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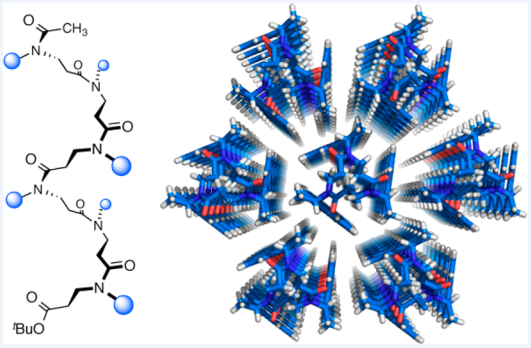
β-Peptoid Foldamers at Last

Jonas S. Laursen, Jens Engel-Andreasen, and Christian A. Olsen*

Center for Biopharmaceuticals & Department of Drug Design and Pharmacology, University of Copenhagen, Universitetsparken 2, DK-2100, Copenhagen, Denmark

CONSPECTUS: For a long time, peptides were considered unsuitable for drug development due to their inherently poor pharmacokinetic properties and proteolytic susceptibility. However, this paradigm has changed significantly in the past decade with the approval of numerous antibodies and proteins as drugs. In parallel, research in the field of synthetic molecules that are able to mimic or complement folding patterns exhibited by biopolymers, but are not recognized by proteases, have received considerable attention as well. Such entities were coined "foldamers" by Professor Gellman in an Account published in this journal in the late 1990s.



Oligomers of *N*-alkylated 3-aminopropionic acid residues have been called β-peptoids due to their structural similarity to β-peptides and peptoids (*N*-alkylglycines), respectively. Because bona fide foldamer behavior has been demonstrated for both parent architectures, we wondered if the β-peptoids could serve as a successful addition to the known ensemble of peptidomimetic foldamers. When we entered this field, only the seminal description of libraries of β-peptoid dimers and trimers by Hamper et al. had been published a number of years earlier [*J. Org. Chem.* **1998**, *63*, 708]. Perhaps somewhat naïvely in retrospect, we envisioned that elongation of chain length combined with introduction of bulky α-chiral side chains would deliver folded structures as reported for the α-peptoid counterparts. Initially, we, and others, were unsucessful in obtaining stable secondary structures of β-peptoid oligomers, and instead, these residues were either incorporated in cyclic structures or in combination with other types of residues to give peptidomimetic constructs with heterogeneous backbones. Amphiphilic architectures with various membrane-targeting activities, such as mimics of antimicrobial peptides or cell-penetrating peptides, have thus been particularly successful. Introduction of β-peptoid residues in histone deacetylase inhibitors mimicking nonribosomal cyclotetrapeptides have also been reported.

In the present Account, we will sketch the scientific journey that ultimately delivered robustly folded β-peptoid oligomers. Contributions involving biological evaluation of peptidomimetic constructs containing β-peptoid residues, as mentioned above, which were investigated leading up to these recently reported high-resolution helical structures, will thus be discussed. On the basis of the work described in this Account, we envision that β-peptoids will find future utility as peptidomimetics for biomedical investigation containing both heterogeneous and homogeneous backbones. The recent demonstration of control over the secondary structure of a homogeneous β-peptoid backbone now enables structure-based design of scaffolds with predictable display of desired functionalities in three dimensions.

1. INTRODUCTION

Peptides and proteins perform vital tasks in living organisms. These oligomeric compounds are constructed from a set of just 20 amino acids but possess the ability to display functional groups accurately in three-dimensional space through well-defined folding patterns, which enables their extraordinarily diverse functional space. The high degree of binding affinity and selectivity often achieved by peptides, antibodies, and proteins are desirable properties in relation to the development of novel pharmaceutical agents, and interest in such compounds has increased tremendously with the successful marketing of recombinant protein therapeutics.[1] Traditionally, however, these compounds were considered unsuitable for drug discovery as they often suffer from poor cell-penetrating properties and are susceptible to proteolysis. To circumvent these inherent drawbacks, studies toward unnatural compounds capable of mimicking or complementing the secondary structures of proteins have been undertaken. These efforts have demonstrated the ability of non-natural oligomers to form well-defined displays of side chain functionalities; such oligomers have been termed foldamers (for examples, see Figure 1).[2−5]

Relatively small structural alterations have proven to greatly change the folding behavior of certain peptidomimetics as compared to native peptide folding. For example, the additional methylene in β-amino acids enables different substitution patterns of the individual residues (β^2, β^3, or $\beta^{2,3}$), which has great effect on the overall folding propensity.[6,7] Furthermore, it has been shown that connecting the two side chains to give cyclopentane- or cyclohexane-constrained β-amino acids has a stabilizing effect on certain helical motifs.[8] Building on

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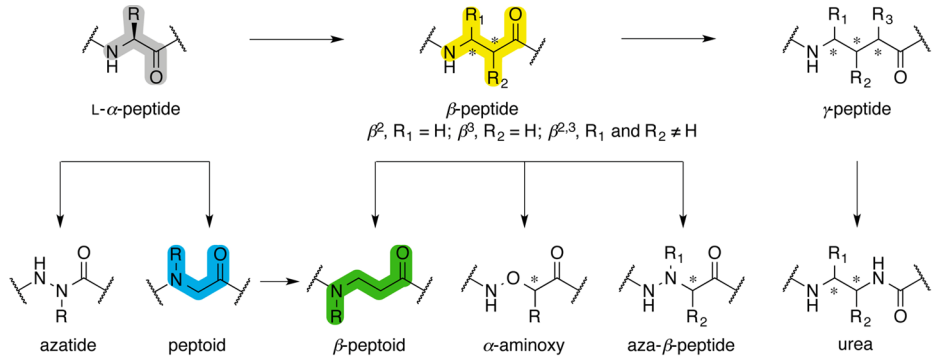

Figure 1. Structures of selected peptidomimetic backbones.

