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Folding Propensity of Cyclohexylether-δ-peptides

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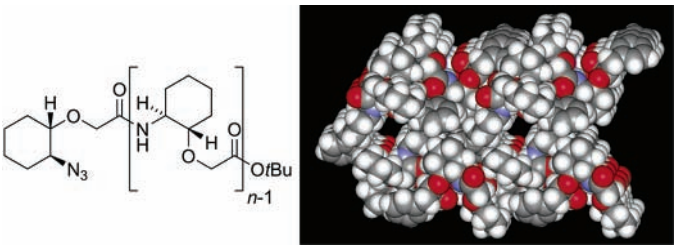
ABSTRACT



Linear (*n* = 2–18) and cyclic oligomers (*n* = 3–8) of a cyclohexylether-δ-amino acid (COA) were prepared in high yield and stereopurity. CD spectra of the linear oligomers were indicative of secondary structure formation. X-ray crystal structures of cyclic COA oligomers revealed hydrophobic packing and internal 5- and 10-membered-ring hydrogen bonds. Ether and amide oxygens reside preferably in an *ap* orientation. This conformational locking is apparently broken by a C-2 substituent in an asymmetric cyclotrimer, for which a zeolithe-like tubular structure was found.

Oligomers capable of folding into defined secondary structures have received considerable attention recently.[1] Among them the β-, γ-, and δ-peptides,[1,2] as well as a growing array of aromatic amide oligomers,[1,3] are most prominent. Oligomers featuring heteroatoms in the backbone remain comparatively unexplored, with the exception of sugar amino acids,[4] α-aminoxy acids,[5] and α-hydrazino acids.[6]

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(1) Reviews: (a) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015−2022. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (d) Hill, D. J.; Mi'o, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem Rev.* **2001**, *101*, 3893−4011. (e) Sanford, A. R.; Gong. B. *Curr. Org. Chem.* **2003**, *7*, 1649−1659. (f) Huc, I. *Eur. J. Org. Chem.* **2004**, *69*, 17−29. (g) Balbo Block, M. A.; Kaiser, C.; Khan, A.; Hecht, S. *Top. Curr. Chem.* **2004**, in press.

(2) Recent examples: (a) Gademann, K.; Hane, A.; Rueping, M.; Jaun, B.; Seebach, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1534−1537. (b) Langenhan, J. M.; Guzei, I. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2402−2405. (c) Brückner, A. M.; Chakraborty, P.; Gellman, S. H.; Diederichsen, U. *Angew. Chem., Int. Ed.* **2003**, *42*, 4395−4399. (d) Sharma, G. V. M.; Reddy, K. R.; Krishna, P. R.; Sankar, A. R.; Narsimulu, K.; Kumar, S. K.; Jayaprakash, P.; Jagannadh, B.; Kunwar, A. C. *J. Am. Chem. Soc.* **2003**, *125*, 13670−13671. (e) Hayen, A.; Schmitt, M. A.; Ngassa, F. N.; Thomasson, K. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 505−510. (f) Zhao, X.; Jia, M. X.; Jiang, X. K.; Wu, L. Z.; Li, Z. T.; Chen, G. J. *J. Org. Chem.* **2004**, *69*, 270−279.

(3) Recent examples: (a) Jiang, H.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448−3449. (b) Hecht, S.; Khan, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 6021−6024. (c) Estroff, L. A.; Incarvito, C. D.; Hamilton, A. D. *J. Am. Chem. Soc.* **2004**, *126*, 2−3. (d) Jiang, H.; Dolain, C.; Leger, J.-M.; Gornitzka, H.; Huc, I. *J. Am. Chem. Soc.* **2004**, *126*, 1034−1035. (e) Goto, H.; Heemstra, J. M.; Hill, D. J.; Moore, J. S. *Org. Lett.* **2004**, *6*, 889−892. (f) Yang, X. W.; Yuan, L. H.; Yamamoto, K.; Brown, A. L.; Feng, W.; Furukawa, M.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 3148−3162.

