

Editorial

Peptoids at the 7th Summit: Toward Macromolecular Systems Engineering

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ABSTRACT:

Methods for facile synthesis of extraordinarily diverse peptide-like oligomers have placed peptoids at the center of a broad and vibrant area of foldamer science and technology. The 7th Peptoid Summit offered a perspective on the current state of peptoid science and technology and on prospects for engineering supramolecular assemblies that rival the complexity of biomolecular systems.

Methods for engineering biomolecular systems based on DNA and protein are advancing rapidly, building a technology platform for engineering increasingly large and complex self-assembled nanosystems. A comparative review of the physical basis for DNA, protein, and peptoid engineering indicates that the characteristics of peptoids suit them for a strong role in developing self-assembled nanosystems. Physical parallels between peptoids and proteins indicate that peptoid engineering, like protein engineering, will require specialized software to support design. Access to novel side-chain functionality will enable peptoid designers to exploit novel binding interactions, including many that have been discovered and exploited in crystal engineering, a field that has extensively explored the self-assembly of small organic molecules to form well-ordered structures. Developments in DNA, protein, and inorganic nanotechnologies are converging to provide a technology platform for the

design and fabrication of complex, functional, atomically precise nanosystems. Peptoid-based foldamer technologies can contribute to this convergence, expanding the scope of the emerging field of atomically precise macromolecular nanosystems. © 2011 Wiley Periodicals, Inc. *Biopolymers* (Pept Sci) 96: 537–544, 2011.

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INTRODUCTION: AT THE SUMMIT

The presentations and discussion at the 7th Peptoid Summit (August 2010) offered a stimulating cross-sectional view of current progress and directions in peptoid science and technology. The topics ranged from foundations to applications, and together the presentations painted a picture of an expanding field with far-ranging potential. Here, I'd like to offer a brief overview of the meeting, then examine peptoid-centered technologies in the context both of current biomolecular engineering and of progress toward self-assembling systems at the level of complexity and functionality that we find in nature.

Directing Conformation

Techniques for modeling, synthesizing, and controlling peptoid structures are fundamental to peptoid engineering, and these foundational topics dominated the first day of the 7th Peptoid Summit.

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The opening presentations by Aaron Crapster (University of Wisconsin) and Bishwajit Paul (New York University) reported advances in directing peptoid conformations by incorporating side-chains that induce either *cis*- or *trans*-amide geometries. Today's extensive toolkit for controlling peptoid secondary structure¹⁻⁶ includes chiral side-chains that restrict conformation through steric constraints. These can induce helical structures comparable to the peptide α -helix, but stable to $>75^\circ\text{C}$ in 8M aqueous urea.⁷ The advances described at the meeting expand this toolkit and thereby expand the range of side-chain choices that are compatible with a given target conformation. These are strong contributions toward the use of peptoid oligomers as building blocks for engineering macromolecular systems.

Modeling and Design

Experience in the parallel field of protein engineering indicates that design of complex peptoid assemblies will require support from software tools that integrate design and modeling. To this end, Vincent Voelz (Simprota) examined the strengths and weaknesses of existing molecular mechanics force fields as a basis for molecular dynamics simulations of peptoids and Dina Mirijanian (Lawrence Berkeley National Laboratory) described extensions of the CHARMM⁸ force field that improve the accuracy of peptoid modeling. Glen Butterfoss (New York University) discussed applications of high-level quantum mechanics calculations to map energies across backbone-conformation space,⁹ providing results that can enable energy calculations and molecular dynamics methods that more closely track reality.

In the parallel field of protein engineering, the Rosetta-Design software toolkit (part of the Rosetta toolkit for Protein Science¹⁰) has supported developments that range from novel¹¹ and highly stable¹² folds to enzymes that catalyze Diels-Alder and retro-aldol reactions.^{13,14} I was pleased to learn over lunch that Glenn is involved in extending the RosettaDesign code to support peptoid engineering.