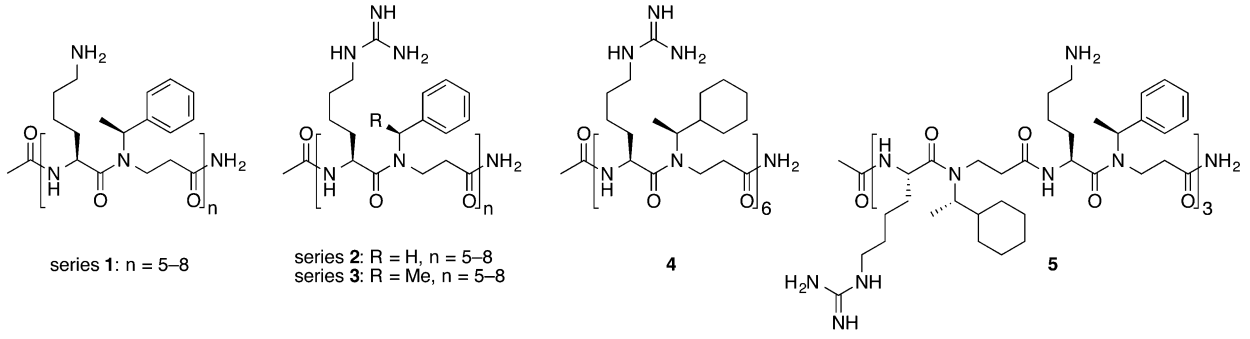

Figure 2. Examples of α-peptide/β-peptoid hybrid compounds.

structural insight, a number of bioactive compounds have been synthesized from either pure β-amino acids or by point mutations in peptide constructs.[9]

Unlike the β-peptides, the so-called peptoids[10,11] are devoid of hydrogen bond donors in the backbone, which renders the stabilization of secondary structure in these compounds fundamentally different. Furthermore, *cis*−*trans*-amide bond isomerization has proven to be an important factor in secondary structure formation, and these equilibria may be influenced by the nature of the side chains[12−16] or backbone.[17]

Our laboratory has taken a keen interest in a backbone design combining the features of β-peptides and peptoids to give oligomers of *N*-alkylated 3-aminopropionic acid residues (β-peptoids). The first description of this backbone was reported by Hamper and co-workers in a seminal publication describing synthesis of libraries of dimers and trimers.[18] A synthetic strategy resembling the "sub-monomer" approach used for peptoid synthesis[11] was developed in which the appropriate side chains were incorporated by Michael addition to resin bound acrylamides. A number of years later, computational simulation of β-peptoids provided support of the existence of low energy conformations corresponding to helical oligomers displaying either all *cis*- or all *trans*-amide bonds.[19] However, two following circular dichroism (CD) studies provided ambiguous conclusions regarding folding due to the lack of high-resolution structural data.[20,21]

In response to the initial difficulties in achieving robustly folded conformers, we decided to pursue peptide/β-peptoid hybrids to include the hydrogen bonding capability of the α-amino acids as well as easy access to oligomers by dimer coupling on solid-phase.[22] Both antimicrobial, antiplasmodial, and cell-penetrating compounds were discovered using this backbone design.[23,24]

2. β-PEPTOID RESIDUES IN HYBRID BACKBONES

2.1. Antimicrobials

Since the introduction of penicillins, in particular, into the clinic, most bacterial infections have been considered minor medical challenges. However, development of pathogenic resistance to conventional antibiotics has become an increasingly serious threat to human health, and development of antibiotics with new modes of action are therefore in demand.[25] Antimicrobial peptides (AMPs) have been considered as such candidates due to their role in the innate antibacterial defense system found in many organisms, including humans.[26] Although detailed mechanisms of action of these compounds are debated, it is generally accepted that interaction with the negatively charged membranes of bacteria plays a role whether this involves internalization, membrane disruption, or both.[27,28] Most AMPs are relatively short peptides (<50 residues) with an overall positive charge and a substantial amount of hydrophobic residues (>30%) as well as amphipathic three-dimensional structures.[26−28] The great diversity within this class of peptides has made AMP mimics attractive for development of novel antibiotics. Several backbone constructs have been utilized to furnish antimicrobial peptidomimetics, including β-peptides,[29,30] peptoids,[31] and β-peptoids.[32] The latter mentioned study offered preliminary insight into the relationship between sequence and potency, but the oligomers in this initial investigation displayed only modest activities against the tested microbes.

