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# Ion Pairing Between the Chain Ends Induces Folding of a Flexible Zwitterion in Methanol

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*Dedicated to Prof. Dr. Peter Welzel on the occasion of his 70th birthday*

**Keywords:** Ion pairing / Guanidinium cations / Supramolecular chemistry / Foldamers / Amino acids

A well defined folded loop structure can be induced in a flexible zwitterion **10** in the polar and protic solvent methanol by charge interactions between the two termini of the zwitterion. In **10** a (guanidiniocarbonyl)pyrrole moiety, a highly efficient oxoanion binding site, and a pyrrole-2-carboxylate unit serve as complementary binding sites at the ends of a flexible strand in which two amino acids, alanine and valine, are linked via a butylene spacer in a head-to-head orientation. Intramolecular ion pair formation between the carboxylate and the (guanidiniocarbonyl)pyrrole cation leads to the formation of a well defined loop as could be shown by NMR analysis (NOESY and H/D-exchange experiments) as well as molecular modelling calculations. Without this intramolecular charge interaction, as in the protected and hence uncharged precursor **9**, no loop is formed but rather weak intermolecular dimerization is observed.


## Introduction

The design of intrinsically flexible molecules which adopt a predictable and defined conformation in solution based on specific intramolecular non-covalent interactions is still a challenge despite the recent progress in this area over the last years,[1,2] especially in cases where structure formation in polar and protic solvents is considered. Most systems reported so far adopt specific structures only in organic solvents (e.g. chloroform), because they rely mainly on hydrogen bonds, which are easily disrupted when the polarity of the solvent increases. One way to overcome this problem is to use the much stronger metal–ligand interaction as a structure-dictating principle.[3] Also rigid scaffolds[4] or structurally biased turn-elements[5] have been used to induce a certain conformation within otherwise flexible molecules. We want to present here a zwitterion **10** with a flexible linker in between the two opposite charges which due to strong and directed charge interactions between the two termini of the molecule adopts a specific and well defined folded loop-structure even in the polar protic solvent methanol.

We reasoned that in a molecule of the general structure shown in Figure 1 strong interactions between the two chain ends should lead to an ordered, folded structure even without the need for a structure-inducing linker.[6] This, however, requires a very efficient ion pair formation in polar solution.[7] For this purpose we chose a (guanidiniocarbonyl)pyrrole– carboxylate ion pair,[8] as this modified guanidinium cation is one of the most efficient binding motifs for carboxylate anions.[9] Hence, in zwitterion **10** two amino acids were linked in a head-to-head orientation via a fully flexible 1,4-diaminobutane linker and were further modified at the chain ends with a (guanidiniocarbonyl)pyrrole and a pyrrole-2-carboxylate moiety, respectively.

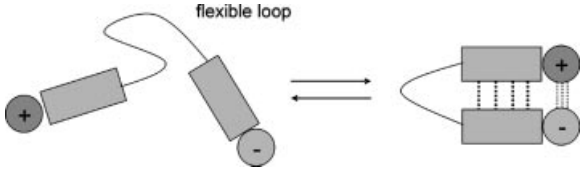


Figure 1. Inducing a folded structure by ion pairing between the chain ends of an otherwise flexible zwitterion.

## Results and Discussion

The synthesis of zwitterion **10** is described in Scheme 1. Cbz–Val–OH was coupled with mono-*t*Boc-protected 1,4-diaminobutane **1**[10] using HCTU in DMF to obtain **2** in excellent yields of 98%. The *t*Boc-protecting group was cleaved off (with TFA) and the resulting amine was treated with *t*Boc-Ala–OH to give **3** (yield 50%). Again, the *t*Boc group was removed with TFA and the free amine **4** was