(4) Review: (a) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491−514. Recent examples: (b) Chakraborty, T. K.; Srinivasu, P.; Bikshapathy, E.; Nagaraj, R.; Vairamani, M.; Kiran Kumar, S.; Kunwar, A. C. *J. Org. Chem.* **2003**, *68*, 6257−6263. (c) van Well, R. M.; Marinelli, L.; Altona, C.; Erkelens, K.; Siegal, G.; van Raaij, M.; Llamas-Saiz, A. L.; Kessler, H.; Novellino, E.; Lavecchia, A.; van Boom, J. H.; Overhand, M. *J. Am. Chem. Soc.* **2003**, *125*, 10822−10829. (d) Smith, M. D.; Claridge, T. D. W.; Sansom, M. S. P.; Fleet, G. W. *J. Org. Biomol. Chem.* **2003**, *1*, 3647−3655. (e) Grotenbreg, G. M.; Timmer, M. S. M.; Llamas-Saiz, A. L.; Verdoes, M.; van der Marel, G. A.; van Raaij, M. J.; Overkleeft H. S.; Overhand, M. *J. Am. Chem. Soc.* **2004**, *126*, 3444−3446.

(5) (a) Yang, D.; Qu, J.; Li, W.; Zhang, Y.-H.; Ren, Y.; Wang, D.-P.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 14452−14457. (b) Yang, D.; Qu, J.; Li, W.; Wang, D.-P.; Ren, Y.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 14452−14457.

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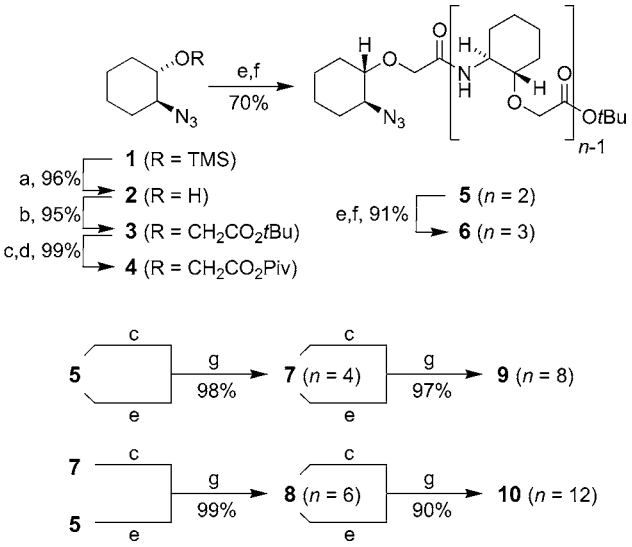
Scheme 1. Synthesis of Discrete COA Oligomers[a]



[a] (a) Cat. TFA, MeOH; (b) $BrCH_2COOtBu$, NaOH, cat. TBABr, toluene; (c) TFA/CH_2Cl_2 1:1; (d) PivCl, NEt_3; (e) **3**, H_2, 5% Pd/C, MeOH; (f) **4**, DMF, 0 °C; (g) HOBt, EDC, $EtN(iPr)_2$, CH_2Cl_2.

We have studied THF[7,8] as well as cyclohexylether-δ-amino acids[9] (COAs) as building blocks in artificial ion channels.[8,9] Cyclohexylether-δ-amino acids have been found to induce novel ion channel properties when inserted into the gramicidin A peptide sequence.[9] To gain insight into the secondary structure forming ("foldamer") properties of ether-δ-amino acids, a study of COA oligomers was initiated. Of particular interest was the influence of the ether oxygens on the resulting δ-peptide's conformation.

Toward this goal COA oligomers from $n = 2-12$ were independently synthesized, purified, and characterized (Scheme 1). The synthesis was initially based on Jacobsen's asymmetric ring opening of cyclohexene oxide.[10] Azide **1** (93% ee) was desilylated and alkylated under phase-transfer conditions[11] to yield δ-amino acid monomer **3** on a 30-g scale. The dimerization to **5** was best achieved via the mixed anhydride **4**, as normal peptide coupling conditions (HOBt/EDC, HATU) were hampered by δ-lactam formation to variable degrees. Dipeptide **5** was obtained isomerically pure by crystallization[9] and then extended to tripeptide **6** in the same fashion. At this stage, diastereomeric impurities could be removed by chromatography.

