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Peptides

Reversible Covalent End-Capping of Collagen Model Peptides

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Abstract: The combination of supramolecular aggregation of collagen model peptides with reversible covalent end-capping of the formed triple helix in a single experimental set-up yielded minicollagens, which were characterized by a single melting temperature. In spite of the numerous possible reaction intermediates, a specific synthetic collagen with a leading, middle and trailing strand is formed in a highly cooperative self-assembly process.

Collagen is a fibrous protein that occurs in different forms of life such as glass sponges or mammalians.[1,2] Its high structural diversity originates from a multitude of mutations and post-translational modifications (PTMs) which bulge or kink the triple-helical framework formed by the dominant tripeptide motif proline–hydroxyproline–glycine (POG).[3–5] Glycosylation, phosphorylation, hydroxylation and inter- or intra-triple-helical crosslinks lead to a multi-facetted local structural microheterogeneity which make collagen a scaffold for cell adhesion, biomineralization and many more physiological processes.[6–12] The local twisting, bending, widening of the triple-helical structure guides mobile cells such as a braille code through the connective tissue.[13] Collagens from natural sources are not suitable for the quantification of stabilizing or destabilizing effects of a selected type of PTM without the simultaneous interference of others. Synthetic minicollagens were developed to investigate one type of PTM at a specific position within the triple helix. The deconvolution achieved in such model systems (Figure 1) identifies stabilizing or destabilizing effects which are measured as increased or decreased melting temperatures of the model triple helix.[6–18] Comparing different collagen model peptides (CMP) with a reference helix such as Ac-$(POG)_7$-NH_2 identifies the effect of a selected PTM.[7,11,14] Most trimeric CMPs are assembled from one type of collagen strand but there are also heterotrimeric CMPs, which are stabilized by complementary charges.[19–21] Other trimers are stabilized by metal coordination, although its only moderate stabilizing effects found no application beyond the proof of principle.[17,18] Furthermore, collagen single-strands were linked by biological methods[22–24] or stabilized with polymers or dendrimers.[25,26] In spite of the progress in synthetic collagen-like aggregates with selected properties such as predetermined register of single strands or amino acid building blocks that increase the melting temperature of the triple-helix, a method for the assembly of a natural host–guest sequence in a predetermined register as a substrate for collagen binding proteins is still missing.[27] Therefore, we set out to develop a chiral end-cap that can fix the single strands in a registers of leading middle and trailing strand in a covalent reversible manner.

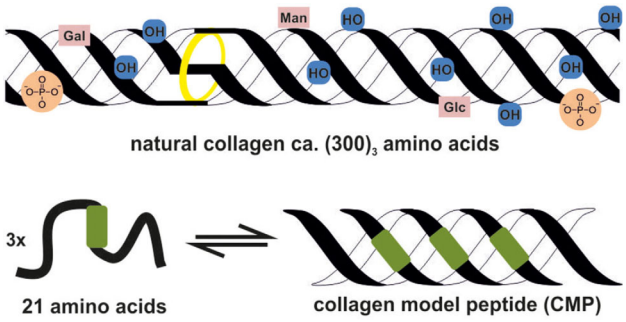

Figure 1. Top: The hydroxylation of Pro (blue: Hyp) is the most common stabilizing PTM of collagen. The combined influence of carbohydrates, phosphorylation etc. are less well understood. The yellow ring symbolizes interstrand covalent bonds. Below: The deconvolution of microheterogeneity in synthetic triple-helices with a single PTM (green) on each peptide strand.