Our initial α-peptide/β-peptoid chimeras consisted of alternating hydrophilic α-amino acid residues and hydrophobic β-peptoid residues with a chain length of n = 8 in series **1**−**3** (Figure 2), which addressed the importance of chirality in the β-peptoid unit and the type of cation in the α-amino acid side chain (Lys vs *h*Arg).[24] This study revealed that the alternating

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chimeric backbone design was able to accommodate relatively potent antibacterial compounds, with activities resembling those of magainin-2 (MIC ∼8−62 μg/mL against the tested microbes).[24] To further investigate the potential of these hybrid oligomers, the compound collection was expanded to address the effect of chain length, the type of hydrophobic residue (**4**), and combinations of the two types of cation (**5**) (Figure 2). These compounds were tested against a larger battery of pathogens and evaluated for hemolytic, prehemolytic, and cytotoxic activity.[33] Elongation of series **1**−**3** (10 → 16 residues), gave rise to an increase in potency against all bacteria except *Escherichia coli*, where the shortest mimic displayed the highest activity. It was shown that substitution of phenyl groups for cyclohexyl (**4**) generally increased the antimicrobial activity, however, the increased activity was accompanied by a significant increase in hemolytic activity. In an attempt to overcome this increase in toxicity, compound **5**, which contains a combination of phenyl and cyclohexyl groups as well as guanidino and amino functionalities, was prepared. Although this compound displayed a 2−4-fold decrease in potency compared to **4** against the tested microbes, a remarkable >20-fold decrease in hemolytic activity was measured. Interestingly, circular dichroism (CD) spectroscopy of these compounds showed a decrease in Cotton effect upon interaction with lipid vesicles, indicating random coil membrane-active structure. This is in contrast to previous studies of α-peptoids showing importance of a helical fold resulting in an overall amphipathic structure.[34] However, simultaneously with our first report,[24] Mor and co-workers also described an unstructured backbone design consisting of alternating 8-aminooctanoic acid and lysine residues, which exhibited potent antimicrobial activity in mice.[35]

In a following study, hexadecamers of series **1**−**3** together with octamers, dodecamers, and hexadecamers in which the cation was alternated between amino and guanidino groups were investigated by correlation of ATP leakage with killing kinetics.[36] To improve on the antimicrobial efficiency of peptidomimetic compounds, Franzyk and co-workers prepared a series of hexadecamers with alternating Lys and Phe side chains on different backbone constructs.[37] The compounds contained L-, D-, and β-amino acids as well as peptoid and β-peptoid residues, including both homooligomers and hybrid oligomers of the various residues. These combinations were tested against a panel of multidrug resistant bacterial strains. The study showed that the backbone composition had a significant influence on the antimicrobial activity of these compounds, with the mixed compounds being generally more potent than the pure peptide compound as well as the homomeric peptidomimetic compounds.[37]

In a follow-up study, dodecamers of series **1** and **2** exhibited increased potencies against *E. coli* in the presence of 50% blood serum (decreased MIC values by 4−32-fold),[38] which is in stark contrast to expectation.[39] However, this was explained by a possible partial disintegration of the outer membrane of Gram-negative species prior to attack from the antimicrobial compound because potentiation was observed for Gram-negative species but not for the Gram-positive *Staphylococcus aureus*. It was also shown that *E. coli* could develop resistance toward the hybrid mimics when administered at sublethal doses in the absence of serum.[40] Importantly, however, when these resistant strains were subsequently incubated in serum-containing medium, the compounds exhibited antibacterial activity.

Most recently, a compound series was investigated to gain insight into the effect of length, type of cation, and choice of α- vs β-peptoid units on antibacterial activity and cytotoxicity (for examples, see compounds **6**−**9** in Figure 3).[41] This design thus

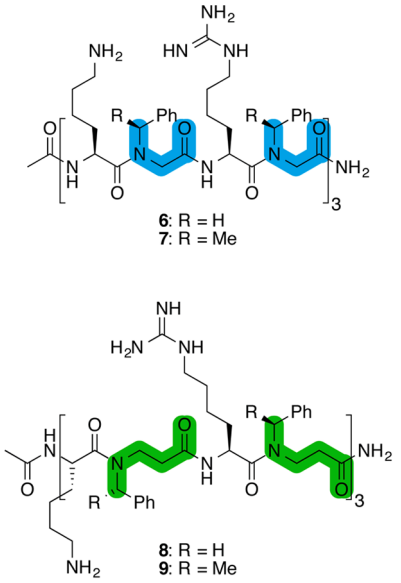

Figure 3. Examples of α-peptide/peptoid (**6** and **7**) and α-peptide/β-peptoid (**8** and **9**) compounds for investigating the influence of cation type and side chain chirality on cytotoxicity.

accommodated the high activity of guanidino groups while retaining a low degree of cytotoxicity as we previously reported for compound **5**.[33] In this study, Franzyk and co-workers concluded that the longer chain lengths (12- or 14-mers) combined with a lack of α-branching gave rise to superior selectivities.[41] Finally, incorporation of α- and β-peptoids furnished equally potent compounds in this study.