To avoid the cumbersome accumulation of minor stereoisomers, the higher COA oligomers were assembled in high

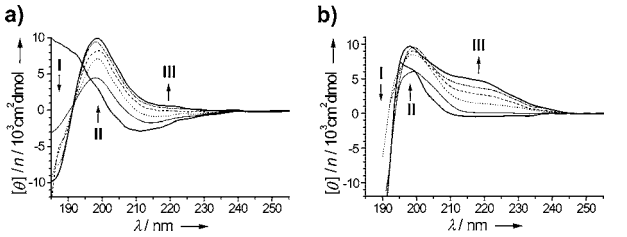


Figure 1. Overlay of normalized CD spectra of COA oligomers **5**−**10** at constant concentration of residues: $c = 1/n$ mM for $n = 2, 3, 4, 6, 8, 12$ in (a) H_2O/CH_3CN 75:25 or (b) *n*-hexane/*i*-PrOH 95:5.

yields by recursive fragment couplings from the stereopure building blocks **5** and **6** using standard solution-phase peptide technology (Scheme 1). Interestingly, albeit dimer **5** was a solid, all of the higher linear oligomers **6**−**10** ($n = 3-12$) were found to be noncrystalline and freely soluble in many solvents.

Severe signal overlap in the spectra of the homooligomeric peptides prohibited the extraction of sufficient 3-D information from NMR spectra. Therefore, CD spectra of the peptides were recorded for characterization (Figure 1). In going from dimer **5** to dodecamer **10**, strong negative (**I**, ca. 182 nm) and positive (**II**, 198 nm) bands developed with increasing chain length in polar protic solvents. In nonpolar organic solvents the bands **I** and **II** were equally observed, but an additional positive band (**III**) at 218 nm appeared with increasing chain length.

It can be concluded that a higher ordered structure is formed in either case. Whereas in polar solvents a single species seems to predominate, a more complex fold (or mixture) is realized for the COA-δ-peptides in nonpolar solvents. Although some resemblance with reported CD spectra for helical oligomers was apparent, notably, with β-peptide helices,[1c] more structural information was needed, and we turned our attention to cyclic COA-δ-peptides.

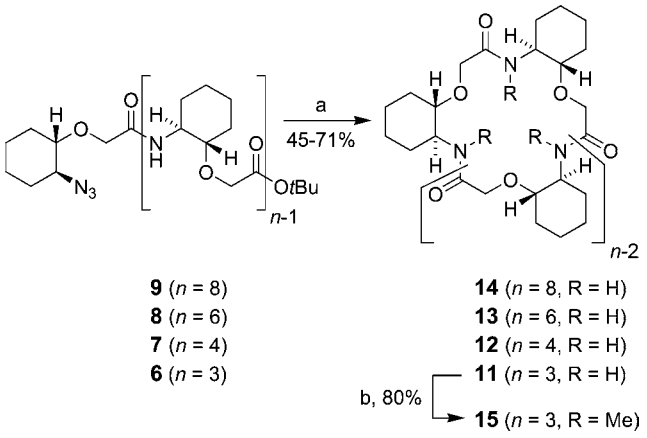
Toward this end, the free amino acids resulting from C- and N-terminal deprotection of **6**−**9** were cyclized using HATU/HOAt.[12] Good yields of the cyclic δ-peptides **11**−**14** were obtained (Scheme 2) under high-dilution conditions. Even the largest compound **14** (ring size, 48 atoms) was isolated in 45% yield, with the shorter COA-δ-peptides giving better results. Notably, no products resulting from premature oligomerization (dimers, trimers) were detected.

The observation of the rather facile ring closures indicated an apparent reduction in the degrees of freedom for the cyclization precursors (vide infra). However, a strictly helical preorganization should lead to an increased propensity for oligomerization instead of cyclization for the longer ether-δ-peptides (especially **9**) and was therefore deemed less likely at this point.