Covalent cross-links that connect the three peptide strands of a triple-helix as well as linkages between different triple-helices increase the stability of natural collagens.[9,12,28] The dominant crosslinks in natural collagens are formed by condensation of hydroxylysine side chains between two triple helices as well as by disulfide bonds that fix the register of three single strands within a triple helix.[29] Artificially linked CMPs were investigated to better understand the influence of covalent crosslinking in natural collagens. Bonds between all three strands are feasible with at least one strand bearing two reactive groups.[9,12] Fixing the natural register of leading, middle and lagging strand of the triple helix by correctly placing the disulfides was incentive for the development of other collagen models.[12,30–33] Yet, installing covalent bonds between all three single-strands of the collagen helix requires numerous synthetic transformations and restricts the application of these techniques. A simpler approach towards covalently linked triple helices is the covalent end-capping of the CMP with an end-cap bearing three functional groups of complementary reactiv-

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ity to. Triesters were used by Goodman and Raines to efficiently end-cap triple-helices.[14,15,34] The Lys_2 branch also found application.[8,35] The concurrent C- and N-terminal end-capping to obtain a macrotricyclic ring system was a heroic effort.[16] Spacers such as 6-aminohexanoic acid between the collagen model peptides and the C-terminal Lys_2 end-cap decouple the triple-helix register from the potentially enhancing helicity of the chiral end-cap.[8] We recently described CMPs tethered with triamine caps formed by dipeptides of different stereochemistries and investigated the melting temperature of the end-capped helix and its biomimetic silicification properties.[36] Yet, the preparation of covalently end-capped helices is time-consuming because the separation of deletion mutants is tedious.

For the present study, we set out to reduce the synthetic effort towards covalently end-capped CMPs significantly by using reversible self-assembly from modular components what appeared as a practical method for triple-helical collagen. The self-assembly was expected to yield the thermodynamically most stable triple-helical product as schematically shown in Figure 2 together with the complex network of various not fully assembled species. Quantitative spectroscopic methods in solution are necessary to prove the completeness of the assembly process with defined assembly and register.

Cooperative effects from adequately chosen reactive groups are expected to shift the equilibrium directly from the disassembled state to the covalently end-capped triple helix. A two-state folding process requires NMR analytics because it is sensitive for the secondary structure (fast conformational exchange) and simultaneously quantifies the progress of the condensation reaction (slow chemical exchange). Benzoboroxoles and aromatic 1,2-diols such as catechols appeared as a good choice for the bio-orthogonal linkage between collagen and end-cap. Benzoboroxole was utilized for carbohydrate recognition by Hall, who described its reversible condensation with diols.[37–46] The heterogenic mixture of stereo- and regioisomers limits the NMR characterization for most carbohydrates or oligosaccharides. We recently described 1,2-*cis*-dihydroxylated bicyclic dipeptides that spontaneously form boronate esters with high diastereoselectivity. NMR spectroscopy identified the stereochemistry of the newly formed boron stereocenter within the spiro-oligocyclic ringsystem.[47] We characterized oligomeric supramolecular assemblies of branched amyloid-type peptides up to 10 kDa in water.[48] The present study uses similar boronate esters as reversible linkage between end-caps and CMP. The cooperative triple-helix formation of a CMP is expected to positively influence the threefold esterification of an end-cap. Reversibly end-capped CMPs were not reported so far, although boronate based reversible end-capping seemed very appropriate to enforce the supramolecular assembly of the triple-helix from three individual peptide strands. The modular self-assembling components allow the quantification of the melting temperature of the non-covalently assembled triple-helical strands and of the covalently assembled triple-helices from the same molecules by measuring the collagens without and in the presence of the cap. Even competition experiments between different peptides are possible. We expected that the moderate tendency of an individual boroxole to spontaneously form the boronate from the condensation with a diol under physiological conditions is pushed to completion by the trivalent character of the collagen-helix formed in the process.