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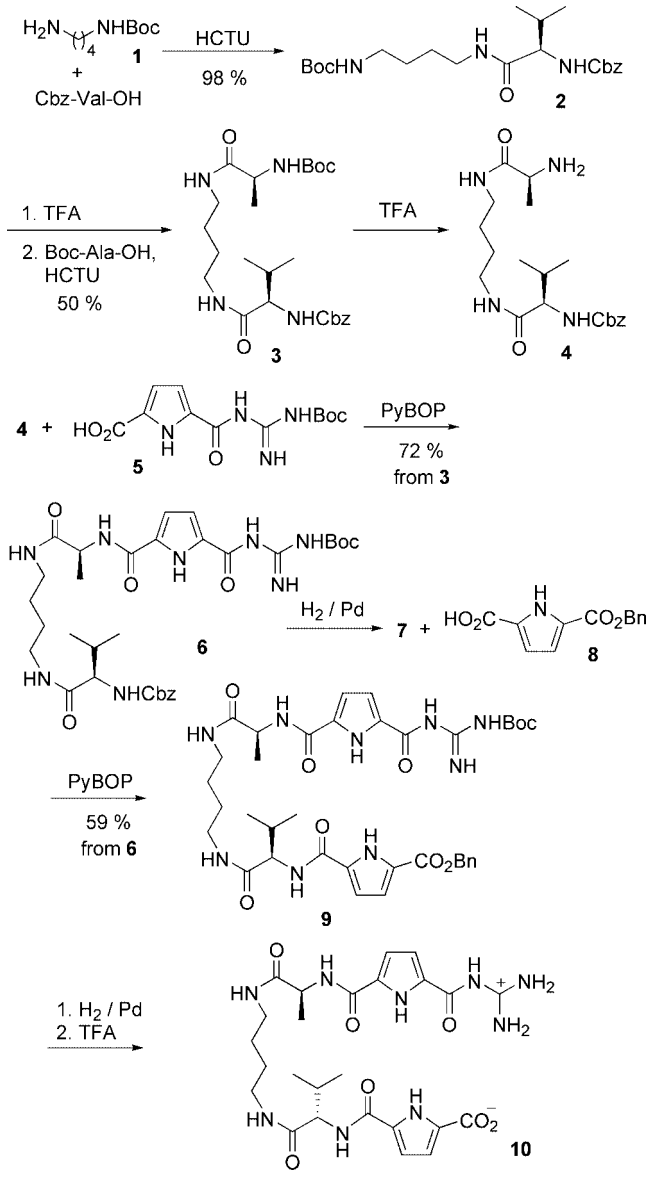
coupled with the *t*Boc-protected (guanidinocarbonyl)pyrrole **5**[11] using PyBOP in DMF to give **6** in good yields of 72%. The Cbz-goup on the valine residue in **6** was removed ($H_2$/Pd) and the resulting amine **7** was treated with pyrrole dicarboxylic acid mono benzyl ester **8** again using PyBOP as the coupling reagent to provide the protected model system **9**. Finally, the remaining protecting groups were removed with first $H_2$ and then TFA to give zwitterion **10**.




Scheme 1. Synthesis of the flexible zwitterion **10**.

The conformation of zwitterion **10** was probed by NMR in $CD_3OH$ and compared to the fully protected precursor **9**, in which now charge interactions are possible. A dilution study showed, that for zwitterion **10** the shifts in the $^1H$ NMR are concentration independent at least in the range 0.1–25 mM. Accordingly, no intermolecular self-association occurs and **10** exists as a monomeric species at least in this concentration range. This is in contrast to the protected molecule **9**. $^1H$ NMR dilution studies showed small concentration-dependent shift changes in the same range indicating a weak intermolecular self-association probably by formation of a H-bonded dimer. However, even though zwitterion **10** is present as a monomeric species, the NMR shifts show that **10** adopts a conformation in which the guanidinium cation forms a strong ion pair with the carboxylate. For example, the guanidinium amide NH occurs at $\delta$ = 12.95 which is a clear indication of an ion pair interaction which therefore must occur intramolecularly in this case. The reference value for a non-ion paired guanidiniocarbonyl pyrrole cation is around $\delta$ = 10.7, respectively.[8]

The structure of both the zwitterion **10** and the protected monomer **9** were then probed by NOESY NMR experiments (Figure 2). Significant diagnostic interstrand cross peaks are found for **10** which are absent in the protected compound **9**. For example, among others NOE signals are observed between the two alkyl groups of the amino acid side chains and also between the two pyrrole NHs. Furthermore, the NOEs observed for the two amino acid amide NHs are significantly different from each other. Whereas the valine amide–NH shows cross peaks to the methyl group of the alanine as well as the two different types of methylene groups of the butylene linker, the alanine amide-NH does only show a cross peak with the alanine methyl group but neither with the isopropyl group of the valine nor the methylene groups of the linker. These selected diagnostic NOEs, summarized also in Figure 2, are indicative of