As opposed to their linear counterparts **5**−**10**, the cyclic COA-δ-peptides **11**−**14** were found to be solids of low

(6) Lelais, G.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 4152−4168.
(7) (a) Schrey, A.; Osterkamp, F.; Straudi, A.; Rickert, C.; Wagner, H.; Koert, U.; Herrschaft, B.; Harms, K. *Eur. J. Org. Chem.* **1999**, 2977−2990. (b) Koert, U. *J. Prakt. Chem.* **2000**, *342*, 325−333.
(8) (a) Schrey, A.; Vescovi. A.; Knoll, A.; Rickert, C.; Koert, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 900−902. (b) Fidzinski, P.; Knoll, A.; Rosenthal, R.; Schrey, A.; Vescovi, A.; Koert, U.; Wiederholt, M.; Strauss, O. *Chem. Biol.* **2003**, *10*, 35−43. (c) Vescovi, A.; Knoll, A.; Koert, U. *Org. Biomol. Chem.* **2003**, *1*, 2983−2997.
(9) Arndt, H.-D.; Knoll, A.; Koert, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 2076−2078.
(10) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898.
(11) Pietraszkiewicz, M.; Jurczak, J. *Tetrahedron* **1984**, *40*, 2967−2970.
(12) (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398. (b) Ehrlich, A.; Heyne, H.-U.; Winter, R.; Beyermann, M.; Haber, H.; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1996**, *61*, 8831−8838.

Scheme 2. Synthesis of Cyclic COA Oligomers[a]



[a] (a) (i) 50% TFA, (ii) H_2, 5% Pd/C, MeOH, (iii) slow addition (6 h) to HATU, HOAt, EtN(*i*Pr)$_2$, CH_2Cl_2/DMF 10:1; (b) NaH, MeI, DMF.

solubility, indicating a high tendency for aggregation.[13] Crystallization efforts led mainly to microcrystalline powders or high levels of included solvent. Both facts prohibited X-ray structure elucidation up to now.

In an attempt to break the apparent aggregational tendency,[14] the cyclic trimer **11** was permethylated at the amide nitrogens to yield cycle **15** devoid of H-bond donors (Scheme 2). Gratifyingly, **15** could be obtained from acetone in single crystals suitable for X-ray structure analysis (Figure 2). Two molecules of **15** with very similar conformations are located with a molecule of acetone in the asymmetric unit. The conformation of **15** is nonsymmetric[15] and dominated by the *N*-Me groups, which adopt a *ap* orientation with regard to the neighboring C−H bond. Two amide bonds are found in the *cis*-configuration, leading to a general saddle-shaped molecule. The acetone molecules line up in channel-like voids formed by the packing of the rigid saddles of **15**. Interestingly, no stable single crystals could be obtained in the absence of acetone.

It was reasoned that breaking the symmetry and repetitiveness of individual oligomers might not only result in more disperse NMR signals but moreover lead to materials with local orientation and ultimately better folding properties. We decided to explore C-2 substitution, as present in the THF and THP amino acids.[7] Initial attempts to alkylate monomer **3** led to unseparable mixtures. Additionally, we were unable to obtain **3** or its precursors in an enantiopure form via the present route. Therefore, an alternative route was developed (Scheme 3).

Cyclohexene oxide **16** was ring opened[16] with readily available (*S*)-phenethylamine and derivatized with chloroacetyl chloride to yield **17** and its diastereomer, which were easily separated by chromatography or crystallization. KO*t*Bu induced the ring closure to ether **18**, which was characterized by X-ray crystallography. The auxiliary group was then removed with HCOOH[17] (**18** → **19**), and the amide nitrogen was derivatized with Z-Cl to give amide **20**. Lactam **19** was independently synthesized from **1** for comparison, confirming all stereochemical assignments. Lactam **20** was found to be quite sensitive under enolate alkylation conditions and prone to overalkylation. However, the alkylation proceeded with excellent stereocontrol (149:1) using LiHMDS under stoichiometric conditions.[18]

Ring opening of **21** with LiOOH[19] then provided C-2 benzyl-substituted δ-amino acid monomer **22**. Elongation with COA dimer **4** gave the δ-tripeptide **23**. After C- and N-terminal deprotection this was cyclized under the same conditions as the COA oligomers to cyclo-δ-peptide **24** in 86% isolated yield. This exceptional yield indicates that δ-peptide **23** must be conformationally set up very well for cyclization.