In general, all the SAR performed on this class of compounds suggest that increased length, increased hydrophobicity, and increased number of guanidino groups result in higher potency against most pathogens tested. However, these effects are somewhat microbe-specific and, more importantly, needs to be balanced with respect to toxicity as evidenced by hemolytic effects. It is therefore difficult to derive simple design rules for these compounds.

2.2. Cell-Penetrating Peptides

The compounds described above also share some common features with another class of peptides, namely the cell-penetrating peptides. These peptides were discovered as domains of viral proteins, such as the human immunodeficiency virus 1 (HIV-1) trans-activating transcriptional activator (Tat) domain,[42,43] and short peptides that mediate transport across cell membranes, have been designed based on these sequences, including Professor Wender's oligoarginines.[44] On the basis of the finding that some of our α-peptide/β-peptoids were found to alter erythrocyte membranes at subhemolytic concentrations, we speculated that these compounds potentially could have cell-penetrating properties.[23] This encouraged a study of the cellular uptake of the hybrid oligomers by using fluorescence labeling with carboxyfluorescein (CF) (Figure 4).[45]

It was found that the labeled hybrids possessed efficient cellular uptake properties to an extent that exceeded the cell-penetrating peptides such as the Tat−peptide fragment. As

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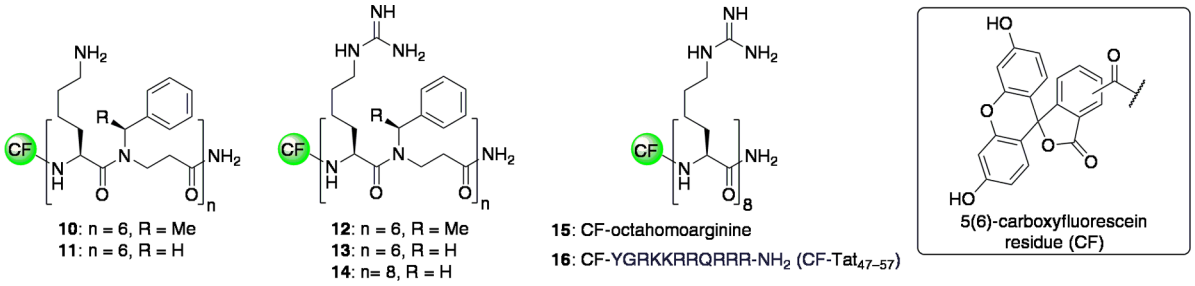

Figure 4. Examples of α-peptide/β-peptoids used in determining cellular uptake.

shown for other backbone constructs,[46,47] the guanidinylated analogues displayed superior cell penetration compared to the lysine-containing compounds (for examples of confocal laser scanning micrograms see, Figure 5). Furthermore, hydrophobic

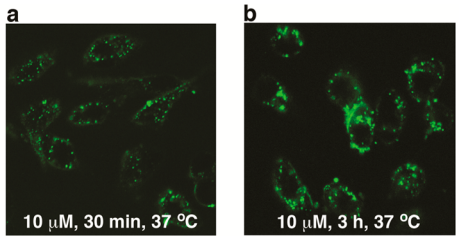

Figure 5. Confocal laser scanning microscopy showing cellular uptake of compound **12** at different incubation times. The figure is adapted with permission from ref 23. Copyright 2007 from John Wiley and Sons.

residues proved to have an activating effect on the cellular uptake as even the lysine-containing analogues **10** and **11** exhibited efficiencies comparable to the tested Tat analogue (**16**).[45] Interestingly, Wender and co-workers investigated oligoarginines with a peptoid backbone,[47] and more recently, it has been shown by Kodadek and co-workers[48] as well as Lokey and co-workers[49] that peptide to peptoid substitutions may improve cell penetration.

To elaborate on the interactions with model membranes, Nielsen and co-workers studied the effects of series **3** (Figure 2) and compounds **13** and **14** on a POPC−palmitoyl-oleyl-phosphatidylglycerol (POPG) (80:20) membrane using isothermal titration calorimetry (ITC) and ellipsometry. By applying these techniques, it was possible to extract thermodynamic data, which was correlated to cellular uptake in living cells.[50] The data showed a good correlation between the interaction with the model membranes and the cellular uptake, which indicates that the initial interaction with the membrane is a key step in the uptake process.

2.3. Macrocyclic Histone Deacetylase Inhibitors

The interest in macrocyclic peptides and peptidomimetics has increased considerably with the identification of numerous natural cyclic peptides with a wide range of biological activities.[51] One such compound, apicidin, displays inhibitory activity against histone deacetylase (HDAC) enzymes,[52] which are validated as targets for anticancer chemotherapy.[53] In an effort to expand the conformational space of apicidin analogues, Ghadiri and co-workers introduced α- and β-peptoid residues into the apicidin backbone.[54] The two most potent compounds in this study contained an *N*-isobutyl-β-peptoid and a tryptamine-based peptoid residue (**17** and **18**; Figure 6a), and molecular dynamics simulations showed a good overlap of