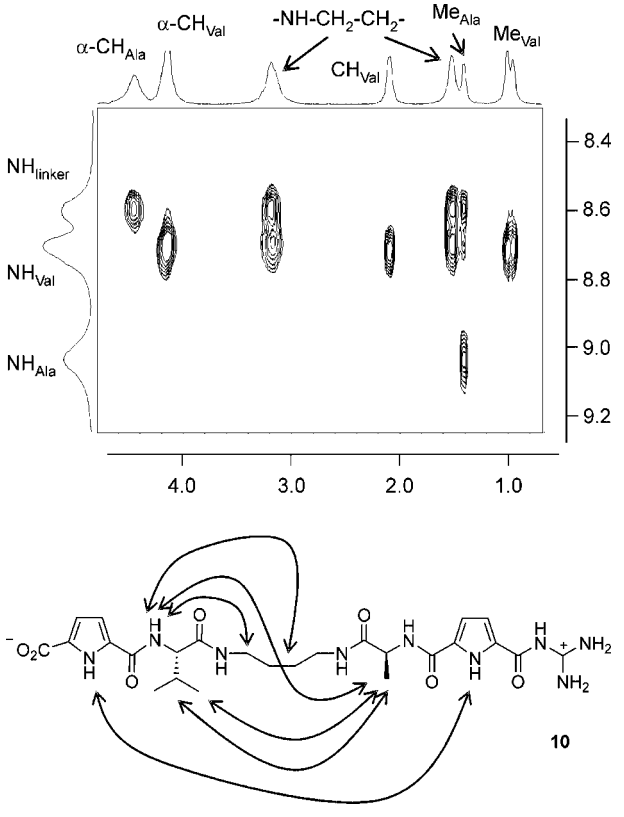



Figure 2. Top: Part of the NOESY spectrum of **10** (600 MHz, $CD_3OH$, room temp.) showing the different NOEs and hence the different environment of the two amino acid amide NHs. Bottom: Schematic representation of selected non-sequential diagnostic NOEs.

a folded loop-like conformation in which the chain ends are close to each other. Otherwise, in a more extended random structure no NOE signals between the two pyrrole NHs or the two alkyl groups of the amino acid side chains would be observable. This situation is found for the protected compound **9**, which hence most likely only adopts an unordered random-coil like structure in solution. None of the diagnostic NOEs shown in Figure 2 for zwitterion **10** are observed for the protected precursor **9**.

Structural differences between the two amid NHs are also obvious from a comparison of the coupling constants between the protected compound **9** and zwitterion **10**.[12] Whereas the coupling constant of the valine amide NH with the α-CH significantly increases from $^3J$ = 7.3 to 8.6 Hz going from **9** to **10** (in $CD_3OH$), it only slightly changes for the alanine amide NH (from $^3J$ = 7.9 to 7.6 Hz). This indicates a more ordered, probably more beta-sheet like structure around the valine amide NH in **10** compared to **9**, but not for the alanine amide NH which seems to exhibit a similar local environment in **10** as in **9**.

Also a H/D-exchange experiment confirmed a strikingly different chemical environment for the two amino acid amide-NHs. The kinetics with which an amide-NH exchanges with the solvent depends on whether it is H-bonded or not.[2h] And indeed, whereas the alanine amide NH rapidly exchanges upon the addition of $D_2O$ to a NMR sample of **10** in [$D_6$]DMSO, the valine amide NH exchanges much more slowly (Figure 3). This suggests that the valine amide NH is engaged in intramolecular hydrogen bonding as shown in Figure 4 (top), which slows down the exchange, whereas the alanine amide NH is only interacting with the solvent.[13] Also the two butylene NHs exchange with the solvent, much more slowly but both with similar rates. As they are less acidic than the amino acid amide NHs, no direct comparison can be made with the absolute exchange rate of the two amino acid amides. But the fact that both linker amide NHs exchange with similar rates indicates a similar hydrogen bonding situation for both of them.