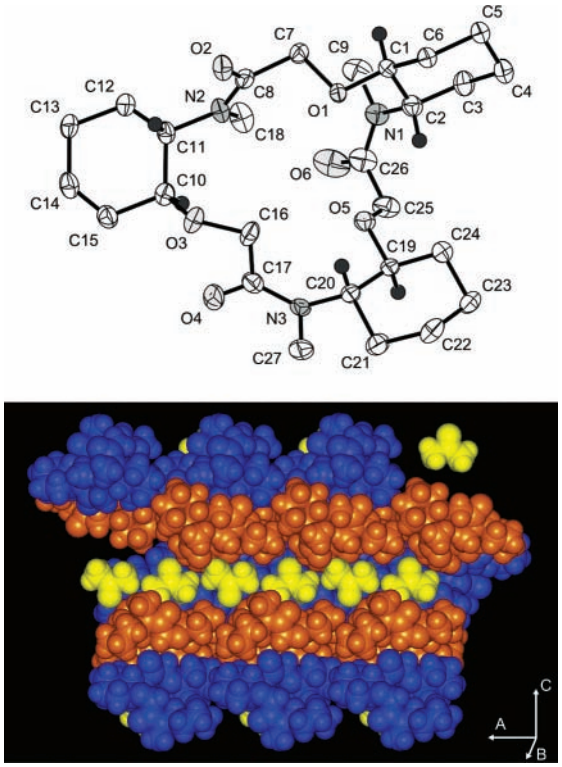


Figure 2. Crystal structure analysis of methylated cyclotrimer **15**. (Top) Conformation in the solid state; only one molecule is shown. H-atoms at ring junctions are highlighted in gray. (Bottom) Crystal packing viewed along the *B*-axis. The two non-symmetry-related molecules of **15** in the asymmetric unit are color coded in blue and orange, and acetone molecules are color coded in yellow.

(13) Interestingly, the cyclotrimers **11** and **15** were found to form stable 1:1 adducts with KI, which were freely soluble in CH_2Cl_2.

(14) Ghadiri, M. R.; Kobayashi, K.; Granja, J. R.; Chaha, R. K.; McRee, D. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 93−95.

(15) In solution, compound **15** does not adopt an averaged C_3-symmetric conformation. As a result of slowly interconverting amide bond rotamers, a complex mixture of conformers is observed.

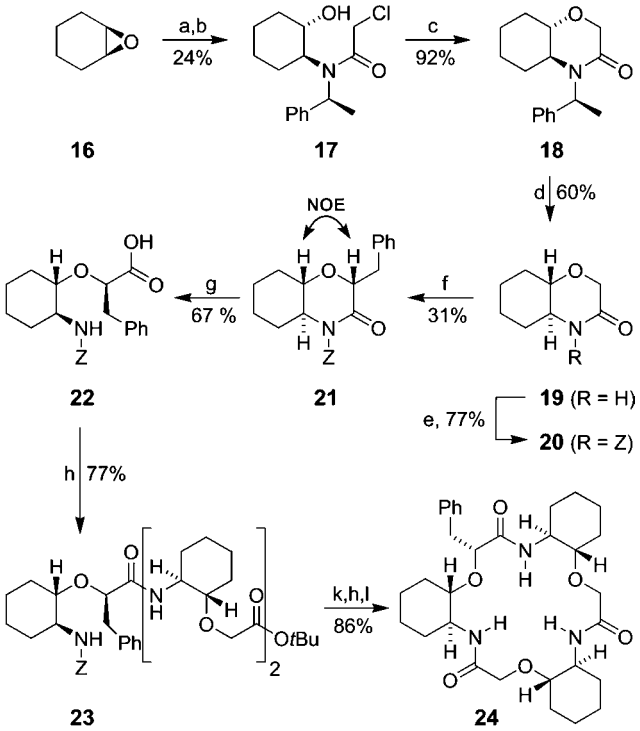
(16) de Parrodi, C. A.; Juaristi, E.; Quintero, L.; Clara-Sosa, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1075−1082.

(17) Semple, J. E.; Joullié, M. M.; Lysenko, Z.; Wang, P. C. *J. Am. Chem. Soc.* **1980**, *102*, 7505−7510.

(18) A base-catalyzed equilibration of C-2 cannot be ruled out at this point. The stereochemistry was initially deduced from characteristic NOE data and later confirmed by the X-ray structure of **24**.