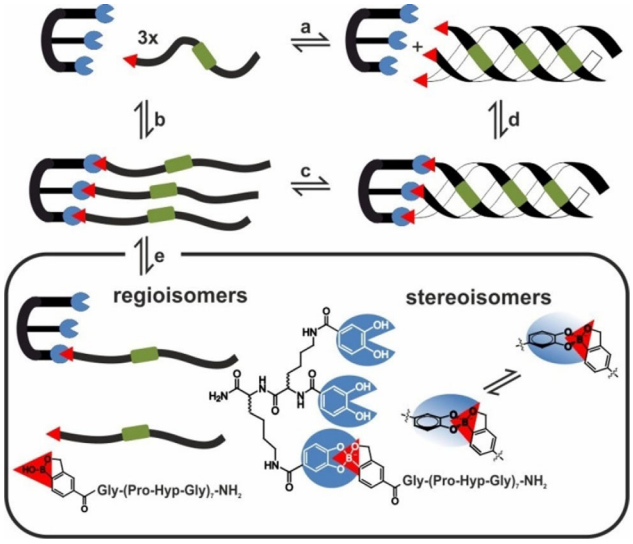

Figure 2. Four equilibria have to be considered for the reversible end-capping of a collagen triple-helix. (a) The formation of the CMP triple-helix without condensation with the end-cap. (b) The threefold condensation without triple-helix formation. (c) The triple-helix formation after condensation and (d) the threefold condensation after triple-helix formation. A potential PTM which either increases or decreases the cooperativity is shown as a green bar. (e) All incomplete condensation reactions are shown together with the functional groups of this study. Further details of the cooperative condensation reaction are discussed in the main text.

Figure 3 shows that the condensation of single benzoboroxole (**1**) with catechole (**2**) is in slow exchange on the NMR time scale (600 MHz). Spontaneous esterification is not complete under equimolar amounts of educts and high dilution conditions. The catechol shows 80% conversion at pH 7.4. The condensation of boroxoles to sugars needs significant excess of one component for completion.[40–43,47]

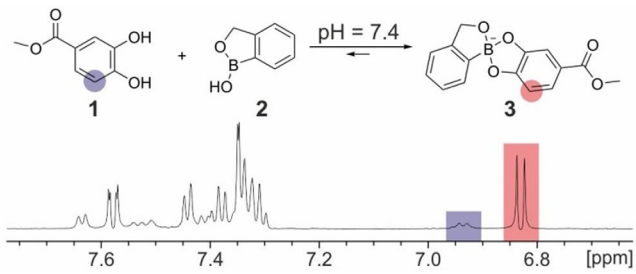

Figure 3. ^{1}H NMR (600 MHz) of 3 mM 3,4-dihydroxybenzoic acid methyl ester (**1**) and 3 mM benzoboroxole (**2**) in 50 mM pH 7.4 phosphate buffer at 300 K shows 80% conversion to boronate **3**.

Both functional groups are compatible with solid phase peptide synthesis (SPPS) and the boronate formation is complementary to other functional groups found in a CMP. Collagen single-strand **4** (Figure 4) was synthesized according to the op-

