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Foldamers: A Manifesto

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Introduction

Nature relies on large molecules to carry out sophisticated chemical operations, such as catalysis, tight and specific binding, directed flow of electrons, or controlled crystallization of inorganic phases. The polymers entrusted with these crucial tasks, mostly proteins but sometimes RNA, are unique relative to other biological and synthetic polymers in that they adopt specific compact conformations that are thermodynamically and kinetically stable. These folding patterns generate "active sites" via precise three-dimensional arrangement of functional groups. In terms of covalent connectivity, the groups that comprise the active site are often widely spaced along the polymer backbone.

The remarkable range of chemical capabilities that evolution has elicited from proteins suggests that it might be possible to design analogous capabilities into unnatural polymers that fold into compact and specific conformations. Since biological evolution has operated under many constraints, the functional properties of proteins and RNA should be viewed as merely exemplifying the potential of compactly folded polymers. The chemist's domain includes all possible combinations of the elements, and the biological realm, vast and complex though it may be, is only a small part of that domain. Therefore, realization of the potential of folding polymers may be limited more by the human imagination than by physical barriers.

I use the term "foldamer" to describe any polymer with a strong tendency to adopt a specific compact conformation. Among proteins, the term "compact" is associated with tertiary structure, and there is as yet no synthetic polymer that displays a specific tertiary structure. Protein tertiary structure arises from the assembly of elements of regular secondary structure (helices, sheets, and turns). The first step in foldamer design must therefore be to identify new backbones with well-defined secondary structural preferences. "Well-defined" in this case means that the conformational preference should be displayed in solution by oligomers of modest length, and I will designate as a foldamer any oligomer that meets this criterion. Within the past decade, a handful of research groups have described unnatural oligomers with interesting conformational propensities. The motivations behind such efforts are varied, but these studies suggest a collective, emerging realization that control over oligomer and polymer folding could lead to new types of molecules with useful properties. The purpose of this "manifesto" is to introduce a large audience to the broad research horizons offered by the concept of synthetic foldamers.

The path to creating useful foldamers involves several daunting steps. (i) One must identify new polymeric backbones with suitable folding propensities. This goal includes developing a predictively useful understanding of the relationship between the repetitive features of monomer structure and conformational properties at the polymer level. (ii) One must endow the resulting foldamers with interesting chemical functions, by design, by randomization and screening ("evolution"), or by some combination of these two approaches. (iii) For technological utility, one must be able to produce a foldamer efficiently, which will generally include preparation of the constituent monomers in stereochemically pure form and optimization of heteropolymer synthesis. Each of these steps involves fascinating chemical challenges; the first step is the focus of this Account.

Principles

As one sets out to create synthetic foldamers, it is useful to identify general principles that govern the conformations of the biofoldamers, proteins and RNA. Three principles seem to be particularly important: (i) hierarchical organization of conformation (secondary structure vs tertiary structure); (ii) cooperativity in higher order structures; (iii) sequence heterogeneity. These three principles are elaborated upon below.

Conformational analysis of both proteins[1] and RNA[2] is hierarchical. For proteins, the term "secondary structure" refers to local conformational preferences of the poly(α-amino acid) backbone. The most common regular elements of secondary structure include α-helices, β-turns, and β-strands; β-strands are usually found in side-by-side sets that comprise β-sheets. The "tertiary structure" of a protein is the way in which various elements of regular secondary structure, and irregular connecting segments, are packed together. For RNA, secondary structure refers to the pattern of base pair formation, and tertiary structure is the three-dimensional packing of duplex and nonduplex segments. Thus, the concepts of tertiary structure are comparable for the two biofoldamers, but the concepts of secondary structure differ, which reflects a key difference in the network of noncovalent forces that specifies folding in proteins and RNA. In proteins, regular secondary structures are defined largely in terms of H-bonding between sites embedded in the polymeric backbone, while in RNA, regular secondary structure is defined in terms of base pairing. It should be noted that these defining interactions are not necessarily the only, or even the major, driving forces for observed secondary structures;

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other important factors include the intrinsic conformational preferences of the backbone, dispersion interactions, polar interactions, and solvation (e.g., the hydrophobic effect).