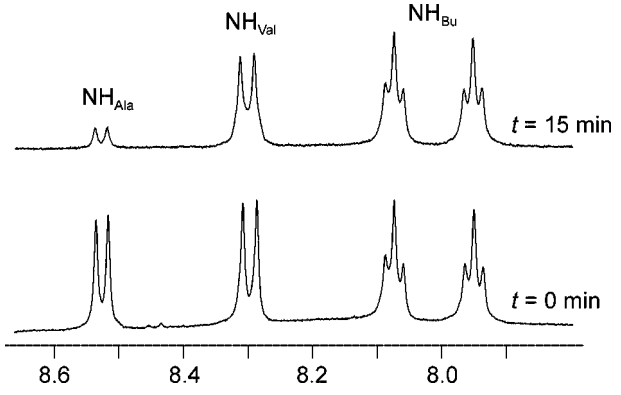



Figure 3. H/D exchange experiment of **10** ($D_2O$ added to a 10 mM solution of **10** in [$D_6$]DMSO at room temperature, 400 MHz).

The most likely structure of zwitterion **10** was calculated using molecular mechanics [Macromodel V8.0, MMFFs force field, GB/SA water solvation, MC conformational search with 100.000 steps].[14] The resulting energy minimized structure shown in Figure 4 (top) is fully consistent with the observed experimental data discussed above.[15] The two alkyl side chains of the amino acids are facing each other, giving rise to non-sequential NOEs between them. Whereas the valine amide NH points inwards and is involved in hydrogen bonding to the pyrrole carbonyl group at the other chain end, the alanine amide NH points outwards and is interacting with the solvent. Hence, the alanine amide NH should exchange more easily with the solvent in contrast to the valine amide NH. Also, the formation of this intramolecular H-bond is fully consistent with the observed NOEs: only the valine amide NH shows a cross signal with the alanine methyl group as it points towards the alanine but not vice versa. The alanine amide NH points to the backside and hence no NOE with the isopropyl group of the valine is seen. The different environment of the two amino acid amide NHs is also in agreement with the larger $^3J$ coupling constant for the valine amide NH relative to the alanine amide NH and the non-structured protected precursor **9**.

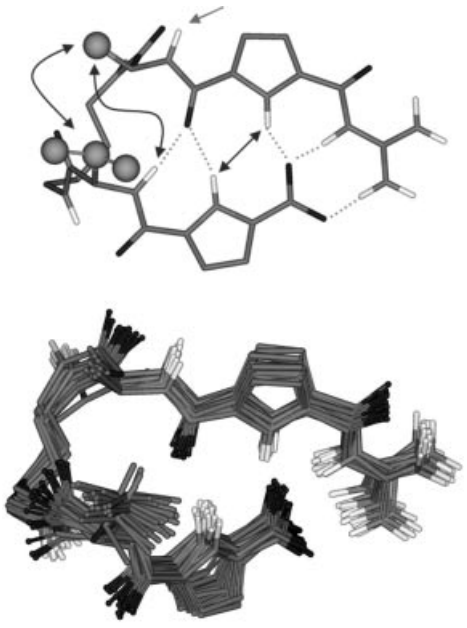


Figure 4. (Top): Calculated structure of zwitterion **10** showing intramolecular H-bonds (dotted lines) and the experimentally observed diagnostic non-sequential NOEs (double-headed arrows). The more rapidly exchanging alanine amide NH pointing backwards is also indicated. (Bottom): MD simulation (500 ps at 300 K) of structure of zwitterion **10**, snapshot taken every 20 ps [non-polar hydrogen atoms omitted for clarity].

The loop structure that zwitterion **10** adopts even in a polar and protic solvent such as methanol is also conformationally rather rigid at least according to modelling studies.[16] A MD simulation (300 K, 500 ps, water solvation) was performed to probe the flexibility of the loop. As shown in Figure 4 (bottom) the general structure of the loop stays intact, even over a rather long time period of 500 ps. There are no significant changes in the principal binding interactions (ion pairs, H-bonds, van der Waals interactions) that hold the loop together.

## Conclusions

In conclusion, we have demonstrated here that the conformation of a flexible linear molecule can be controlled by using directed charge interactions between the termini of the molecule. This however requires very efficient charge interactions that are strong enough even under competitive solvation conditions. Using a guanidiniocarbonyl pyrrole/carboxylate ion pair, zwitterion **10** which does not possess any rigid or structurally biased linker was shown to adopt a predictable and specific loop-conformation even in methanol. We are currently investigating how this approach can be used to build even larger self-assembled structures.