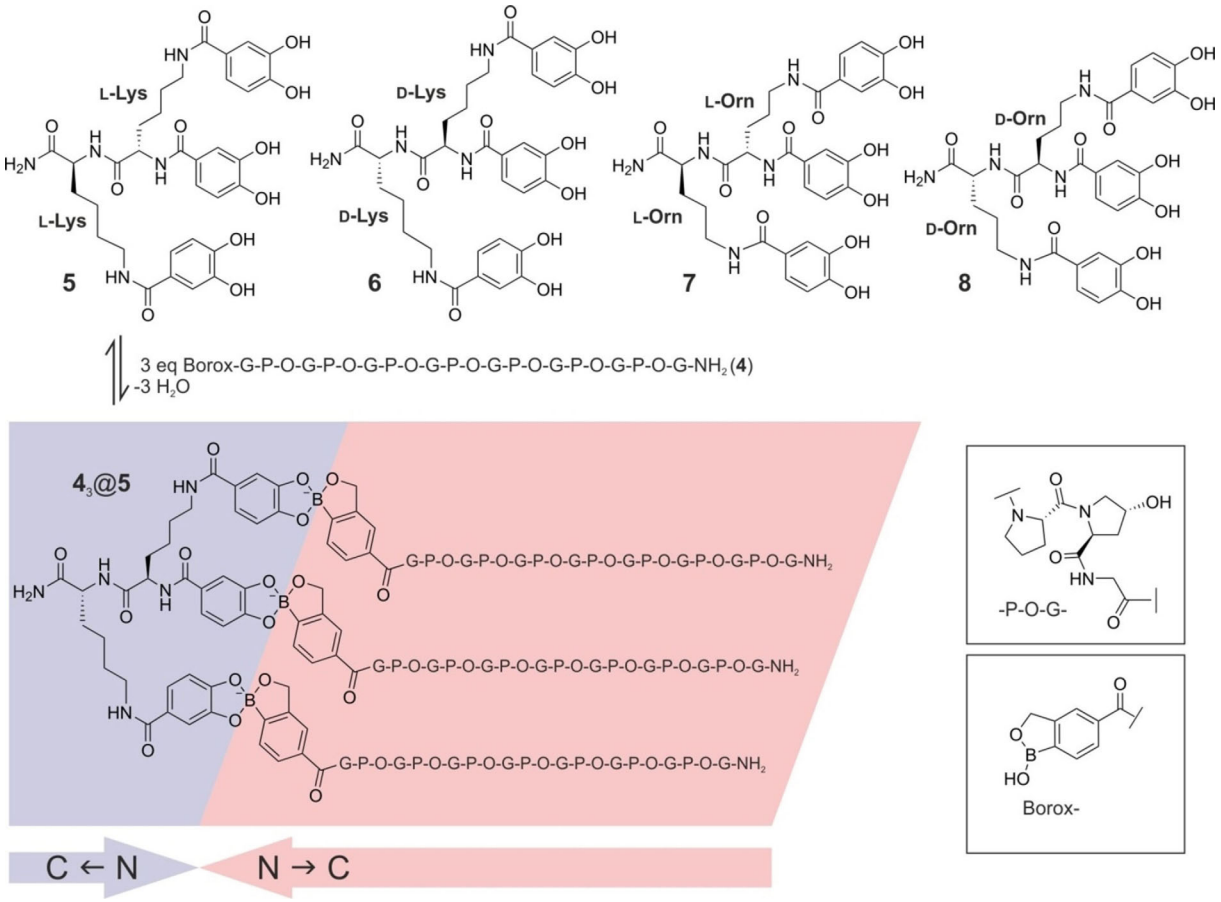

Figure 4. Four different dipeptide end-caps consisting of either L-Lys (**5**), D-Lys (**6**), L-Orn (**7**) or D-Orn (**8**) were investigated for the ability to stabilize the triple-helical assembly of peptide **4** which contains a $(POG)_7$ repeat functionalized with a N-terminal boroxole. The boronate ester $\mathbf{4_3}$**@5** is shown; the other esters $\mathbf{4_3}$**@6**, $\mathbf{4_3}$**@7**, and $\mathbf{4_3}$**@8** were obtained analogously. Arrows are drawn in the direction of *N*- to *C*-terminus of the peptides.

timized SPPS protocol described earlier.[11] The N-terminal glycine served as spacer between boroxole and the heptameric POG repeat (Further synthetic details are described in the Supporting Information). The main advantage of a modular approach was the combination of peptide **4** with different end-caps without the necessity to restart the synthesis from the building blocks. End-caps are easily accessible in alternative stereochemistries bearing three catechol functionalities which are expected to condense spontaneously with the benzoboroxole moiety. The use of dipeptides containing lysine or ornithine, modified with three catechol functionalities on side chains and N-terminus fulfilled these requirements. We investigated four dipeptide end-caps **5**–**8** with either butylene (Lys) or propylene spacer (Orn) and L,L or D,D stereochemistry, respectively (Figure 4).