The sophisticated chemical functions carried out by the biofoldamers nearly always require a specific tertiary fold, presumably because it is only at the level of tertiary structure that there is enough structural variation to allow wide latitude in the arrangement of the functional groups that constitute the active site. Proteins and RNA seem to teach us, however, that we will not be able to generate new tertiary structures until we know how to identify unnatural backbones that are predisposed to adopt specific secondary structures. The types of secondary structure most crucial for foldamer development are those that display long-range order, helices and sheets. Chan and Dill have predicted that these two long-range secondary structures will be characteristic of all compactly folded polymers.[3] Strictly local secondary structures, like β-turns and other loops, should be relatively easy to contrive once a backbone with suitable long-range folding properties is identified.

Cooperativity is probably essential to sophisticated chemical functions, since this feature guarantees the integrity of active sites in the folded state. Active sites are generally comprised of functional groups drawn from different regions of the linear polypeptide chain. A cooperatively folded structure will have all the important groups in place at the same time, since the entire structure is more stable than the sum of its parts. A single long segment of α-helix, for example, is more stable than several short α-helical segments, of equivalent total length.[4] Protein tertiary structure formation is also cooperative: partially folded states are less stable than either the native state or the denatured state.[1] Therefore, proteins tend not to unravel a little bit at a time, but rather, when sufficiently mistreated, to come apart all at once. This behavior means that a protein's tertiary structure is more stable than any of the component α-helices or β-sheets in isolation. For RNA, secondary structure (duplex) formation is cooperative, and tertiary structure also appears to be cooperative, at least at high Mg^{2+} concentrations.[2b] Interestingly, RNA duplexes are generally more stable than tertiary structures built up from duplexes;[2b] thus, the relative stability of secondary and tertiary structure is reversed in RNA relative to proteins.

It is not clear whether cooperativity at the tertiary structure level requires that the component secondary structures themselves be cooperatively stabilized. It should be possible to probe this intriguing question with synthetic foldamers, since some of the unnatural backbones currently being explored may not display cooperativity at the secondary structure level.

For a foldamer to favor a single tertiary structure, the molecule must be a heteropolymer, i.e., composed of two or more types of monomers.[3] Homopolymers can adopt compact conformations, but there will be multiple folding patterns of equal free energy if all residues are the same. Sequence heterogeneity is not required in the first phases of foldamer development, however, since heterogeneity is not necessary to explore the possibility of long-range secondary structural order in a given backbone.

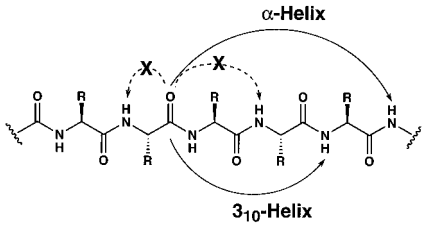


FIGURE 1. Poly(α-amino acid) backbone. The solid curved arrows indicate H-bonds associated with the two types of helices in proteins. The dotted curved arrows indicate "nearest-neighbor" H-bonds, which are unfavorable.

β-Peptides: A Case Study

Within the past decade, the folding properties of several types of synthetic oligomers with unnatural backbones have been explored. I will focus on oligo(β-amino acids) ("β-peptides"), because this type of oligomer is among the most thoroughly characterized at present, in terms of folding properties. Seebach's group at the ETH in Zürich[5] and our group[6] have been the most active in the exploration of short β-peptides.[7]

Our initial efforts were aimed at identifying backbones that favored helical secondary structures. Devising minimum increments of helix is simpler than devising minimum increments of sheet, since creating a sheet increment requires that one identify a nonsheet segment with which to link adjacent strands. This topological distinction underlies a remarkable dichotomy in protein science: there is considerable information on the properties of isolated helices,[8] but little information on the properties of isolated sheets, because soluble helix models are readily available, while soluble sheet models are hard to come by.

We suspected that two features of protein helices (α and 3_{10}) might be generalizable.[6a] First, formation of a specific protein helix is associated with a particular type of backbone H-bond (Figure 1). Thus, we speculated that synthetic foldamer backbones must contain complementary "sticky sites". Although the complementary sticky sites are H-bond donors and acceptors in proteins, any sites that can engage in specific noncovalent attraction can serve this function. Second, H-bonding between nearest-neighbor backbone amide groups in proteins is unfavorable. Nearest-neighbor interactions involve five- or seven-membered H-bonded rings (Figure 1), which do not allow optimal H-bond geometries. We therefore proposed that compact folding patterns would be most likely when nearest-neighbor sticky interactions are unfavorable.