In an engineering context, it is important to note that conservative design can substantially compensate for inaccurate modeling. Making design choices that are, in aggregate, predicted to *strongly* stabilize an intended fold or binding interaction can mask errors in predicting the magnitude—and even the sign—of the effects of individual choices within that set. In scientific analysis, masking errors is a problem; in design, it is a source of robustness. As a (superficially) paradoxical consequence of this, a force field that cannot reliably predict the conformations of small structures may nonetheless prove to be a robust basis for engineering larger structures, because these can be stabilized by a larger set of cooperative interactions.

Further, while the aim in science is to find a unique answer to a question (the answer that corresponds to reality), the aim in engineering is more forgiving: It is to identify one or more effective solutions to a problem, and there will typically be many. These considerations—the masking of modeling errors by strong stabilization, the associated advantage of larger structures, and the typical multiplicity of solutions—should encourage boldness in undertaking the engineering of large self-assembled nanosystems.

Peptoid Nanosheets

In peptoid self-assembly, the most exciting development of the past year has been the synthesis of peptoid nanosheets, crystalline bilayers with a thickness of 2.7 nm and transverse dimensions that can exceed 100 μm .¹⁵ Peptoid nanosheets sandwich hydrophobic side-chains between surfaces that display alternating strips of positive and negative charge carried by parallel all-*trans* peptoid oligomers bearing 2-aminoethyl and 2-carboxyethyl side-chains. These structures resemble β -sheet secondary structures found in proteins and could potentially play a similar role in peptoid engineering. The potential diversity of peptoid nanosheet variants offers unique opportunities for functional engineering and suggests prospects for extensive applications as robust lipid-membrane analogs.¹⁵ At the meeting, Romas Kudirka reported advances in understanding how these nanosheets form: The crucial first step is the formation of amphiphilic monolayers at the air-water interface. The monolayers grow as interfacial area increases (for example, by bubble formation), and they are driven to fold into solution-phase bilayers as the interfacial area is reduced (for example, by bubble coalescence and collapse). A key to this insight was the discovery that the peptoid cocktail must be shaken, not stirred.

Synthesis

The submonomer method of peptoid synthesis established the field as we know it today,^{16,17} but recent developments, some described at the meeting, can play a complementary role. I will say more about the special characteristics of the submonomer method below, and about the value of augmenting main-chain synthesis with methods for creating macrocycles, a topic addressed at the meeting by Donghui Zhang (Louisiana State University), Mia Huang (New York University), and Hyun-Suk Lim (Indiana University).

Applications

Application-oriented peptoid research has been driven largely by objectives in biology and medicine,¹⁸⁻²³ which exploit not only the ability of peptoids to mimic peptide functions, but also their greater stability against enzymatic

degradation and a more facile access to nonbiological side-chain functionality. The 7th Peptoid Summit reflected the strength of innovation in this area, with presentations spanning the fields of biomolecular sensing, drug delivery, antimicrobial and anti-biofilm agents, and cancer therapeutics, alongside advances in the combinatorial synthesis and screening techniques that support much of this work. I expect that the spectrum of biological and medical applications will expand together with the scope of peptoid engineering, and in concert with applications that may reach far beyond biology, deep into the world of nanostructured materials²⁴ and self-assembling nanosystems.²⁵

THE PEPTOID TECHNOLOGY PLATFORM

The 7th Peptoid Summit offered a perspective on the status of the field; in the following sections, I will outline what the fundamental nature of peptoid science and technology indicates regarding its prospective contributions to engineering atomically precise macromolecular systems.²⁵ This motivates a review of the physical basis for recent achievements in protein and DNA engineering and an examination of the suitability of peptoids and related polymers for implementing analogous molecular components with extended capabilities.

Accessing Diverse Functionality

The submonomer method of solid-phase peptoid synthesis provides facile access to an unprecedented range of side-chain functionality by enabling the direct incorporation of inexpensive and commercially available primary amines.¹⁷ Access to diverse peptide sequences, by contrast, is hampered by the limited commercial availability and challenges of synthesizing protected α -amino acids. The wide range of readily available unprotected and side-chain protected primary amines is partly a consequence of the demand for diverse building blocks to support drug discovery.