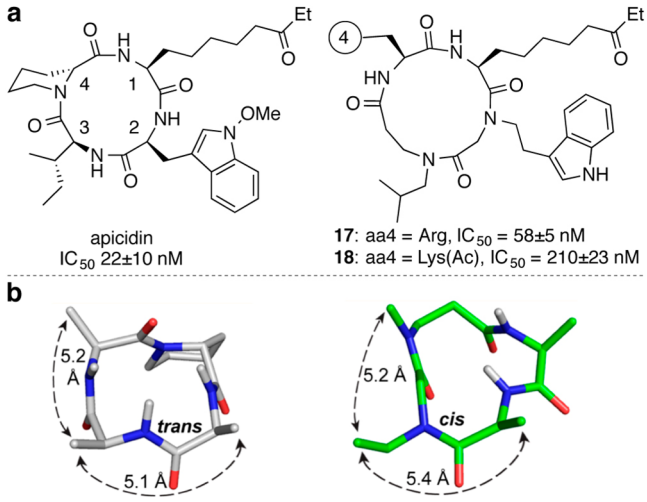

Figure 6. (a) Apicidin and β-peptoid-containing analogues **17** and **18** and their corresponding IC_{50} values measured against the HDAC activity in HeLa nuclear extract. (b) Comparison of the NMR structure of apicidin (in gray) and one of the simulated low-energy structures of compounds **17** (in green). Adapted with permission from ref 52. Copyright 2012 ACS Publications.

the projection of side chains even though the backbone conformations were different from that of apicidin (Figure 6b). Interestingly, the two remaining backbone amide protons were perpendicular to the macrocycle in the same direction as the extended ethylketone-containing side chain, which was recently shown to be important for potent HDAC inhibition by similar macrocyclic peptides.[55]

Furthermore, Taillefumier and co-workers designed macrocyclic homo-β-peptoids with *N*-propargyl side chains that can be readily functionalized by Cu(I)-catalyzed azide−alkyne cycloaddtion and varying number of residues (2−6).[56] The unfunctionalized tetramer was crystallized and X-ray diffraction as well as NMR spectroscopy in solution revealed all *cis*-amide conformations in the backbone of this compound.[56] Another study dealt with the conformational behavior of macrocycles of alternating α,β-peptoid residues, which demonstrated that both side chain functionality and ratio of chiral−nonchiral residues had an influence on the conformation.[57]

3. *CIS*−*TRANS* ISOMERISM OF TERTIARY AMIDE BONDS

Research within biological polymers has provided an understanding that function is closely related to three-dimensional structure. Despite the lack of hydrogen bond donors in their backbone and access to both *cis*- and *trans*-amide bonds, computational[58] and experimental[59−61] studies have shown that

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peptoids can fold into helical structures. Control over the isomerization of the tertiary amide bonds can be achieved by choice of side chains, which in turn may aid the de novo design of folded peptoids or in our case β-peptoids.

3.1. Peptoids

Briefly, the primary driving forces controlling rotameric preference are steric, $n \rightarrow \pi^*_{aryl}$, and electrostatic interactions between the side chains and the backbone. Especially, the *cis*-amide conformation can be predominantely populated by choosing sterically bulky side chains, such as *N*-1-(1-naphthyl)-ethyl[13] or *tert*-butyl,[16] or side chains containing positively charged groups, such as pyridinium[13] or triazolium.[15] Control of the *trans*-amide conformation can also be accomplished with *N*-aryl side chains.[14]

The $n \rightarrow \pi^*$ interaction between adjacent amide carbonyls in the backbone has also been suggested as a putative stabilizing noncovalent interaction in peptoids.[13] This type of interaction contributes to stabilization of protein secondary structures[62] and has been investigated in both proline[63] and peptoid model systems.[12,17] Our recent study showed that backbone permutations such as thioamidation and haloacetylation enabled X-ray crystallographic evidence for $n \rightarrow \pi^*$ interaction between adjacent amide carbonyls in the C $\rightarrow$ N direction, while peptoids with unmodified backbones showed no evidence of this interaction.[17]

3.2. β-Peptoids

The additional methylene group in the backbone of β-peptoids may potentially give rise to altered amide rotamer equilibria compared to peptoids, and we therefore investigated the effects of side chain and backbone permutations on the conformational behavior of β-peptoid monomers as well.[64] β-Peptoid monomer model compounds containing various side chains as well as thioamidation and trifluoroacetylation were synthesized and their conformational preferences analyzed by NMR spectroscopy, X-ray crystallography, and density functional theory (DFT) calculations. The NMR spectroscopic results demonstrated that the model compounds with varying side chains generally exhibit *cis*–*trans* isomerization equilibria in solution similar to their peptoid analogues (for examples, see Figure 7). Trifluoroacetylation proved to have both steric and stereoelectronic effects depending on the side chain. For example, steric clash between the bulky *N*-1-(1-naphthyl)ethyl group and the trifluoromethyl group resulted in even higher preference for the *cis*-amide conformation than that observed for *N*-acetylated compounds. Thioamidation of either the C- or the N-terminal proved to have little effect on conformational behavior. However, thioacetylation combined with the *N*-1-(1-naphthyl)ethyl side chain gave rise to an increase in $K_{cis/trans}$, which indicated an interaction between the thiocarbonyl and the naphthyl side chain. Further inspection of the model compound by 2D NMR spectroscopy and DFT calculations suggested the presence of thioamide–aromatic interactions through $C(sp^2)$–H···S_{amide} hydrogen bonding. This was also supported by X-ray crystallographic examination of a peptoid model analogue.[64]