The incomplete (80%) esterification of each individual boroxole may either destructively multiply to a mere $0.8^3 = 50\%$ overall yield or, the condensation is pushed to completion by the cooperativity of triple-helix formation after formation of the first ester bond. The two alternative scenarios which depend on pH and temperature were already shown in Figure 2. NMR spectroscopy is the method of choice for the analytical characterization of the supramolecular assemblies in solution because it is not influenced by aromatic rings which may act as chromophores in CD spectroscopy. NMR identifies the esterification from chemical shift variations and quantifies the triple-helical formation from the high-field shift of Pro-δH. The shielding of an individual proton which is caused by the triple-helix formation is a reliable proof of the temperature dependence of collagen.[10,11,15] This proton characterizes the cooperative unfolding of CMPs at elevated temperatures by its sigmoidal decrease of intensity and quantifies the triple-helix formation of boroxole-modified CMP **4** ($T_m = 48.2\,^\circ C$). Well-resolved ^1H NMR spectra were observed over the whole range between triple-helix (7 °C) and monomer (77 °C) (see Supporting Information.). The end-caps showed a high-resolution ^1H NMR and allowed for a complete signal assignment as well. Different from the individual components however, the equimolar mixture of boroxole peptide **4** and cap **7** (**4**/**7** = 3:1) showed severely broadened signals, similar to the NMR spectra observed for boroxols and carbohydrates[45] wherein the microheterogeneity of numerous regio- and diastereoisomeric boronates having slightly different chemical shifts prohibits the signal assignment. A complete NMR titration was expected to yield more data. Therefore, we titrated CMP **4** to a solution of cap **7** at pH 7.4 in phosphate buffer and monitored the consumption of the end-cap by ^1H NMR (Figure 5, complete spectra in the Supporting Information). Cap **7** was used because a

