PROGRESS IN BIOORGANIC CHEMISTRY AND MOLECULAR BIOLOGY

Editor

Yu. A. Ovchinnikov

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PREFACE

There is nothing new in the statement that the scientist nowadays has to spend more and more of time and effort simply trying to follow what is being done by his colleagues all over the world. Daily library work is essential for this, but there is one more effective (and pleasant) way to be constantly in touch with the latest advances in your field - that is to meet your colleagues during scientific meetings - to exchange information, to establish new contacts. The number of such conferences, national and international, is growing every year. This book deals with the one of such meetings, which is memorable in many ways.

The International Symposium "Frontiers in Bioorganic Chemistry and Molecular Biology" was held in Moscow and Alma-Ata, June 19-24, 1984 as a satellite conference of the 16th FEBS Meeting. It was also co-sponsored by the International Council of Scientific Unions and the International Union of Biochemistry. The Symposium which in fact became a "summit" meeting of world top scientists in the rapidly developing field of physicochemical biology, was also meant to commemorate the 25th anniversary of the Shemyakin Institute of Bioorganic Chemistry of the USSR Academy of Sciences.

The Symposium programme covered a wide range of aspects of modern physicochemical biology and biotechnology: investigations into structure-functional relations in peptides and proteins, nucleic acids, carbohydrates, lipids, and other bioregulators, elucidation of the structure, synthesis, study of conformational peculiarities, mechanism of biological action, membrane and receptor systems responsible for transfer of genetic information, regulation, as well as the most challenging problems of immunology, neurobiology, oncology, endocrinology, in order to solve them novel approaches and methods of chemistry and physics are employed.

Naturally, fundamental researches in these areas have become vitally important for modern medicine, agriculture, and industry. The advances of genetic and cell engineering, chemical and enzymatic synthesis, hybridom analysis, that is of biotechnology, are widely applied to facilitate their development.

The global geography of the countries represented, the variety of the areas discussed, together with an exceedingly high level of presentation, make this book particularly valuable.

I believe, the atmosphere of the Symposium promoted mutual understanding, strengthening of friendly ties and collaboration among scientists throughout the world. The Organizing Committee of the Symposium "Frontiers in Bioorganic Chemistry and Molecular Biology" expresses deep gratitude to all participants for their activity and interesting presentations.

Professor Yu.A. Ovchinnikov

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PEPTIDES AND PROTEINS SPATIAL ORGANIZATION AND FUNCTION

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PEPTIDE AND PROTEIN RESEARCH AT THE SHEMYAKIN INSTITUTE

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The 50s are marked by great advances of the world science in protein-peptide chemistry. Since 1949 the α-helix proposed by L.Pauling triumphed all over the world that opened wide the doors for penetrating into the structure of protein molecules.

V. du Vigneaud completed the chemical synthesis of the most important peptide hormone, oxytocin, later F.Sanger decipherd the amino acid sequence of the first protein, insulin. Undoubtedly studies of peptide-protein substances occupied a prominent place and captured scientists' attention.Just that time the USSR Academy of Sciences faced the necessity of organizing an Institute engaged in studies of life science, especially its chemical aspects and in 1959 the Institute for Chemistry of Natural Products was founded.

The impetuous progress in the protein and peptide chemistry made us change the traditional trends in the study of natural low molecular weight compounds of alicyclic or heterocyclic series: steroids, alkaloids, antibiotics of chloramphenicol or tetracycline groups, etc., and side with those for whom the main notions were amino acid, peptide bond, α-helix, β-structure.