Ease of synthesis is important, and the synthesis of peptoid oligomers is easy enough to be recommended as an exercise for second-year undergraduates.²⁶ Much of the promise of peptoid technology stems from its applications in solving problems in areas where peptoids *per se* are not the focus of the research. The low barrier to entry can contribute greatly to the growth of the field, and it deserves to be more widely publicized.

Although reaction yields limit solid-phase synthesis to chains no longer than a few tens of monomers, this places no direct limit on the scale of peptoid-based assemblies. Main-chain ligation, side-chain crosslinking, and non-covalent assembly are among the means available to combine building blocks of modest size to form structures of indefinitely large

size. The functional diversity of peptoids supports the use of a wide range of assembly strategies.

Extending a Compatible Family

In an engineering context (no holds barred!) “peptoid technology” can be regarded as shorthand for a family of foldamers built using compatible chemistries for main-chain synthesis. The submonomer method can be applied to peptoids with altered or mixed backbone structures: examples include β -peptoids^{27,28} and “extended peptoids”²⁹ that employ aromatic building blocks. Peptoid chain-elongation cycles can also be interleaved with cycles that incorporate N-protected α - and β -amino acids,³⁰ typically by means of the standard Boc/Fmoc strategy. Thus, the power of peptoid side-chain diversity can be combined with backbone diversity and can be integrated with a range of other foldamer technologies—including, of course, incremental modification of naturally occurring peptide structures.

As noted above, chiral, structure-directing side-chains can induce peptoids to form stable secondary structures comparable to the peptide α -helix; hybrid backbones provide access to a range of additional helical secondary structures.^{27,30} This diversity of secondary structures available within the peptoid family of foldamers expands options for organizing side-chain functionality to satisfy design constraints on the geometry and functionality of higher-order structures.³¹

Encoding Folding and Self-Assembly

Strategies for atomically precise self assembly begin with control of covalent structure. As illustrated in molecular biology, sequential steps can assemble a sequence of components that encodes the folding of robust, pre-organized structures, and these, in turn, can direct their own assembly into larger structures. Synthetic foldamers have a similar capacity.

An important objective in foldamer engineering is to induce pre-organization that constrains ligands to geometries compatible with their intended binding modes. Pre-organization reduces the entropic penalty of binding and can destabilize or preclude alternative binding modes. These effects improve both the strength and specificity of interactions that drive folding and higher order assembly.

At the bottom of the structural hierarchy, multi-dentate ligands can be incorporated as peptoid side-chains³² and can bind to one another through coordination to a shared metal ion (a principle widely exploited in supramolecular chemistry).

At a higher level of the structural hierarchy, the formation of secondary structure can pre-organize side-chains to form complementary patterns that favor stable, selective binding within and among yet larger structures. (And, of course, the

formation of larger structures can cooperatively stabilize the secondary structures themselves.) Peptoids designed around pre-organized helical secondary structures have demonstrated protein-like folding,³³ metal binding,³⁴ and enantioselective catalytic activity.³⁵

DNA, PROTEIN, AND PEPTOID ENGINEERING

The accomplishments of structural DNA and protein engineering illustrate what could be achieved by similar engineering methods applied to peptoid and peptoid-class foldamers, and these biomolecular technologies also help to define the engineering context for developing functional peptoid-enabled systems.

In general, to the extent that peptoids can imitate or improve on the essential properties of a given class of biopolymers, one can reasonably expect that similar design methods could yield similar engineering results. To the extent that peptoid technology can incorporate components with an expanded range of physical properties (geometrical, chemical, mechanical, optical, electronic, and so forth), one can reasonably expect to find that it can deliver products with an expanded range of functional properties.

Aside from specifically biological functional properties, peptoids and peptoid-class oligomers can imitate or improve on many of the desirable features of natural biopolymers, while also providing access to components with a dramatically expanded range of physical properties. This suggests that the non-biological functional properties of products produced by means of a biopolymer-based engineering technology could typically be matched or improved upon by means of a comparably well-developed peptoid engineering technology.