We carried out model studies to determine the suitability of β- and γ-amino acids as foldamer building blocks.[6a] We found that the unsubstituted γ-amino acid backbone was conducive to nearest-neighbor H-bonding, while the unsubstituted β-amino acid backbone was not, which suggested that β-peptides were more promising as

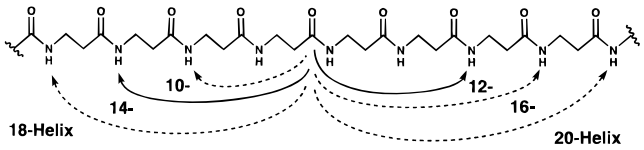


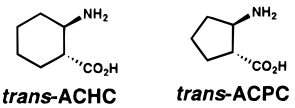
FIGURE 2. Poly(β-amino acid) backbone. The curved arrows indicate H-bonds associated with the six tightest helices available to β-peptides. The solid arrows indicate the two helices that have been documented in short β-peptides.

foldamers than γ-peptides. Figure 2 shows the H-bonds that define the six tightest helices available to the β-peptide backbone (nearest-neighbor H-bonds neglected). We designate these helices with a numeral that defines the H-bonded ring size.

Homopolymers constructed from β-amino acids (members of the nylon-3 family) have been studied since the 1960s, although no high-resolution structural data are yet available for these materials. Poly-β-alanine, $[NHCH_2\text{-}CH_2C(=O)]_n$, is believed to adopt a sheet secondary structure in the solid state, but to be disordered in solution.[9] A number of optically active nylon-3 derivatives have been examined, with poly(α-isobutyl-L-aspartate) receiving particularly intensive scrutiny.[10] This polymer was first reported to adopt sheet structure in the solid and solution, but later workers concluded that the solid state conformation is helical, specifically, 16-helix.[11] A second crystalline polymorph was subsequently discovered, and assigned as 20-helix.[12] Further analysis of these two forms of poly[α-isobutyl-L-aspartate], however, led to a reassignment of the solid state conformations as 14- and 18-helix.[13,14] Since none of the methods employed to analyze these polymers provide detailed structural insight, these proposed conformations are still subject to verification.

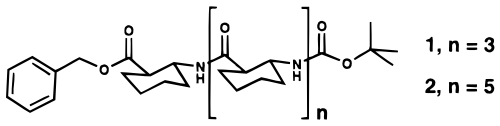
We focused on conformationally rigidifed residues in constructing helical β-peptides, because of our long-term interest in generating stable tertiary folding patterns with a minimum number of residues. β-Amino acids, and other extended amino acids, are intriguing in this regard, because it is possible to incorporate the amino acid backbones into small rings, which greatly restricts flexibility without blocking H-bonding sites. Natural proteins typically require >100 residues to display stable tertiary structure, particularly in the absence of internal disulfides, but chemical synthesis of specific heteropolymers of this length is not practical. Careful choice of preorganized monomers may lead to foldamers of <40 residues with stable tertiary structure.

To identify specific targets for synthesis, we used computational techniques to screen a library of hypothetical β-peptide helices composed of rigidified residues.[6b] With the flexible β-alanine backbone (ten residues), each of the six helices indicated in Figure 1 is stable, according to common force fields (i.e., each deca-β-alanine helix is a local minimum on the conformational energy surface). For each helix, the two saturated carbon atoms of each residue were incorporated into a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl ring. For each ring size, both *cis* and *trans* configurations of the carboxyl and amino substituents were explored, and for the *cis* rings, both of the possible ring orientations relative to the helix axis were examined. This process generated 72 β-peptide homodecamers (six helix types × four cycloalkyl types × [one *trans* + two *cis* forms]). These 72 helical decamers were then subjected to minimization and, in some cases, dynamics. Two helices were predicted to be particularly stable: the 14-helix with *trans*-2-aminocyclohexanecarboxylic acid (*trans*-ACHC) and the 12-helix with *trans*-2-aminocyclopentanecarboxylic acid (*trans*-ACPC). The 12-



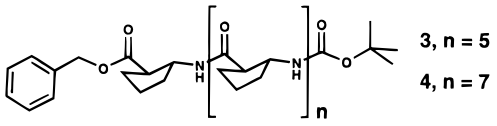
and 14-helices are very different conformations, because the H-bonds of these two helices point in opposite directions, relative to the termini (Figure 2). Thus, the conformation-dependent dipoles of the 12- and 14-helices also point in opposite directions. There is no precedent among α-amino acid-based peptides for such a switch in H-bond directionality.