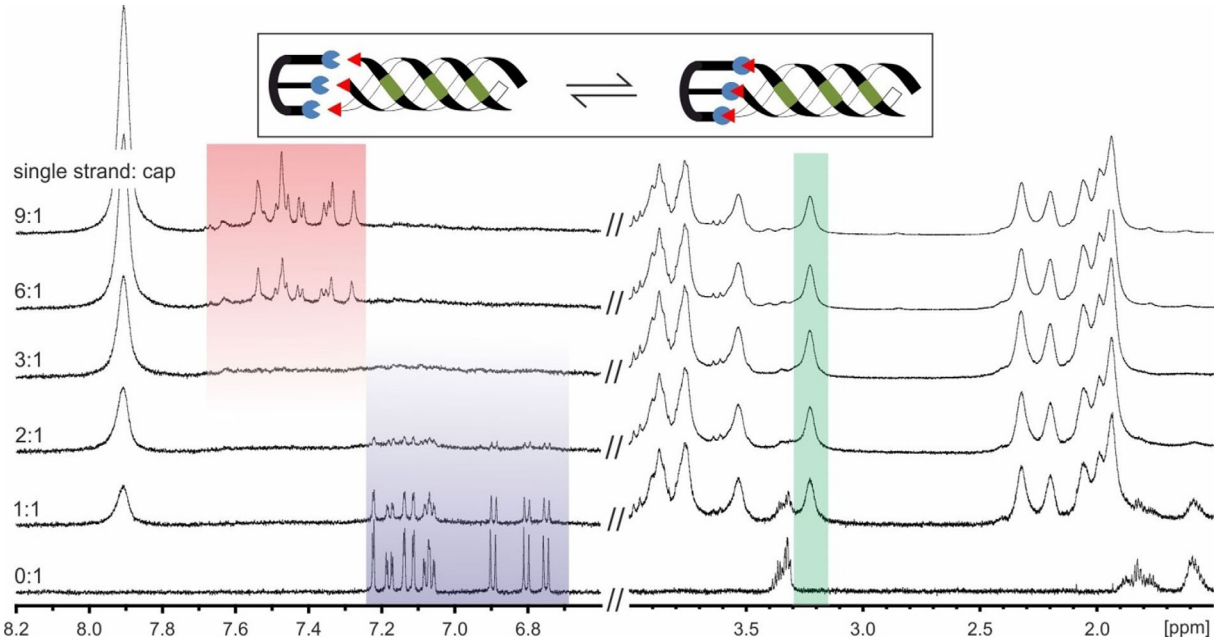

Figure 5. Expansions from the ^{1}H NMR (600 MHz, 300 K, D_2O) titration of benzoboroxole-substituted CMP **4** and the end-cap **7**. Due to the cooperative reversible condensation in a 3:1 ratio (**4**/**7**) at pH 7.4 phosphate buffer, there is neither unbound end-cap (aromatic protons in blue), nor unbound CMP (aromatic protons in red) visible, thus indicating that the boronate capping of this CMP yielding $\mathbf{4}_3$**@7** is largely complete.

the Orn–Orn dipeptide structure yields the highest stabilization of the triple-helix.[8,14,16,36] Substoichiometric amounts of **4** left completely unbound end-cap in the solution until the 3:1 ratio of peptide/cap (**4**/**7**) was reached. The detection of completely unbound end-cap with substoichiometric amounts of peptide is expected only for a cooperative threefold esterification. When the helix unfolds at temperatures above its melting temperature, significantly different NMR spectra are obtained because the esterification is no longer cooperative and leads to a complex mixture of incompletely esterified regioisomers (see Supporting Information). CD melting curves are interpreted under the assumption of quantitative triple-helix formation at low temperatures while NMR integrals quantify a maximum of 80% folded triple-helix for uncapped CMPs and for the end-capped CMPs of this study, too.[11] In a solution containing an equimolar 3:1 ratio of end-cap and triple helix, the cap quantitatively formed the desired boronate and the signals of the end-cap and the boroxole broadened close to disappearance. The signal broadening of the end-capped triple helix is restricted to the end-cap including the boroxole moiety of the CMP while the aliphatic signals of the POG heptamer are well resolved and not effected by signal broadening (Figure 5). Only after addition of an excess of CMP **4**, unbound triple helix appears in the ^{1}H NMR, indicated by well resolved aromatic boroxole protons. The exchange broadening of these specific protons at the equal ratio of end-cap and triple-helix proves the quantitative esterification, characteristic for a highly cooperative folding of the triple-helix and the complete binding of all three catechol moieties of the end-cap in a cooperative manner.

The absence of aromatic signals is interpreted by the microheterogeneity of the stereogenic esterification process as shown in Figure 2. Aliphatic protons are well resolved und not affected by line broadening (Pro-δH in green identifies the triple-helical assembly). The intensity of the signals between 1.5 and 4 ppm scales with the amount of added CMP **4** but integrals was adjusted for better clarity. Temperature dependent ^{1}H NMR spectra quantified the effect of capping on the melting temperature of the triple-helix. We used the characteristic upfield shift of Pro-δH in triple-helical environment (green in Figure 5) to calculate the folded fraction as reported previously.[11] The melting temperature of the CMP **4** without end-cap, served as reference with a value of 48.2 °C. The N-terminal benzoboroxole is a relatively bulky functionalization of the N-terminus in CMPs and showed neither significant stabilizing nor destabilizing effects on the helix. The increased melting temperature compared to Ac-$(POG)_7$-NH_2 (T_m = 44.6 °C) of about 4 °C is explained by the N-terminal glycine and boroxole. The stabilizing effect is roughly a third of 10–12 °C for a Pro-Hyp-Gly triplet.[11,49] To investigate of origin of this stabilization, we synthesized Ac-G-$(POG)_7$-NH_2 (**9**, T_m = 46.4 °C, see Supporting Information) and identified an equal contribution of the glycine und boroxole moiety to the increased melting temperature of CMP **4**. All end-caps from Figure 3 stabilized the triple helix from 7.2 to 10.1 °C. The D-Lys–D-Lys cap **8** had the lowest influence on the triple-helical stability resulting in an increase of the melting temperature of only 7.2 °C. End-capping with **5**–**7** led to a stabilization of 9.2, 10.1, and 9.6 °C, respectively (Figure 6). These values are in a similar range that is obtained by coordinative reversible stabilization with metal ions (4–10 °C)[17,18] but below the values measured for covalent irreversible C-terminal end-capping (up to 20 °C increase in T_m).[18,36] Our former study on covalent irreversible end-capping showed strong differences for T_m in the region 15 °C between