## Experimental Section

**General Procedure A for the Deprotection of the *t*BOC Group:** A solution of the corresponding protected compound (100 mg) in trifluoroacetic acid (5 mL) and dichloromethane (5 mL) was stirred for 1 h at room temperature under TLC control. After completion of the reaction, the trifluoroacetic acid was evaporated in vacuo yielding a slightly yellow oil. 10 mL of water were added, the solution was lyophilised and the white solid was dried in vacuo (yield: quantitative).

**General Procedure B for the Deprotection of the Cbz Group:** A solution of the corresponding protected compound (100 mg) and 10% Pd/C in methanol (10 mL) was hydrogenated at room temp. for 0.5 h (TLC control). The mixture was filtered through a pad of Celite to remove the catalyst (Pd/C) and the solvent was removed under reduced pressure. The crude product was used in the following steps without further purification.

**General Procedure C for Coupling of Amino Acids:** A mixture of the corresponding *N*-protected amino acid (1.0 mmol), HCTU (1.0 mmol) and NMM (3.0 mmol) in DMF (5 mL) was stirred at room temp. for 15 min. Then the corresponding amine component (1.0 mmol) was added to the solution and the reaction mixture stirred overnight (at room temp.). Then 30 mL of water were added and the solution was stirred in an ice-bath for further 30 min. The white precipitate was filtered, washed several times with water and lyophilised to give the desired product.

**General Procedure D for Coupling of the Pyrrolecarboxylic Acids 5 and 8:** A solution of the pyrrole derivative **5** or **8** (0.68 mmol), PyBOP (0.68 mmol) and NMM (2.04 mmol) in DMF (10 mL) was stirred at room temp. for 15 min. Then the corresponding amine component (0.68 mmol) was added and the solution was stirred at room temp. overnight. After adding 60 mL of water the solution was stirred in an ice-bath for another 30 min. The white precipitate was filtered, washed several times with water and lyophilised to give the desired product.

***tert*-Butyl (4-Aminobutyl)carbamate (1):** A solution of 1,4-diaminobutane (19.33 g, 220 mmol) in chloroform (150 mL) was cooled to 0 °C and then treated under continuous stirring with a solution of $Boc_2O$ (9.60 g, 44 mmol) in chloroform (50 mL). The reaction was stirred overnight at room temperature. The suspension was filtered and the solution was concentrated under reduced pressure. The colourless oil was dissolved in ethyl acetate (500 mL) and washed twice with brine (60 mL). The aqueous phases were combined and extracted once with ethyl acetate. The combined organic layers were dried with sodium sulfate and evaporated under reduced pressure. The resulting oily residue was dried in vacuo to give the desired product: 7.62 g (92%); m.p. 88 °C. $^1$H NMR ([D$_6$]-DMSO, 400 MHz): $\delta$ = 6.75 (s, 1 H), 3.30 (d, 2 H), 2.88 (m, 2 H), 1.37 (m, 13 H) ppm. $^{13}$C NMR ([D$_6$]DMSO, 100 MHz): $\delta$ = 155.54 ($C_q$), 77.21 ($C_q$), 41.43 ($CH_2$), 30.70 ($CH_2$), 28.25 ($CH_3$), 27.02 ($CH_2$) ppm. MS (EI) = *m*/*z* 189.3 [M + H$^+$].

**Compound 2:** Procedure **C**. Cbz-Val–OH: 251 mg, HCTU: 414 mg, NMM: 330 μL, **1**: 188 mg; yield 413 mg (98%); m.p. 193 °C. $^1$H NMR ([D$_6$]DMSO, 400 MHz): $\delta$ = 7.87 (t, 1 H), 7.33 (m, 5 H), 7.18 (d, *J* = 8.96 Hz, 1 H), 6.75 (t, 1 H), 5.02 (s, 2 H), 3.77 (dd, 1 H), 3.07 (m, 2 H), 2.98 (m, 2 H), 2.89 (m, 4 H), 1.91 (m, 1 H), 1.37 (s, 9 H), 0.83 (d, *J* = 6.84 Hz, 6 H) ppm. $^{13}$C NMR ([D$_6$]DMSO, 100 MHz): $\delta$ = 170.60 ($C_q$), 136.84 ($C_q$), 128.03 (CH), 127.45 (CH), 127.34 (CH), 77.03 ($C_q$), 65.05 ($CH_2$), 60.04 (CH), 37.96 ($CH_2$), 29.97 (CH), 27.98 ($CH_3$), 27.08 ($CH_2$), 26.86 ($CH_2$), 18.93 ($CH_3$), 17.97 ($CH_3$) ppm. MS (EI): *m*/*z* = 206.2 ($M^+ - C_{10}H_{19}N_2O_3$).