Both the 14-helix/*trans*-ACHC prediction and the 12-helix/*trans*-ACPC prediction proved to be correct. Crystal structures of a tetramer (**1**) and a hexamer (**2**) of optically



active *trans*-ACHC revealed perfect 14-helical conformations in each case (Figure 3).[6b] We have not yet been able to acquire high-resolution structural data in solution for **1** or **2**, because of extensive overlap among the ^{1}H NMR resonances of these homooligomers; however, H/D exchange studies involving the backbone amide groups suggest that the hexamer adopts an exceedingly stable internally H-bonded conformation in methanol. Independent of our work with *trans*-ACHC oligomers, Bode and Applequist predicted that *trans*-ACHC would be particularly prone to 14-helix formation.[14b]

Crystal structures of a hexamer (**3**) and an octamer (**4**) of *trans*-ACPC show the predicted 12-helical conformations (Figure 3).[6c] These homooligomers proved to be



amenable to NMR structure determination in pyridine-d_5 and methanol-d_3. The solution conformations generated by NOE-constrained molecular dynamics were very similar to those observed crystallographically. The fact that the computer correctly led us to two very different helices suggests that it may be generally possible to design (or at least discover), in a rational way, residues that promote specific secondary structures of β-peptides and other foldamers.

As our laboratory began to examine β-peptide foldamers, Seebach and co-workers were also exploring this class

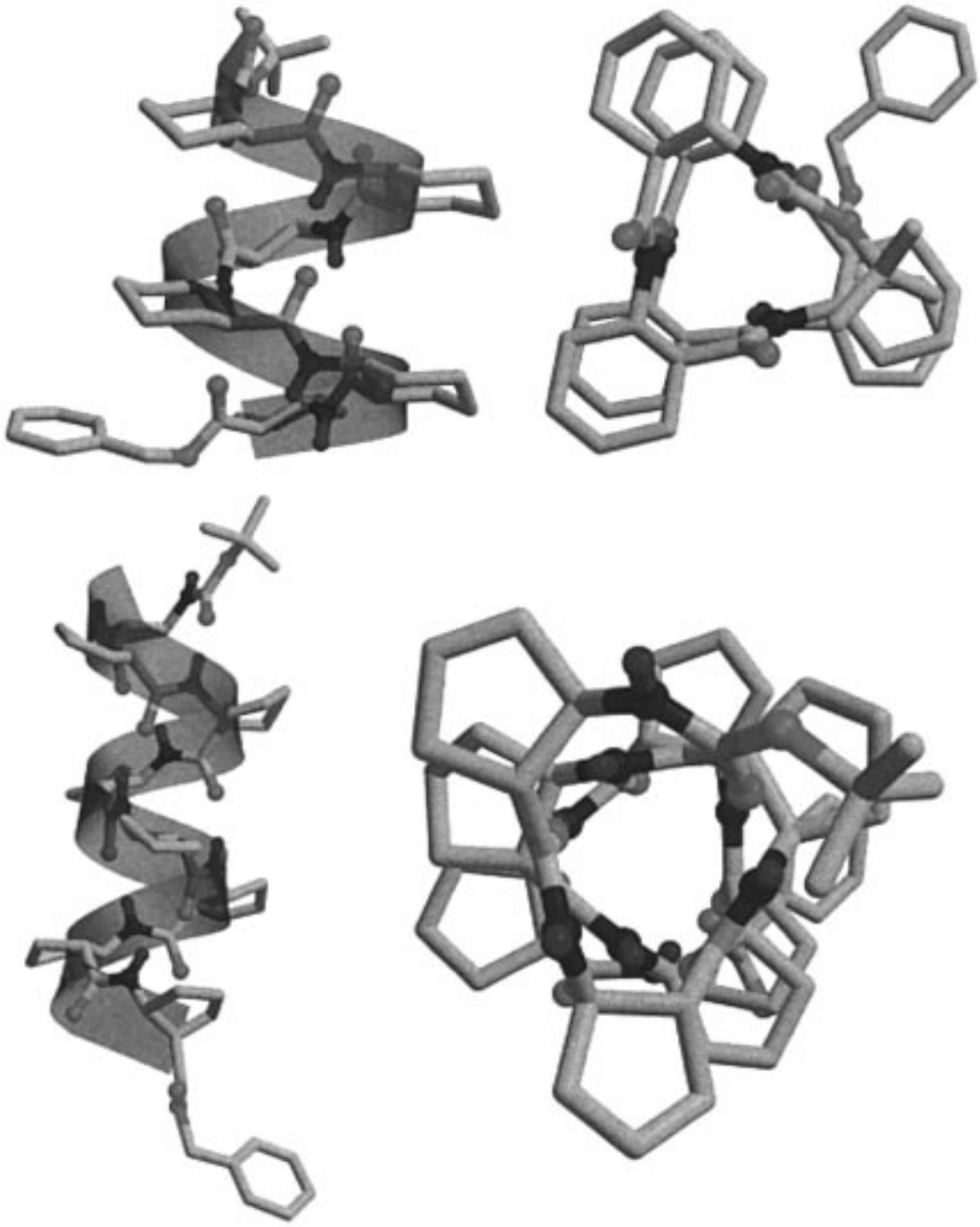
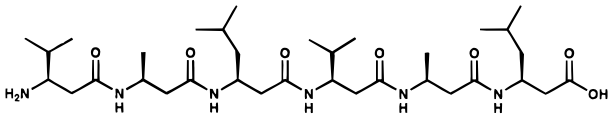