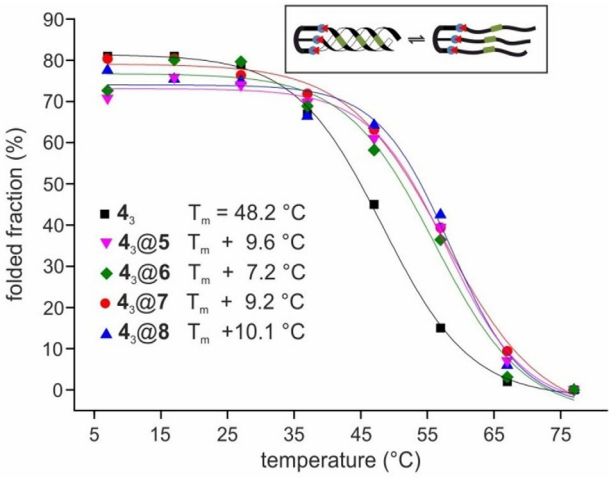

Figure 6. Melting curves of the uncapped CMP **4** and in presence of caps **5**, **6**, **7** or **8**. The percentage of folded fraction was derived from temperature dependent ^{1}H NMR (500 MHz) in pH 7.4 phosphate buffer at a CMP concentration of 3 mM.

ornithine and lysine that could not be observed for the Lys- and Orn-based caps here.[36] We explain the less pronounced influence of the structure and stereochemistry of the end-cap with the structural adaptability of the boroxole spacer that at least partially decouples the influence of the N-terminal cap. Consequently, the difference between the two Lys-based caps (**5** and **6**) is more pronounced than between the shorter Orn caps (**7** and **8**). Cap **7** has a similar stabilizing effect than the Lys caps but is more constrained and will serve as a basis for further optimisation of *N*-caps. Interestingly, end-capping has also a negligible influence of the overall folded fraction of about 80% based on the proline δ-protons in triple-helical environment.

In summary, we describe a novel modular approach for the covalent reversible end-capping of CMPs. The template effect of the triple-helix drives the boronate formation of catechol and benzoboroxole to completion even in aqueous solution, what enabled the quantitative binding of CMP **4** with caps **5**–**8**. In temperature dependent ^{1}H NMR studies also showed that all end-caps stabilized the triple-helix from 7 to 10 °C, but had little influence on the overall folded fraction of the triple-helix. Reversible end-capping of CMPs is not limited to boronates. The combination of two or even three different functional groups on the end-cap is an outlook to the straightforward assembly of covalently tethered CMPs.

Conflict of interest

The authors declare no conflict of interest.

Keywords: collagen model peptides · end-capping · NMR spectroscopy · supramolecular assembly

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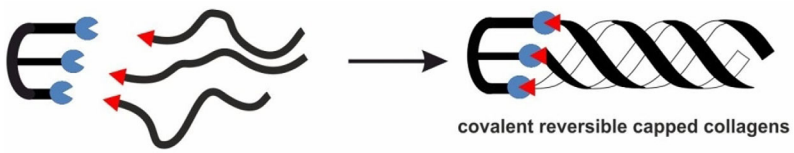

Supramolecular assembly of collagen model peptides was combined with reversible covalent end-capping. The quantitative formation of a single-capped triple helix was analysed via NMR spectroscopy. This leads to a novel class of end-capped collagen model peptides with less effort.

Peptides

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Reversible Covalent End-Capping of Collagen Model Peptides