M.M.Shemyakin initiated the study of peptides of a new type and since the first years of the Institute's foundation systematic investigations of atypical naturally occurring peptides, depsipeptides, containing hydroxy and amino acid residues started. Antibiotics-depsipeptides, valinomycin and enniatins, were the first in this row. In 1955 H.Brockmann and G.Schmidt-Kastner[1] isolated valinomycin from extracts of the strain *Streptomyces fulvissimus*. The structure (cyclooctadepsipeptide) proposed by. H.Brockmann and H.Geeren[2] was erroneous. As shown valinomycin is a cyclododecadepsipeptide, built of three identical tetradepsipeptide moieties[3]. The structures for enniatin antibiotics isolated by P.Plattner in 1947[4,5] from cultural liquids of *Fusarium* turned out to be also incorrect. The total synthesis showed that enniatins A and B were not cyclotetradepsipeptides, but cyclohexadepsipeptides[6,7]. The Institute developed a novel synthesis of depsipeptides: natural cyclodepsipeptides, valinomycin (Fig. 1), enniatins A, B, C, beauvericin (Fig. 2), and their numerous analogues[8].

The structure-functional studies of cyclodepsipeptides permitted the use of a topochemical principle of the peptide molecule modification for the analysis of many biologically active peptides. Now active analogues are constructed by changing the molecule as a whole, but not local regions, to maintain stereoelectron

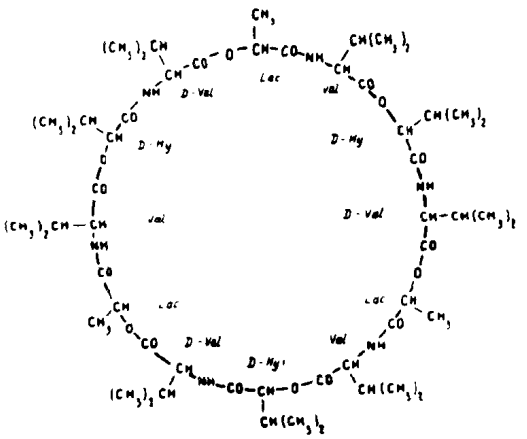

Fig. 1. Valinomycin.

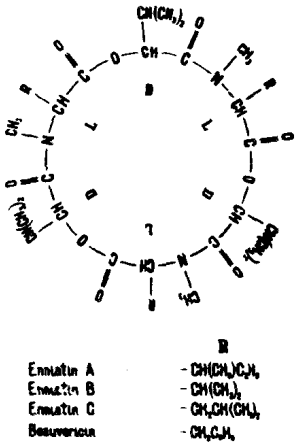

Fig. 2. Enniatin ionophores.

characteristics of the peptide. Topochemical transformations include change in the direction of acylation of residues (retro-isomers), in configuration of asymmetric centers (enantio-isomers), make possible obtaining retroenantiomers, cyclization of linear peptides, and other transformations. The topochemical approach was successfully used for investigation of structure-functional dependence for membrane-active cyclopeptides, valinomycin, enniatins, gramicidin S, and antamanide[9-11].

The work in the laboratory of Prof. V.Prelog (Switzerland), a world-known stereochemist, stimulated this approach to the peptide system modification. First publications summarize data on simple cyclopeptides, built of glycine and alanine residues[12,13].

The proper studies of depsipeptides of valinomycin and enniatin groups resulted in their wide use when studying ion permeability of artificial and biological membranes. That became possible only when B.Pressman[14] discovered the effect of valinomycin on mitochondria, American and Soviet investigators developed the concept of ionophore action of depsipeptides[15,16]. The elucidation of the mechanism of K^+ ion-binding to valinomycin, the bracelet structure for the valinomycin K^+-complex proposed in the USSR crowned the research[15]. Just this elegant molecule decorates the entrance to the Shemyakin Institute of Bioorganic Chemistry.

As established later[17] enniatins are also effective complexones of Na^+, K^+, Rb^+, and Cs^+ ions, correlation between their antimicrobial and complexing activities was discovered. Spectral methods were employed to determine enniatin B conformations in solutions in free state as well as in complexes with alkali metal ions. Enniatins A, B, C and beauvericin in solutions are characterized by equilibrium of two forms, polar (P) and nonpolar (N)[18]. Conformation of enniatin B complexes