4. HELICAL β-PEPTOIDS

Building on the insight from the various monomer studies discussed above, two series of homooligomeric β-peptoids were synthesized to evaluate the folding propensity of this scaffold. These series contained either the *N*-1-phenylethyl (**19**–**23**) or *N*-1-(1-naphthyl)ethyl side chains (**24**–**29**) (Figure 8a).[65] The

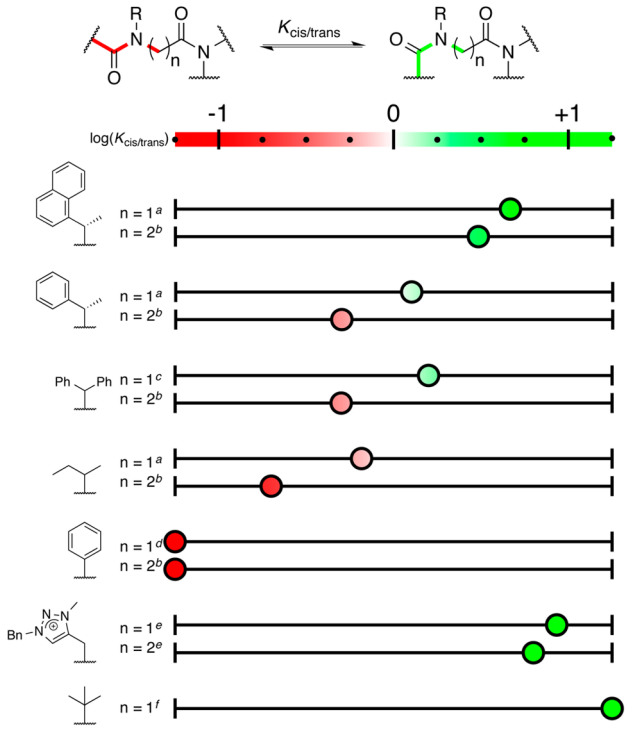

Figure 7. Rotamer equilibrium constants [(log($K_{cis/trans}$)] for a representative selection of peptoid and β-peptoid monomer model compounds measured in CD_3OD (12–15 mM) at ambient temperature. (*a*) ref 13, (*b*) ref 64, (*c*) ref 17, (*d*) ref 14, (*e*) ref 15, and (*f*) ref 16.

strongly *cis*-amide inducing *N*-1-(1-naphthyl)ethyl side chain was chosen for our second series (**24**–**29**) due to the computational evidence that β-peptoids may adopt helical low energy conformations containing all *cis*-amide bonds.[19]

During synthesis, precipitation was observed at hexamer length (**28** and **29**) and we were able to recrystallize this material to achieve X-ray diffraction quality. Thus, X-ray crystal structures were obtained (Figure 8b–e), which revealed helical displays with all *cis*-amide bonds and a highly ordered arrangement of the naphthyl groups along three faces of the helix. The structures featured a helical pitch of three residues per turn and 9.6–9.8 Å distance between turns. In hexamer **29**, the N-terminal acetylation appeared to force the final side chain into a *cisoid* conformation, giving a fully helical arrangement throughout the hexamer (Figure 8c,e). Inspection of the crystal structures did not indicate any stabilizing effects from noncovalent $n \rightarrow \pi^*$ interactions, which is also in agreement with the data obtained in our model studies outlined above.

These structures represented the first high-resolution evidence for the presence of secondary structures in linear oligomeric β-peptoids.

NMR spectroscopy indicated a cooperative effect on folding upon increasing the oligomer length as judged by increase in overall $K_{cis/trans}$ values for **24**–**29**. However, due to extensive signal overlap, it was not possible to solve high-resolution structures based on nuclear Overhauser effect (NOE) correlations, and instead circular dichroism (CD) spectroscopy was employed to probe putative folding behavior in solution. All compounds (**24**–**29**) exhibited similar CD spectra, with a minimum at 224–228 nm and a maximum at 215–218 nm, but in addition, new maxima arose at 232 nm as the oligomers reached tetra- to hexamer length (Figure 9a). This peak

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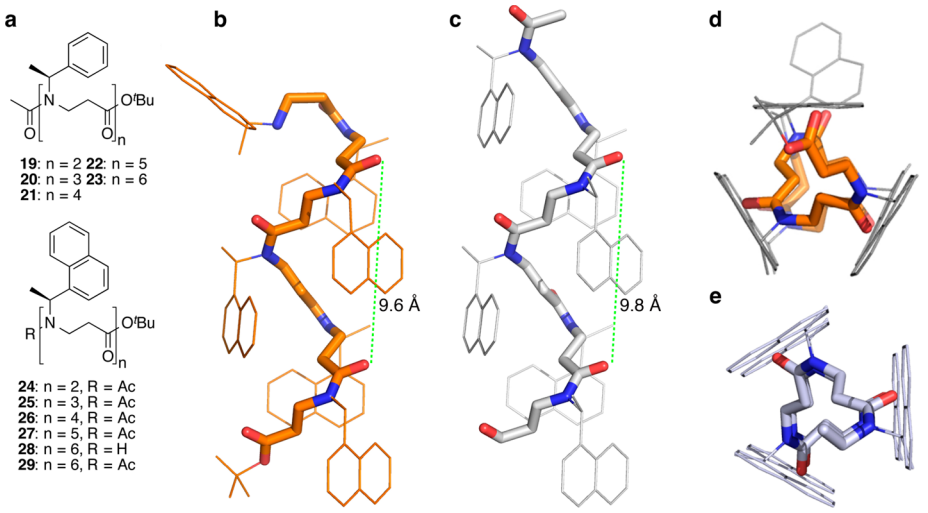