FIGURE 3. (top) Two views of hexamer **2** in the solid state[6b] (along and perpendicular to the helix axis). This hexamer was constructed from (*S*,*S*)-*trans*-ACHC, although the structure shown for hexamer **2** in the text is based on (*R*,*R*)-*trans*-ACHC. (Tetramer **1**, which also displays the 14-helical conformation in the solid state, was constructed from (*R*,*R*)-*trans*-ACHC.) (bottom) Two views of octamer **4** in the solid state[6c] (along and perpendicular to the helix axis). This octamer was constructed from (*R*,*R*)-*trans*-ACHC, as shown in the drawing of **4**. See ref 41 for graphics programs.

of compounds, starting from a different class of β-amino acid building blocks.[5] The interest of Seebach et al. in β-peptides arose from their study of poly(hydroxybutyrate) (PHB).[15] Seebach et al. proposed that PHB could adopt a 3_1-helical conformation (this designation arises from the crystallographic nomenclature for screw axes), and they recognized that this 3_1-helix could be reinforced by interresidue H-bonding if the ester linkages were replaced by secondary amide linkages. The resulting conformation is what we designate the 14-helix (Figure 1). Seebach et al. developed an elegant method for incorporating optically active β-substituted residues into β-peptides.[5a] Two-dimensional ^{1}H NMR data for heterohexa-β-peptide **5** reveal that a 14-helix is adopted in pyridine-d_5[5a] (this conformation was subsequently detected in methanol as well[5b]). Seebach et al. have carefully examined the effects



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of substituent position and configuration on 14-helical folding,[5b,c] and shown that β-peptides are resistant to the action of proteases,[5d] which bodes well for medicinal applications.

It is remarkable that hexamer **5**, composed of only β-substituted β-amino acids, has a strong tendency to adopt a specific helical conformation in a polar solvent, because this molecule appears at first glance to be quite flexible. The behavior of **5** demonstrates that it is not necessary to preorganize the β-peptide backbone with cycloalkyl groups for helical folding in organic solvents. Nevertheless, we suspect that the cycloalkyl rings (e.g., in **1**−**4**) confer enhanced conformational stability, which will be helpful for achieving stable tertiary structures with the fewest possible residues. Further, selecting among alternative secondary structures, e.g., 14- vs 12-helix vs other helices in Figure 1, may be facilitated by the use of conformationally constrained residues.