(19) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

Scheme 3. Synthesis of Asymmetric Cyclic COA Trimer **24**[a]



[a] (a) (*S*)-1-Phenylethylamine, $LiClO_4$, CH_3CN, Δ; (b) $ClCH_2COCl$, NEt_3, CH_2Cl_2; (c) KO*t*Bu, THF, 0 °C; (d) HCOOH, Δ; (e) BuLi, Z-Cl, −78 °C; (f) LiHMDS, BnBr, −78 °C; (g) LiOOH, THF/H_2O; (h) **5**, H_2, 5% Pd/C, MeOH, then **22**, HATU, HOAt, $EtN(iPr)_2$, DMF; (k) 50% TFA; (h) H_2, 5% Pd/C, MeOH, (l) slow addition (6 h) to HATU, HOAt, $EtN(iPr)_2$, CH_2Cl_2/DMF 10:1.

The sensitive single crystals of **24** grown from wet $CHCl_3$ could be analyzed by X-ray crystallography (Figure 3). Again, the cyclopeptide **24** adopts a saddle-like conformation in the crystal but is folded in the opposite direction as **15**. In the unsubstituted COA subunits the glycolic amide portions in **24** adopt a *sp* orientation. Such a five-membered ring H-bond to the ether oxygen was observed before in the crystal structure of dimer **5**[9] and is also present in α-aminoxy acid peptides.[5] On the other hand, the C-2 substituted ether-*δ*-amino acid assumes a conformation where the Bn substituent avoids *syn*-pentane strain.[20] This allows the amide function to rotate and form a transannular, 10-membered-ring H-bond, as well as a connective H-bond with the next molecule in the crystal. Hydrophobic packing of these chains then leads to a zeolithe-like structure with narrow channels along the *a*-axis.

The channels are filled with partially ordered water molecules (12/cell). It is interesting to note, that the channels are not formed by a perpendicular stacking of rings.

(20) (a) Tsuzuki, S.; Schäfer, L.; Goto, H.; Jemmis, E. D.; Hosoya, H.; Siam, K.; Tanabe, K.; Osawa, E. *J. Am. Chem. Soc.* **1991**, *113*, 4665−4671. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054−2070.

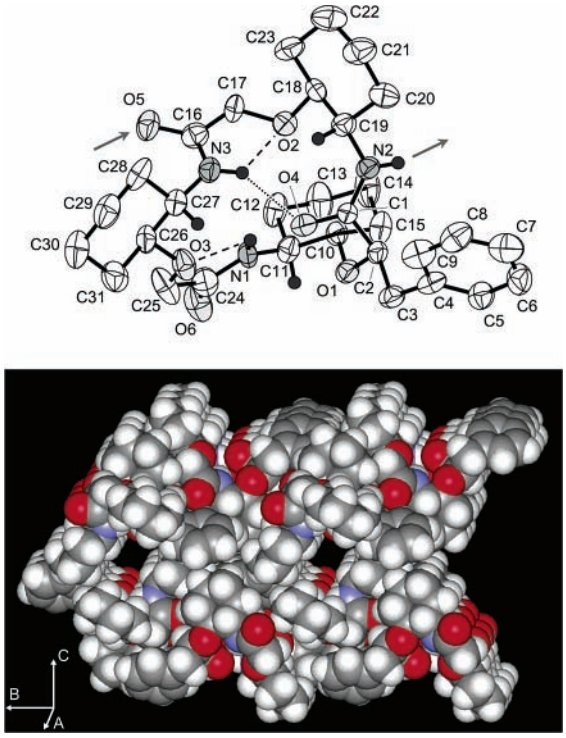


Figure 3. Crystal structure analysis of asymmetric trimer **24**. (Top) Conformation in the solid state; intramolecular five-membered-ring H-bonds are dashed, 10-membered-ring H-bond is dotted. (Bottom) Crystal packing viewed along the crystallographic *A*-axis. Residual electron density in the channels is omitted for clarity.

In summary, the present data suggests that ether-*δ*-amino acids lacking C-2 substituents will adopt one low-energy conformation featuring a five-membered-ring H-bond to the preceding residue oxygen, dominating the general secondary structure. This linearization reduces the degrees of freedom in solution, corroborated by the rather facile cyclization reactions. C-2 substitution obviously breaks this preference and gives rise to a more complex folding pattern. This may become a viable tool for inducing long-range H-bond formation in cyclohexyl ether-*δ*-peptides. In extension the breaking of symmetry and repetitiveness could lead to much better organized foldamers in the future.

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Supporting Information Available: GC and HPLC traces for **1** and **21**, crystal structures of **18** and **19**, experimental procedures, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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