Structural DNA Nanotechnology

From a design perspective, the most striking property of nucleic acids is that they display regular arrays of side-chains that exhibit selective, pairwise affinities, and that this enables strongly cooperative, highly selective binding between oligomers that display pairwise complementary sequences. The simplicity and modularity of this interaction enables complementary nucleic acid interfaces to be designed with a pencil and paper, while designing complementary protein interfaces is a challenge that requires state-of-the-art computational methods.

Structural DNA nanotechnology (SDN) exploits sequence-directed binding to engineer self-assembled systems in which strand-crossover junctions link double-strand DNA segments to form two- and three-dimensional structures.^{36,37} The scope of SDN now extends to the routine design and

fabrication of atomically precise frameworks on a scale of hundreds of nanometers and millions of atoms.^{38–40}

In the “DNA origami” methodology, DNA structures are threaded by long scaffold strands with non-repeating nucleotide sequences. Oligomeric “staple strands” bridge hundreds of distinct subsequences, directing structural organization and providing anchor points for non-DNA components.³⁸ The emerging ability to attach components of distinct kinds to specific framework sites holds great promise.

Research in materials-oriented areas of nanotechnology has developed a host of inorganic nanostructures, including nanoscale particles, rods, and tubes of oxide, metallic, and semiconductor materials (and chemically functionalized derivatives of these). In making these products, however, there is no process analogous to the controlled, information-rich, combinatorial synthesis afforded by foldamer production methods. Because they provide no means for encoding information into diverse complementary surfaces, materials-oriented synthesis methods provide no means for directing the formation of highly complex self-assembling structures.

Structural DNA nanotechnology is therefore a natural partner to materials-oriented nanotechnology: SDN enables the design and production of complex structures comparable to circuit boards, while staple strands provide a means for installing components in specific sockets.^{38,41}

Over the last decade, the global investment in developing nanoscale functional components has risen into the multibillion dollar range. Because SDN potentially offers a way to organize these functional components to form complex nanosystems, it features prominently in a recent roadmap for atomically precise nanotechnologies.²⁴

Structural DNA nanotechnology, however, is not necessarily unique. Its utility stems from a particular property of nucleic acids: highly selective cooperative binding between sequences of pairwise complementary side-chains. This property, however, is by no means limited to structures with phosphodiester backbones or biological nucleobases.^{41,42} SDN provides a model for developing other foldamer systems able to support systematic and scalable engineering of higher order structures.

Protein Engineering

The protein engineering literature traces its origin to the recognition that the problem of predicting how a natural protein will fold is fundamentally different from the problem of designing an artificial protein that will fold predictably^{43–45} and since the initial steps in the 1980s,^{46,47} protein engineering has grown to become a large and capable field. The similarity between peptides and peptoids makes protein engineering a useful model for a substantial portion of the prospective range of peptoid engineering.

The vast functional range of protein-based systems is well known: Protein mechanisms play central roles in virtually every aspect of biology—structural integrity, chemical transformation, macromolecular synthesis, mechanical motion, energy capture, and more. This rich protein functionality stems from the diversity of folded protein structures together with the diversity of the structural and chemical properties of protein side-chains. Nucleic acid structures, by contrast, offer far less structural and chemical diversity, while peptoids offer far more.

Protein engineering has demonstrated the basic capabilities necessary for architecting self-assembling systems: first, sufficient mastery of chain folding to provide stable building blocks for higher order assembly, and second, methods for tailoring building-block surfaces that will bind a wide range of other structures in specific and useful ways. Through methods that include design and directed evolution, proteins have been developed that bind other proteins,⁴⁸ inorganic materials and structures (metals, oxides, semiconductors, and nanotubes),^{49–51} and specific base-pair sequences in duplex DNA.^{52,53}

Together, these achievements make it clear that protein engineering can become a strong partner in developing complex nanosystems organized around structural DNA frameworks. They indicate that proteins can be targeted to bind specific sites on a DNA framework, to assemble larger protein complexes at those sites, and to bind diverse nanoscale functional components with control of their relative positions and orientations.

