG (Figure 4) is comparable to the length-dependent behavior of proline oligomers in spite of the fact that poly-BTG display lower mean residue ellipticity. Indeed, in both the cases, when the number of units was increased, the normalized CD spectra became quite similar, suggesting that the extent of secondary structure formation should reach the maximum.[15c] However, while the secondary structures are stabilized by the formation of the hydrogen bonds in the foldamers described previously by Seebach[2a] and Gellman,[2b] in our poly-BTG a secondary structure could arise from a conformationally restricted rotation around the amide bond.[15] This latter phenomenon could be more dependent upon the external conditions (i.e., temperature, solvent, concentration), and this could explain the differences observed in the complexity either between the CD and ^{1}H NMR spectra or the difference between the CD spectra in MeOH and TFE.

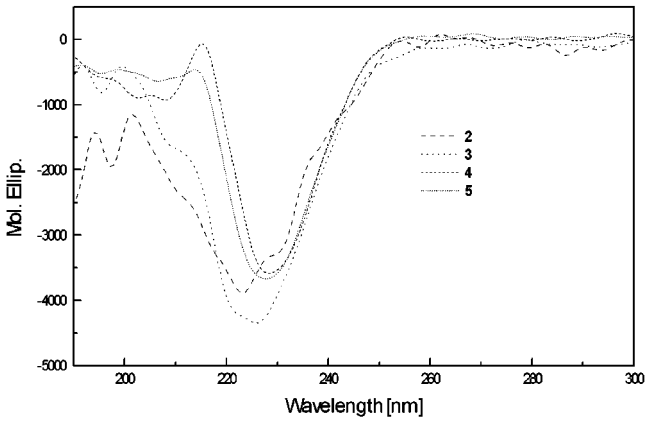


Figure 4. CD spectra of oligo-BTG in TFE (100 μM): dimer **2**, trimer **3**, tetramer **4**, pentamer **5**. Molar ellipticity values for **2**−**5** have been normalized for oligomer concentration and the number of amide groups.

In conclusion, we have demonstrated that oligomers **2**−**5** can be easily prepared using standard solution coupling procedures and have obtained preliminary evidences that poly-BTAa's could form secondary structures (foldamers) in solution.

It is probable that elongation of the polypeptide chain and introduction of a substituent at position 4 of BTAa monomer could affect the *E*/*Z* amide bond equilibrium[16] in the related oligomers, thus further favoring the formation of secondary structures in solution. Studies aimed at ascertaining this possibility are in progress.

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(13) Molecular modeling calculations (MacroModel v.6.5, Amber force-field, Monte Carlo conformational search) showed that there is a free rotation around the C(7′)−C(=O) bond. However, the conformations in which the C(=O) bond forms dihedral angles of about 112° and 150° with the C(7′)−O(6) bond are prevailing at room temperature.

(14) (a) Woody, R. W. *Circular Dichroism: Principles and Applications*; VCH: Weinheim, 1994 (b) Mulkerrin, M. G. In *Spectroscopic Methods for Determining Protein Structure in Solution*; Havel, H. A., Ed.; VCH: New York, 1996.

(15) For non-hydrogen-bonded secondary structure, see: (a) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4303−4308. (b) Armand, P.; Kirshenbaum, K.; Goldsmith, R. A.; Farr-Jones, S.; Barron, A. E.; Truong, K. T. V.; Dill, K. A.; Mierke, D. F.; Cohen, F. E.; Zuckermann, R. N. *Proc, Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4309−4314. (c) Huck, B. R.; Langenhan, J. M.; Gellman, S. *Org. Lett.* **1999**, *1*, 1717−1720. (d) Abele, S.; Vögtli, K.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1539−1558.

(16) (a) Beausoleil, E.; Lubell, W. *J. Am. Chem. Soc.* **1996**, *118*, 12902−12908. (b) Wu, W.-J.; Raleigh, P. *J. Org. Chem.* **1998**, *63*, 6689−6698. (c) Swarbrick, M. E.; Gosselin, F.; Lubell, W. *J. Org. Chem.* **1999**, *64*, 1993−2002 (d) Halab, L. Lubell, W. *J. Org. Chem.* **1999**, *64*, 3312−3321.