Protein Structure, Folding, and Design

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Protein Structure, Folding, and Design

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The table of contents does not necessarily follow the pattern of the plenary sessions. Instead, it reflects the thrust of the meeting as it evolved from the combination of plenary sessions, poster sessions, and workshops, culminating in the final collection of invited papers, submitted papers, and workshop summaries. The order in which articles appear in this volume does not follow the order of citation in the table of contents. Many of the articles in this volume were published in the Journal of Cellular Biochemistry, and they are reprinted here. These articles appear in the order in which they were accepted for publication and then published in the Journal. They are followed by papers which were submitted solely for publication in the proceedings.

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Preface

The field of protein engineering is rapidly approaching maturity. Recently developed technologies for producing modified or mutant proteins virtually at will and more powerful tools for analysis of protein structure have given new impetus to studies on protein structure function relationships. Proteins perform a diverse assortment of biological processes in living cells. They serve as key structural elements in cells as well as catalysists for the digestion of foodstuffs and the biosynthesis of macromolecules. This functional diversity of proteins is matched by the diversity of their structures.

One major challenge for the protein chemist is to reach an understanding of the relationship between protein amino acid sequence and three-dimensional structure. Current attempts to make specific changes that improve the properties of a given protein are still within the realm of guess work. It is clear that much more structural information must be obtained on proteins and their willfully modified derivatives to improve our knowledge of relationships between protein structure and function. Relatively small proteins, for which the three-dimensional structure is known and the gene is available for directed mutagenesis, make ideal model systems for such studies. The short term goal is to produce improvements in the properties of existing proteins, enzymes and hormones, while longer term goals include the production of synthetic enzymes that can catalyze new reactions.

The 1985 conference was in large part planned and developed at a preconference minisymposium held in March of 1984 at the University of Michigan. This minisymposium was attended by 300 scientists drawn from outside the Ann Arbor area. An advisory committee, many of whom spoke at the 1984 minisymposia, met at that time to develop plans for the UCLA symposium held in Keystone March 30–April 6, 1985. We are indebted to the contributions of this advisory committee which consisted of David Jackson, Ray Salemme and Douglas Ohlendorf from Genex Corporation; E. Thomas Kaiser from Rockefeller University; Martin Karplus from Harvard; Thomas Steitz from Yale; David Eisenberg from UCLA; and Samuel Krimm and Martha Ludwig from the University of Michigan. The advisory committee was selected so that a broad range of disciplines from protein structural analysis to analysis of function of altered genes in animals was represented.

This proceedings volume of the UCLA Symposium on Protein Structure, Folding, and Design contains 30 articles describing various approaches to the analysis of protein structure, folding and stability. Other articles describe the modification and design of specific enzymes and hormones using directed mutagenesis or, in some cases, synthetic methods. In addition to this proceedings volume, a textbook entitled "Protein Modification and Design" is being prepared for use in graduate and upper

division undergraduate courses. The textbook is designed to capture the excitement created by expectations of what protein engineering may produce and to encourage graduate students to prepare adequately for this new field. The response to this first meeting has caused us to schedule a second UCLA conference on Protein Engineering to be held April 4–14, 1987 in Steamboat Springs, Colorado.

Travel and subsistence expenses for speakers invited to the conference at Keystone were defrayed in part by a sponsorship contribution from Genex Corp., Gaithersburg, Maryland. Additional contributions were received from Monsanto Corporation Research Laboratories, Pharmacia Chemicals, Agrigenetics Research Corporation, Lilly Research Laboratories, Eli Lilly and Company, Pfizer Central Research, Pfizer, Inc., The Upjohn Company and Boehringer Mannheim Gmbh. We would like to acknowledge the continued support given by the Molecular Biology Institute in maintaining this conference series. In addition, the valuable assistance of members of the UCLA Symposia staff, including Betty Handy, Robin Yeaton and Chris Anderson is gratefully acknowledged.

Dale L. Oxender

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Design and Characterization of Peptides With Amphiphilic β-Strand Structures

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To extend our studies on peptides and proteins with amphiphilic secondary structures, a series of peptides designed to form amphiphilic β-strand structures was designed, synthesized, and characterized by circular dichroism and infrared spectroscopy. Amphiphilic β-strand conformations may be likely to appear in a variety of surface-active proteins, including apolipoprotein B and fibronectin. In a β-strand conformation, the synthetic peptides will possess a hydrophobic face composed of valine side chains and a hydrophilic face composed of alternating acidic (glutamic acid) and basic (ornithine or lysine) residues. The peptides studied had a variety of chain lengths (5, 9, and 13 residues), and had the amino groups either free or protected with the trifluoroacetyl group. While the peptides did not possess a high potential for β-sheet formation based on the Chou Fasman parameters, they possessed significant β-sheet content, with up to 90% β-sheet calculated for the 13-residue protected peptide. The driving force for β-sheet formation is the potential amphiphilicity of this conformation. The β-strand conformation of the 13-residue deprotected peptide was stable in 50% trifluoroethanol, 6 M guanidine hydrochloride, and octanol. The peptides are strongly self-associating in water, which would reduce the unfavorable contacts of the hydrophobic residues with water. It is clear that small peptides can be designed to form stable β-strand conformations.

Key words: self-association, infrared spectroscopy, Merrifield solid-phase peptide synthesis, circular dichroism, β-sheets, amphiphilic β-strand peptides

The importance of amphiphilic secondary structure in biologically active peptides and proteins has become evident in recent years. Peptides may possess a primary sequence that will cause a segregation of hydrophobic and hydrophilic residues when a secondary structure is induced. A structure of this type is ideally suited to interact with amphiphilic surfaces such as cell membranes or lipoproteins. In this laboratory, we have successfully designed and characterized peptide models of apolipoprotein A-I [1], the cytotoxin melittin [2], and peptide hormones including β-endorphin [3,4] and calcitonin [5,6], which possess potential amphiphilic α-helical segments. We have

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