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Cyclic Oligocarbamates

R. Warrass, K.-H. Wiesmüller, G. Jung*

Institute of Organic Chemistry, University of Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen, Germany

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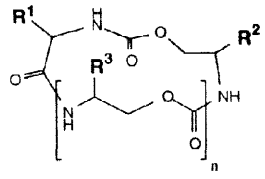
Abstract: Cyclic tri-, tetra-, penta-, and hexacarbamates are obtained in high yield and purity by a very efficient automated solid phase synthesis of side chain protected linear derivatives followed by a condensation reaction in solution. A high diversity of the novel cyclooligomers is accessible by using all amino alcohols of the proteinogenic amino acids.

In addition to automated, parallel small molecule synthesis for high throughput screening, there is an interest in linear and cyclic oligomeric structures, which are synthesized repetitively under identical conditions to allow rapid deconvolution procedures via combinatorial sublibraries. Peptidomimetics are made in order to keep the advantages of peptides, to achieve specific 3D structures and to overcome pharmacological problems simultaneously improving their reactivity in bioassays. A selection of known mimetics includes cyclic peptides[1], urethanes[2], ureas[3], ureapeptoids[4], peptoids[5,6], hydrazinopeptides[7], oligosulfones[8], retro-inverso peptides[9] and β-peptides[10].



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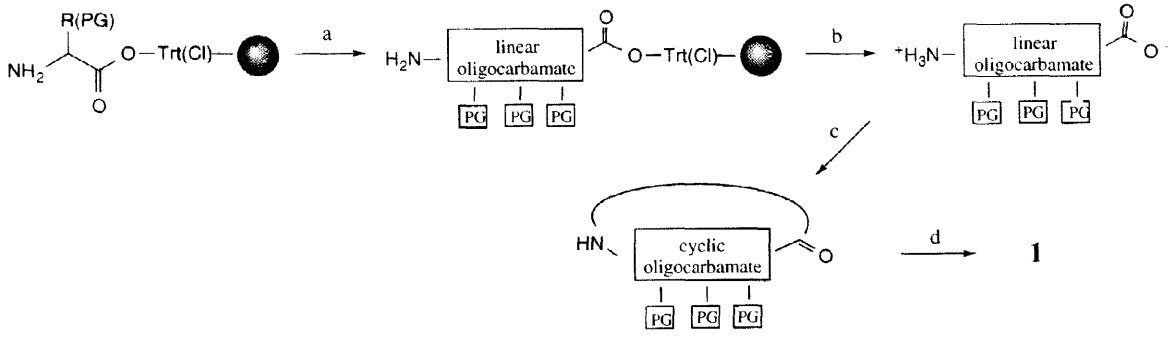
Here we present the first successful synthesis of cyclic oligocarbamates (Scheme 1). For the preparation of the linear oligocarbamates firstly N-Fmoc protected β-amino alcohols are dissolved in NMP and converted to activated carbonates *in situ* by adding solid dibenzotriazolyl carbonate and pyridine in the vials of a synthesizer[11]. After a short warming-up of the suspension a rather stabile clear solution of activated carbonate is obtained, which can be used over a period of a few days.



Scheme 1: Synthesis of cyclic oligocarbamates. (a) Solid phase synthesis of linear oligocarbamates (see text). (b) HFIP/DCM (2:3). (c) TBTU/HOBt in DCM; (d) TFA/TIS/water or TFA/scavenger K; (PG, side chain protecting groups of amino alcohols: C(Trt)-ol, D(tBu)-ol, N(Trt)-ol, R(Pmc)-ol, S(tBu)-ol).

N-Fmoc - protected amino carbonates are coupled to amino acids immobilized on 2-chloro-trityl chlorid resins. The carbamate bond formation is catalyzed by adding DIEA and found to be complete after 3-6 h (ninhydrin test). Following Fmoc removal with piperidine, the next coupling step can be performed.

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Using this strategy linear trimers, tetramers, pentamers and hexamers are synthesized. The side chain protected oligocarbamates are cleaved from the resin with HFIP / DCM (2:3). After removal of solvents, the remaining oligocarbamates are diluted in DCM (0.001 M) and cyclized with TBTU / HOBt. After aqueous washing steps, the side chain protecting groups are cleaved with TFA / scavenger to give the deprotected crude cyclic oligocarbamates in about 65 % yield and high purity (HPLC, MS, Table 1).

Table 1: Characterization of linear oligocarbamates and their cyclic analogs by MS and HPLC.

Entry	Sequences	Protected linear oligocarbamate	Unprotected cyclic oligocarbamate		
		Purity[1] [%]	Purity[1] [%]	MS (theor.) [amu]	Yield [%]
1	c[Pc-Rc-Dc-Fc-dAla]	89	79	707.0 (707.5)	62
2	c[Gc-Rc-Dc-Fc-dAla]	86	73	667.1 (667.5)	55
3	c[Gc-Rc-Dc-Sc-dAla]	86	84	607.1 (607.4)	73
4	c[Nc-Vc-F]	93	96	421.3 (421.5)	74
5	c[Sc-Nc-Vc-F]	95	98	538.3 (538.5)	60
6	c[Ac-Sc-Nc-Vc-F]	95	87	639.3 (639.5)	65
7	c[Cc-Fc-Cc-Fc-Cc-F][2]	62	70	901.3 (901.8)	53

[1] HPLC of the crude products; 0-100% ACN water in 45 min, λ = 214 nm, % purity based on peak areas assuming similar ε.
[2] due to an incomplete coupling of one Fmoc-C(Trt)-ol building block, the linear product (crude yield 62%) was purified by HPLC.

Following our elaborated protocols, a broad class of novel oligomeric tools can be generated. So far all proteinogenic amino alcohols plus several others, have been successfully composed to yield oligocarbamates and heterooligomers containing also amino acids. The constrained conformation of cyclic oligocarbamates, their likely proteolytic stability and the lipophilic character of the backbone make this class of molecules interesting structures in the lead structure discovery process.

Acknowledgements

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References and Notes

Abbreviations: AAc, carbamate residue derived from a amino acid (AA); c[...], cyclized sequence; DBTC, di(1-benzotriazolyl) carbonate; HFIP, hexafluoro-2-propanol; R", side chain residues of amino acids (A, C, D, F, G, N, R, S, V); TBTU, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TFA, trifluoroacetic acid; TIS, triisopropylsilane.

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