There is a great deal yet to be done in the development of β-peptide foldamers, from both fundamental and applied perspectives. It will be interesting to see whether small, discrete β-peptide sheets can be created in solution. The analogous goal has been difficult to achieve with conventional peptides, because sheet-forming segments tend to aggregate and precipitate; however, some success in this area has recently been reported from several laboratories.[16] We have very recently found that β-amino acid residues bearing one substituent at the α-carbon and one substituent at the β-carbon, in the proper relative configuration, are particularly well suited for adoption of sheet secondary structure.[6d] It should be possible to achieve β-peptide tertiary structure in aqueous solution by following strategies for the design of conventional polypeptides that adopt a "helical bundle" architecture.[17]

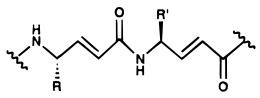
I have stressed the importance of achieving tertiary structure in unnatural foldamers, as a prelude to developing sophisticated functions, but it must be pointed out that short oligomers with discrete and predictable secondary structural preferences are themselves potentially useful. One obvious application would be to use such molecules as scaffolds for combinatorial chemistry. The covalent connectivity between two sites on the backbone of such a molecule translates directly into the geometric relationship between those sites in solution; this relationship does not hold for commonly employed oligomers, such as conventional peptides, because of conformational flexibility.[18]

DNA and RNA Analogues

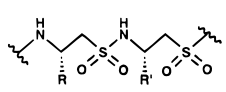
Oligonucleotide analogues, in which the ribofuranoside−phosphate or deoxyribofuranoside−phosphate backbone of RNA or DNA is replaced by other backbones, have been the subject of intensive recent investigation.[19] Much of this work has been motivated by the prospect of developing "antisense" pharmaceutical agents, and the intrinsic conformational properties of these nucleotide analogues have generally not been a central concern, beyond the obvious requirement that there be an accessible conformation that is suitable for heteroduplex or triplex formation. Fundamental studies of the effects of backbone modification on nucleotide analogue secondary structure have been carried out by several groups.[20,21]

Other Foldamers

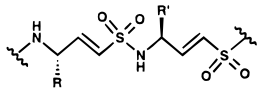
Within the past several years, several groups have examined new types of oligomers intended to adopt secondary structures that are specified by backbone H-bonding. In an effort to generate "new classes of protein-like substances with alternative backbones", Clardy, Schreiber, and co-workers have examined the conformational properties of small peptide analogues containing "vinylogous amino acids".[22] Gennari et al. have pushed beyond the use of carboxamides as the H-bonding sites in the backbone by examining the folding of oligosulfonamides ("β-sulfonopeptides"[23] and "vinylogous sulfonopeptides"[24]).



Vinylogous peptide



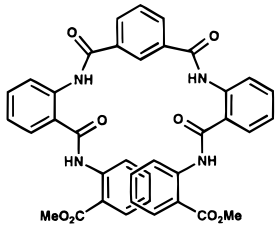
β-Sulfonopeptide



Vinylogous sulfonopeptide

Like α-peptides and β-peptides,[6a] both types of sulfonopeptides eschew nearest-neighbor H-bonding. It will be very interesting to see whether sulfonopeptides containing greater numbers of residues adopt extended secondary structures (helices or sheets). The data reported so far indicate that the folding properties of small sulfonopeptides and small conventional peptides are analogous in nonpolar solvents; in both classes, medium-range intramolecular H-bonds promote specific folding patterns. α-Aminoxy acid residues, on the other hand, appear to have a strong preference for nearest-neighbor hydrogen bonding.[25]

Hamilton et al. have examined oligomers generated from anthranilic acid and pyridine-2,6-dicarboxylic acid units, in which H-bonds between nearest-neighbor groups help enforce particular structures.[26] Heteropentamer **6**



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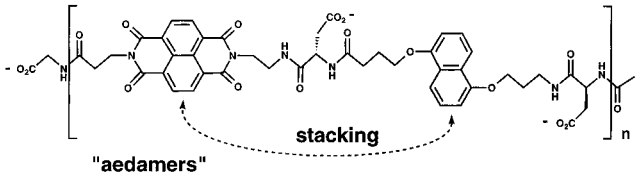
adopts a helical conformation in the solid state and in chloroform solution, with the terminal aromatic rings

partially overlapped. As Hamilton et al. have pointed out,[26b] the structure of **6** is reminiscent of helicene conformations. These structures are also related to those of helicates, in which oligopyridines are organized into helical conformations by coordination to metal ions.[27]

In a creative departure from the use of H-bonds, Lokey and Iverson have employed donor−acceptor interactions between aromatic groups as the intramolecular driving force for adoption of compact conformations.[28] These workers concluded that the resulting "aedamers" adopt a

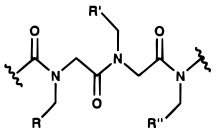


"pleated secondary structure" in aqueous solution. Several conventional polymers display helical conformations in the absence of H-bonding, including polyisocyanides,[29] polyisocyanates,[30] poly[(triarylmethyl) methacrylates],[31] polyaldehydes,[32] and polyproline.[33]