Figure 8. (a) Sequences of compounds **19**–**29**. (b) X-ray crystal structure of **28**. (c) X-ray crystal structure of **29**. (d) End view of **28**. (e) End view of **29**. The figure is adapted with permission from ref 65. Copyright 2015 under a Creative Commons Attribution 4.0 International License.

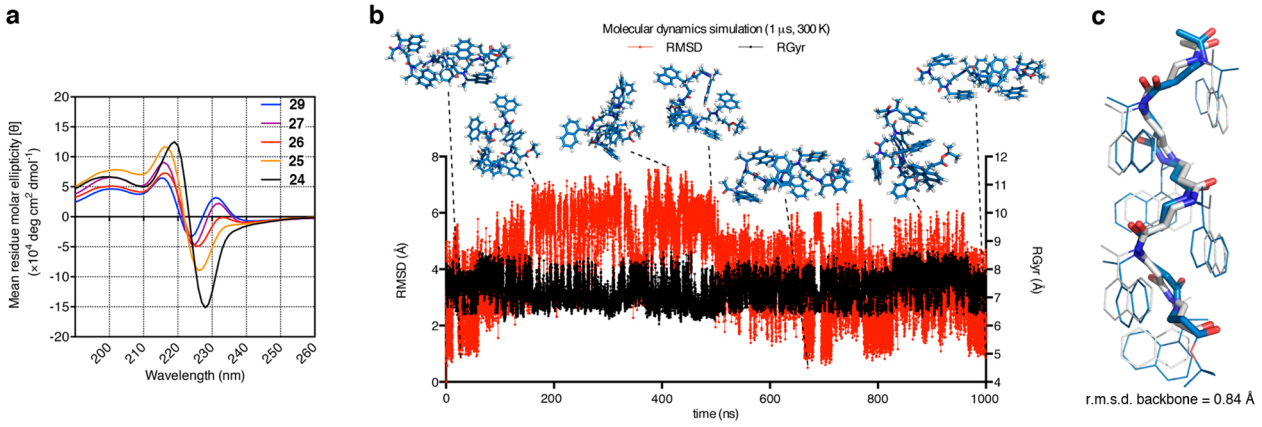

Figure 9. (a) CD spectra for compounds **24**–**27** and **29** at 60 μM in CH_3CN. (b) Molecular dynamics simulation of compound **29** in CH_3CN. (c) Overlay of X-ray crystal structure of **29** (white) and the obtained conformation after 1 μs molecular dynamics simulation (blue). Adapted with permission from ref 65. Copyright 2015 under a Creative Commons Attribution 4.0 International License.

decreased upon heating or addition of methanol, whereas the remaining part of the spectra remained unchanged, indicating that this maximum might be indicative of secondary structure.[65] Moreover, fluorescence measurements at excitations from 230–290 nm and recording of emission from 300–500 nm revealed no evidence for excimer effects caused by π–π interactions between naphthyl side chains.[65] The CD spectra of the *N*-1-phenylethyl series (**19**–**23**), on the other hand, did not provide any new insight compared to previous studies.[20,21]

To provide further support for the existence of helical folding in solution, molecular dynamics simulations were performed on hexamer **29** (Figure 9b). Starting from the fully folded helical conformation obtained by X-ray crystallography, these calculations showed a dynamic system accessing a range of conformations, which after a 1 μs simulation time adopted a conformation remarkably close to the initial structure (Figure 9c).

In proteins, helices are the most common type of secondary structure. It is estimated that a third of all residues in proteins participate in a helical motif,[66] by far the most abundant being the α-helix, which has 3.6 residues per turn and a pitch of 5.4 Å (Figure 10b). This is the most stable helical display because all backbone heteroatoms are engaged in hydrogen bonding, while the side chains are positioned to avoid steric clash. The polyproline type II helix (Figure 10c),[67] on the other hand, is narrow and extended with a pitch of ∼9 Å resembling that of our β-peptoid helices (∼9.8 Å; Figure 10a). Not surprisingly, due to the tertiary amide bonds, peptoid structures resemble those of polyprolines, and thus far, the solved structures have resembled the *cis*-amide bond-containing polyproline type I helix (Figure 10d).

The β-peptides have been found to adopt different helical conformations depending on the backbone substitution pattern.[7] Thus, β-peptides bearing a single side chain (β^2- or β^3-peptides) generally adopt a so-called 14-helix with three residues per turn and a pitch of ∼5.0 Å. This results in a wide internal diameter and side chains distributed along three straight faces along the helical axis (Figure 10e). Taken together, this shows that the β-peptoid helix presents a unique additional conformation with a long pitch of ∼9.8 Å and a relatively small internal diameter.