Peptoid and Composite-System Engineering

How does the peptoid family of foldamers compare to DNA and proteins as a basis for engineering functional self-assembling systems? Aside from the cost of synthesis, the most important considerations in foldamer engineering are first, the ability to incorporate diverse side-chain functionality and second, the ability to fold and organize side-chains into useful spatial patterns. The peptoid family offers advantages in both areas.

As we have seen, the submonomer method of peptoid synthesis affords easy access to an unprecedented range of side-chain functionality, and standard peptoids can form secondary structures that include extraordinarily stable helices. Further, the submonomer method can be used to produce diverse backbone structures (β -peptoids, extended peptoids) and is compatible with the incorporation of non-peptoid segments (α -amino acids, β -amino acids, and others). In conjunction with the expanding toolkit for directing peptoid conformations (discussed above), the peptoid family of

oligomers provides access to a range of secondary structures that subsumes and extends the range accessible through protein engineering.

Assembly directed by cooperative pairwise binding between sequences of side-chains provides the basis for the regularity, scalability, and modularity of structural DNA nanotechnology. This principle of assembly can be (and has been) generalized to synthetic foldamers. Peptide nucleic acids (PNAs) are leading examples^{54,55} and their synthesis by the Fmoc/Boc strategy qualifies them as members of the peptoid family of foldamers. PNAs bind with great affinity to complementary PNAs, and by design, also bind to complementary DNA sequences. Omitting the DNA-binding constraint opens a much broader design space that includes alternative backbone and side-chain structures.

Studies of protein stability enable quantitative estimates of the increments in stability that can be achieved by exploiting an expanded set of side-chains,⁵⁶ for example, by increasing the internal packing density of folded structures. Crosslinking and macrocyclization are particularly effective techniques for stabilizing folds and higher order assemblies, and facile access to diverse reactive functional groups greatly expands the scope of these methods in peptoid engineering.^{57–60} Expanded diversity also enables the use of non-covalent binding interactions beyond those known from biomolecules.^{61–65} Research in crystal engineering, a field that has extensively explored the self-assembly of small organic molecules to form well-ordered structures, has identified and characterized a wide range of these non-biomolecular interactions,^{61,66,67} suggesting novel ways to direct and stabilize foldamer structures.

Table I outlines some of the distinctive and complementary characteristics of protein, DNA, and peptoids, seen in the context of engineering complex, self-assembling nanosystems. Together, these classes of molecules provide an attractive basis for exploiting the diverse functional components provided by current materials-oriented areas of nanotechnology.

TOWARD PEPTOID DESIGN TOOLS

In a fundamental physical sense, the enormous design space opened by modern foldamer technologies offers enormous potential, but to make effective use of that physical potential will require software tools to support what amounts to a new field of engineering. Biology-based evolutionary methods (such as SELEX and phage display) are unavailable in peptoid engineering, and this highlights the importance of developing design-based methods. Protein design provides a model that illustrates the nature of the problem and some of the solutions.

Table I Comparative Engineering Characteristics of Inorganic, Biomolecular, and Peptoid Components for Self-Assembling Nanosystems Organized on Atomically Precise Frameworks

Characteristic	Inorganic Nanostructures	Structural DNA	Engineered Proteins	Peptoid Foldamers
Scale of single units	~1–100 nm	~100 nm	~3 nm	~3 nm
Granularity of design	Particle	Base pair	Monomer	Functional group
Combinatorial design?	No	Yes	Yes	Yes
Atomic precision?	Rarely	Yes	Yes	Yes
Functional diversity	Enormous	Low	Large	Enormous
Potential robustness	Very high	Low	Low	High
Prospective roles in self-assembling nanosystems	Highly diverse functional components	Large-scale addressable frameworks	Diverse functional components, linking structures	Robust, highly diverse functional and structural components

The Nature of the Design Problem

In protein engineering, a designer begins by choosing an objective, for example, to identify a structure that is predicted to bind a given ligand strongly, or fit an intended backbone conformation closely, or to provide a particular functional-group configuration. An algorithm embodied in design software then searches for a sequence of monomers and side-chain conformations that will both achieve the chosen objective and adequately stabilize the folded state. The stabilizing interactions characteristic of proteins—dense packing of a hydrophobic core, formation of internal hydrogen bonds, favorable electrostatic interactions, and so on—depend on global structure and conformation. This contrasts sharply with the local pairwise complementarity that directs the folding of nucleic acid sequences in structural DNA nanotechnology.