**Compound 3:** Procedure **A** and **C**. Boc-Ala–OH: 189 mg, HCTU: 414 mg, NMM: 330 μL, **2**: 493 mg; yield 288 mg (50%); m.p. 177 °C. $^1$H NMR ([D$_6$]DMSO, 400 MHz): $\delta$ = 7.87 (t, 1 H), 7.70 (t, 1 H), 7.33 (m, 5 H), 7.17 (d, *J* = 8.96 Hz, 1 H), 6.76 (d, *J* = 7.08 Hz, 1 H), 5.02 (s, 2 H), 3.90 (m, 1 H), 3.78 (m, 1 H), 3.08 (m, 2 H), 3.00 (m, 2 H), 1.91 (m, 1 H), 1.37 (s, 13 H), 1.14 (d, *J* = 7.04 Hz, 3 H), 0.83 (m, 6 H) ppm. $^{13}$C NMR ([D$_6$]DMSO, 100 MHz): $\delta$ = 170.62 ($C_q$), 136.84 ($C_q$), 128.03 (CH), 127.46 (CH), 127.34 (CH), 65.05 ($CH_2$), 60.04 (CH), 37.88 ($CH_2$), 29.98 (CH), 27.89 ($CH_3$), 26.23 ($CH_2$), 26.06 ($CH_2$), 18.94 ($CH_3$), 18.15 ($CH_3$), 17.96 ($CH_3$) ppm. HRMS (ESI): calculated for $C_{25}H_{40}N_4NaO_6^+$ [M + Na$^+$]: *m*/*z* = 515.284, found 515.285.

**Compound 6:** Procedure **A** and **D**. **5**: 201 mg, PyBOP: 354 mg, NMM: 224 μL, **3**: 267 mg; yield 283 mg (62%); m.p. 184 °C. $^1$H NMR ([D$_6$]DMSO, 400 MHz): $\delta$ = 11.61 (br., 1 H), 10.83 (br., 1 H), 9.37 (br., 1 H), 8.63 (br., 1 H), 8.46 (d, *J* = 7.44 Hz, 1 H), 7.94 (t, 1 H), 7.88 (t, 1 H), 7.34 (m, 5 H), 7.17 (d, *J* = 8.84 Hz, 1 H), 6.83 (m, 2 H), 5.02 (s, 2 H), 4.41 (m, 1 H), 3.78 (m, 1 H), 3.04 (m, 4 H), 1.92 (m, 1 H), 1.46 (s, 9 H), 1.39 (s, 4 H), 1.28 (d, *J* = 7.04 Hz, 3 H), 0.83 (m, 6 H) ppm. $^{13}$C NMR ([D$_6$]DMSO, 100 MHz): $\delta$ = 172.07 ($C_q$), 170.94 ($C_q$), 158.20 ($C_q$), 156.09 ($C_q$), 137.15 ($C_q$), 128.34 (CH), 127.77 (CH), 127.65 (CH), 65.37 ($CH_2$), 60.36 (CH), 48.45 (CH), 38.22 ($CH_2$), 30.29 (CH), 27.80 ($CH_3$), 26.58 ($CH_2$), 26.47 ($CH_2$), 19.25 ($CH_3$), 18.35 ($CH_3$), 18.27 ($CH_3$) ppm. HRMS (ESI): calculated for $C_{32}H_{46}N_8NaO_8^+$ [M + Na$^+$]: *m*/*z* = 693.333, found 693.335.