5. CONCLUSION

This Account summarizes work on β-peptoids performed in our laboratory as well as by others over the past decade. We first became involved in the investigation of these peptidomi-

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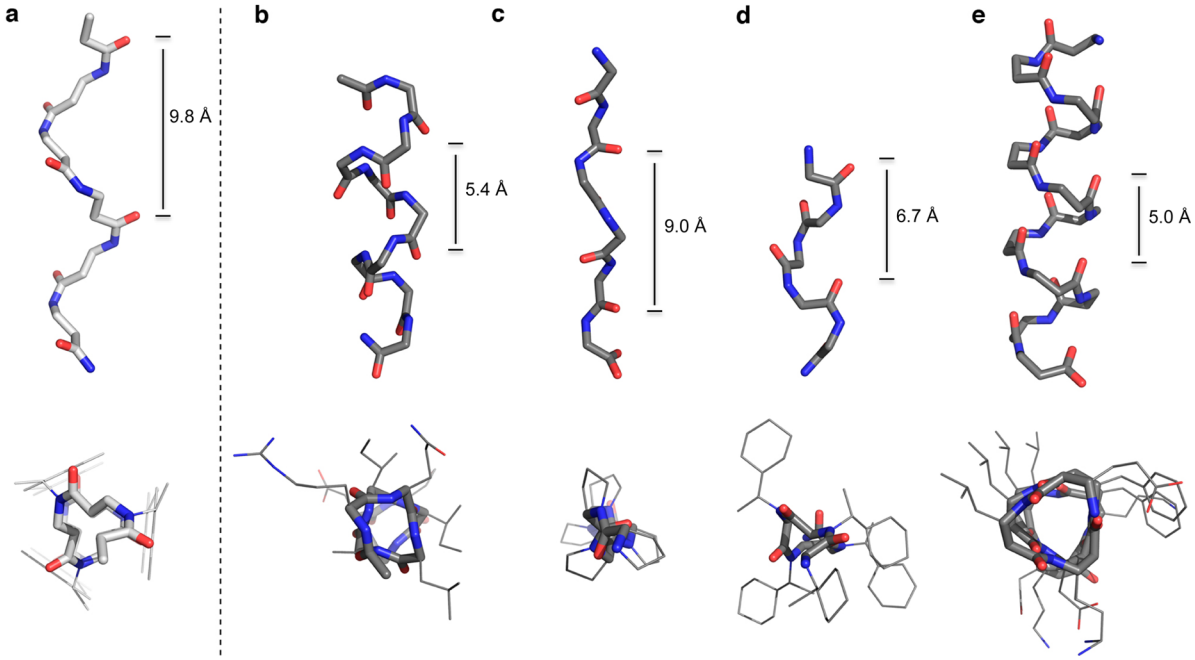

Figure 10. Comparison of (a) β-peptoid helix to (b) α-helix (PDB: 1BXL), (c) polyproline type II helix (CCDC: 1014542), (d) peptoid helix,[61] and (e) β-peptide 14-helix (CCDC: 633286).

metics by asking the question of whether this backbone could serve as a useful addition to the existing types of foldamers. Recently, we were then able to show that β-peptoids can indeed be designed in a fashion that enables robust, and unique, helical folding. En route to this realization, we successfully incorporated β-peptoid residues in a variety of unstructured, biologically active hybrid oligomers mixed with α-amino acids, which furnished peptidomimetics with potent antimicrobial, antiplasmodial, and cell-penetrating activities among others. We now envision that the discovery of well-defined folding patterns should enable structure-based design of β-peptoid-based materials with a variety of novel applications.

AUTHOR INFORMATION

Corresponding Author

* E-mail: cao@sund.ku.dk.

Notes

The authors declare no competing financial interest.

Biographies

Jonas S. Laursen received his M.Sc. in chemistry from the University of Copenhagen under the supervision of Prof. Mogens B. Nielsen. He then moved to the Technical University of Denmark to pursue a Ph.D., studying β-peptoids as novel biomimetic scaffolds in the group of Prof. Olsen. After receiving his Ph.D. in 2014, Jonas continued as a postdoctoral fellow in this group.

Jens Engel-Andreasen received his M.Sc. in pharmaceutical chemistry in 2011 at the University of Southern Denmark under supervision of Prof. Trond Ulven. He then joined the group of Prof. Olsen to complete his Ph.D. in 2015 at the Technical University of Denmark, working on peptidomimetics with new backbone architectures. Jens is currently a postdoctoral fellow in this group.

Christian A. Olsen obtained a M.Sc. in chemical engineering and organic chemistry in 2000 and completed his Ph.D. in 2004 at the Danish University of Pharmaceutical Sciences. After independently working on the development of novel peptidomimetic antimicrobial agents, he joined Prof. Ghadiri's laboratory at The Scripps Research Institute in 2007. In 2010, he returned to a faculty position at the Technical University of Denmark, and in 2014 he moved to his current position as full professor at the University of Copenhagen, Denmark.

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