Modern algorithms for protein design^{68,69} reflect decades of development. Research continues to explore competing methods for guiding search through the space of potential sequences and competing methods for estimating the relative stabilization energy of each candidate sequence.

The above outlines only the basic nature of problems in protein engineering. Current state-of-the-art systems do not assume a fixed backbone conformation, and the constraints of interest (and the scoring functions) may instead represent requirements for binding to a specific surface,⁷⁰ or for constructing a functional enzymatic active site.^{13,14}

Algorithms developed for protein engineering provide a starting point for developing software that is effective in other regions of the universe of peptoid-family foldamers. (Indeed, as I noted above, an effort is underway to apply the RosettaDesign code base^{71,72} to peptoid engineering.) Adapting methods to the peculiarities of a different foldamer backbone will be a necessary first step.

The Protein Data Bank has enabled the development of knowledge-based potentials that have been used to great

advantage in protein engineering. The absence of a source of equivalent information for peptoids (and the prospect of a greatly expanded range of building blocks) indicates that the alternative approach used in protein engineering, physics-based potentials, will be the appropriate model for peptoids. For the reasons noted above, structures and design methods that enable large stability margins will decrease sensitivity to modeling errors, providing a forgiving environment for the development of successful potentials.

From an algorithmic perspective, I am persuaded that the scale of the search space itself presents a more positive and novel challenge: developing methods for effectively exploiting new functional groups and interactions, and for searching across an expanded range of potential solutions. It is crucially important to recognize that, in solving a practical design problem (in sharp contrast to the essentially academic problem of finding a unique optimum with respect to a scoring function), expanding the search space doesn't hide answers: instead, it makes more and better answers available for discovery.

Peptoid, Protein, and Crystal Engineering

Peptoid synthesis methods can access a design space that is not just a few, but *many* orders of magnitude larger than the space available in protein engineering. To reach deep into this space will require new search algorithms together with appropriate models of molecular interactions unlike those found in biology. There may be lessons to learn from methods used to explore combinatorial spaces in drug design⁷³: Here, too, the search space extends far beyond the combinatorics of a small set of side-chains, and ligands that bind through non-biological interactions are common.

Knowledge from crystal engineering can help in this exploration. Crystal engineering is a burgeoning field that has developed a strong, empirical science base for predicting binding interactions among small, closely packed organic molecules. Many of these small molecules can serve as mod-

els for peptoid side-chains. Predictive potential energy functions for an extraordinary range of these interactions can be extracted through statistical analysis of the small-molecule crystal structures (>500,000) in the Cambridge Structural Database.⁷⁴ This approach parallels the use of statistics from the Protein Data Bank to develop knowledge-based potential energy functions for protein engineering.^{75–77} Knowledge gleaned for crystal engineering could play a vital role in exploring the universe of foldamers that lies beyond the familiar world of biomolecules.

Is the Essential Science in Place?

There is no end of useful knowledge yet to be learned about peptoids—better methods of synthesis, further ways to control conformations, more accurate maps of the folding landscape, and so on—and there is no end in sight to the biological questions that peptoids can help answer. The key question for engineering, however, isn't "What remains to be discovered?", but rather, "What is visibly within reach?"

The tool kit in hand for peptoid engineering is large and growing, and has already proved adequate for engineering protein-scale macromolecular objects. Exploiting side-chain diversity offers many ways to increase the predictability and stability of folds, many ways to link folded structures to form larger systems, and many ways to imbue those structures with new functions. This is enough to move forward, and with confidence that the path leads beyond today's horizon.

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