**Bis-Protected Zwitterion 9:** Procedure **B** and **D**. **8**: 167 mg, PyBOP: 354 mg, NMM: 224 μL, **6**: 365 mg; yield 306 mg (59%); m.p. 186 °C. $^1$H NMR ([D$_3$]MeOH, 600 MHz): $\delta$ = 12.74 (br., 1 H), 12.03 (br., 1 H), 9.09 (br., 1 H), 8.95 (s, 1 H), 8.90 (s, 1 H), 8.76 (s, 2 H), 8.61 (s, 1 H), 7.43 (m, 5 H), 6.90 (m, 4 H), 5.19 (s, 2 H), 4.37 (m, 1 H), 4.21 (m, 1 H), 3.19 (m, 4 H), 2.10 (m, 1 H), 1.52 (s, 9 H), 1.41 (s, 4 H), 1.30 (s, 3 H), 0.97 (d, *J* = 24 Hz, 6 H) ppm. $^{13}$C NMR ([D$_6$]DMSO, 63 MHz): $\delta$ = 172.10 ($C_q$), 170.72 ($C_q$), 160.11 ($C_q$), 159.14 ($C_q$), 158.90 ($C_q$), 158.47 ($C_q$), 136.29 ($C_q$), 131.03 ($C_q$), 128.52 ($C_q$), 128.10 (CH), 127.93 (CH), 124.17 (CH), 115.29 (CH), 113.89 (CH), 112.82 (CH), 65.49 ($CH_2$), 58.08 (CH), 48.42 (CH), 38.23 ($CH_2$), 30.54 (CH), 27.78 ($CH_3$), 26.60 ($CH_2$), 26.45 ($CH_2$), 19.29 ($CH_3$), 18.57 ($CH_3$), 18.34 ($CH_3$) ppm. HRMS (ESI): calculated for $C_{37}H_{49}N_9NaO_9^+$ [M + Na$^+$]: *m*/*z* = 786.355, found 768.356.

**Zwitterion 10:** Procedure **B** and **A**. Yield 75 mg (quant.); m.p. 242 °C. $^1$H NMR ([D$_6$]DMSO, 400 MHz): $\delta$ = 12.74 (br., 1 H), 12.25 (br., 1 H), 11.78 (br., 1 H), 8.50 (d, *J* = 7.68 Hz, 1 H), 8.30 (d, *J* = 8.6 Hz, 1 H), 8.07 (t, 1 H), 7.93 (t, 1 H), 6.81 (br., 2 H), 6.77 (dd, 1 H), 6.72 (dd, 1 H), 4.41 (m, 1 H), 4.26 (m, 1 H), 3.06 (m, 4 H), 2.03 (m, 1 H), 1.40 (s, 4 H), 1.29 (d, *J* = 7.08 Hz, 3 H),

0.88 (dd, 6 H) ppm. $^{13}C$ NMR ([D$_6$]DMSO, 63 MHz): $\delta$ = 172.04 ($C_q$), 170.80 ($C_q$), 162.11 ($C_q$), 159.11 ($C_q$), 158.93 ($C_q$), 130.03 ($C_q$), 125.99 ($C_q$), 114.42 (CH), 113.74 (CH), 113.10 (CH), 58.14 (CH), 48.47 (CH), 38.23 ($CH_2$), 30.42 (CH), 26.54 ($CH_2$), 26.45 ($CH_2$), 19.30 ($CH_3$), 18.58 ($CH_3$), 18.34 ($CH_3$) ppm. HRMS (ESI): calculated for $C_{25}H_{36}N_9O_7^+$ [M + H$^+$]: *m/z* = 574.273, found 574.274.

**Supporting Information** (see also the footnote on the first page of this article): NMR spectra ($^1H$, $^{13}C$) of compounds **1**–**3**, **6**, **9** and **10**.

## Acknowledgments

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[12] Unfortunately, due to signal overlap of the α-CHs with the OH signal of the solvent only the coupling constants of the amino acid amide NHs could be analysed reliably.

[13] As the exchange rate of both amides in the protected monomer **9** is very similar, the observed difference in **10** can not be due to a different intrinsic reativity caused by the different steric environment around the two amide NHs but must result form different H-bond features.

[14] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440–467.

[15] The energy minimized structure in Figure 4 as obtained from the force field calculations contains one *cis*-amide linkage. Intramolecular ion pairing is not possible in the same way if that amide adopts a trans conformation. At least there is no energy minimum within 20 kJ/mol of the one shown here, which contains a trans linkage. Hence, the energetical cost for *cis*-amide formation is obviously more than overcome by the strong intramolecular ion pairing.

[16] The rather high stability of the loop structure is also supported by NMR experiments. The $^1H$ NMR spectra of **10** do not change upon the addition of up to 50% water to the methanol solution. With even higher water contents precipitation occurs. Even though the exchanging acidic NH protons, which are most diagnostic for ion pairing, cannot be observed in the presence of water, there are no noticeable shift changes for any proton, suggesting that the loop most likely also exists in water/methanol mixtures.

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