Some oligomers with interesting conformational properties have emerged from experimental efforts aimed at mimicking natural architectures, rather than creating new architectures; nevertheless, these results are intriguing from the unnatural foldamer perspective. One example is work of Nowick et al. on oligoureas designed to serve as scaffolds for parallel β-sheet formation by conventional peptide fragments.[34] Another example, from Smith, Hirschmann, and co-workers, involves oligopyrrolinones intended to mimic extended peptide strands, and thereby function as peptidase inhibitors.[35]

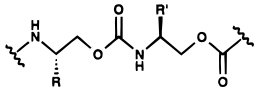
Foldamers vs Sequenceamers

The ever-increasing interest in combinatorial methods has spawned synthetic investigation of many new types of oligomers. We refer to such oligomers as "sequenceamers" rather than "foldamers" if conformational properties are not of central interest and/or not investigated. Development of new oligomeric backbones for combinatorial applications has tended to focus on synthetic concerns, rather than conformational properties. Most tenets of combinatorial chemistry were first explored with conventional peptides, which seldom have well-defined conformations in aqueous solution. Indeed, the conformational flexibility of conventional peptides has been viewed as a positive feature for identifying pharmaceutical lead compounds, since structural rigidification can preclude conformations required by a binding site. "Peptoids", one

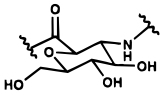


of the first types of unnatural oligomer developed for pharmaceutical/combinatorial applications, were designed with the expectation that they would explore a greater range of conformation space than do peptides constructed from conventional amino acids.[36] (The tertiary amide groups of peptoids sample both *E* and *Z* configurations about the C−N bond, while the secondary amide groups of conventional peptides are limited to the *Z* configuration.) It has recently been shown, however, that oligopeptoids bearing stereogenic centers on the nitrogen appendage adopt helical conformations in water and other solvents.[36b,c] These remarkably stable helices contain *E* configurations about the amide C−N bonds. The new helical peptoids are clearly foldamers rather than merely sequenceamers.

In 1993, Schultz et al. described a family of oligocarbamate sequenceamers constructed from optically active monomers that were, in turn, derived from α-amino acids.[37] Preparation of related sequenceamers has sub-



sequently been reported by several laboratories.[38,39] Particularly interesting from the foldamer standpoint have been recent reports of oligoamides constructed from monosaccharide-derived amino acids,[40] since the pyranose and furanose rings provide conformational rigidification. Indeed, Ichikawa et al. have reported a tetramer of glucosamine-derived β-amino acids (**7**) that is a highly



functionalized analogue of β-peptide tetramer **1**.[40c] Since the conformational properties of carbohydrate-derived oligoamides have not yet been described, I presently class these molecules as sequenceamers. The distinction between sequenceamers and foldamers is not rigid, however, and a set of oligomers may move from the former to the latter category if these oligomers are shown to have well-defined conformational propensities.

Perspective

In light of the remarkably consistent reliance of biological systems on polymeric agents to perform complex chemical tasks, it is very tempting to conclude that unnatural polymeric agents will also prove to be capable of performing useful functions. Such functions could mimic those of the biofoldamers, for therapeutic applications, or one might optimize foldamers for operations that nature has never needed to carry out. Before we can think in detail about the sorts of molecular tasks foldamers might perform, we must have a greater ability to design foldamers with well-defined and predictable shapes. We must also have efficient synthetic routes to these foldamers, which will undoubtedly be heteropolymers of irregular but defined sequence. In the early stages of foldamer research, we can see that the design and synthetic challenges are profound, which should be a cause for celebration among chemists interested in basic research. I

predict that the 20th century will come to be viewed as the period in which chemists acquired synthetic and technical mastery over small molecules, and the 21st century as the period in which that mastery was extended to heteropolymers. Mastery over foldamers should provide access to a new universe of molecules that profoundly influence chemistry and society.

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Note Added in Proof. A set of meta-linked phenylacetylene oligomers that undergo solvent-dependent collapse has recently been described (Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. *Science* **1997**, *277*, 1793). A helical conformation has been proposed for the collapsed conformation. If this proposal can be verified, these meta-linked phenylacetylene oligomers will join the polymers described in refs 15 and 29−33 as examples of non-hydrogen-bonded helices.

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