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A Symposium in Honor of Professor Ephraim Katzir's 70th Birthday

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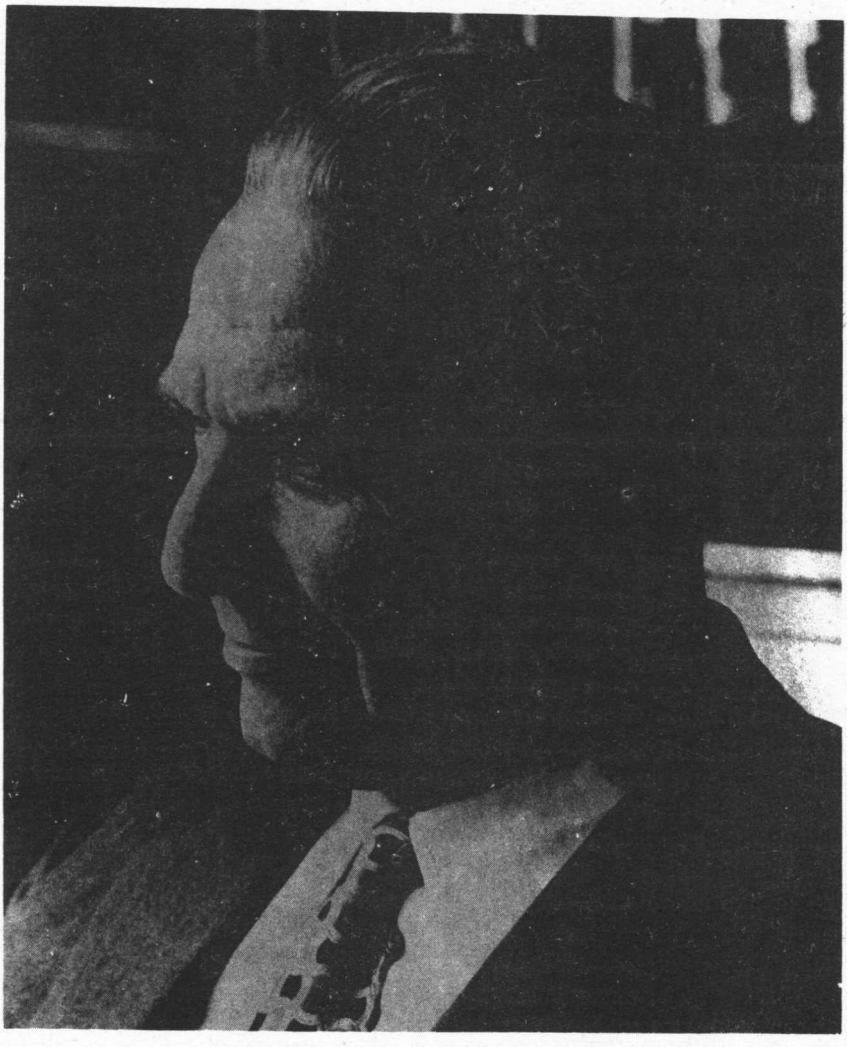

Ephraim (Katchalski) Katzir

Editor's Note

The Editorial Board is delighted to dedicate this issue to Ephraim Katzir, a founding editor of Biopolymers. In 1962, Elkan Blout, Eric Proskauer, Ephraim Katzir and I met and established this journal committed to the study of biological molecules. Ephraim Katzir has not only participated in the formation of this journal but he has also made key contributions to create our scientific field. His work on poly α-amino acids, enzymes attached to solid supports, energy transfer and immunochemistry have been benchmarks. The Symposium at the Weizmann Institute of Science and the University of Tel Aviv is but a small token of the regard and esteem with which we hold Ephraim Katzir. At the age of 70, he remains a vigorous and creative scientist. We look forward to new and exciting scientific discoveries from him.

Many people worked very hard to arrange the Symposium in Israel. The Editorial Board specifically wants to thank Dr. Nathan Sharon who labored so long to bring this meeting about. Its great success is directly attributable to his efforts. We have included two sets of remarks about Ephraim, by Elkan Blout and Michael Sela. The content and warmth of their comments lend a special note of tribute to our dear friend and teacher, Ephraim Katzir.

Murray Goodman
for the Editorial Board

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To Honor Ephraim Katchalski-Katzir

Being given the opportunity to write about my good friend, Professor Ephraim Katzir, can only be characterized as a great pleasure. It is rare to be so fortunate as to have a long-lasting friendship with a great human being, a great scientist, and a distinguished statesman over a span of many years.

I first met Ephraim Katzir, then known as Ephraim Katchalski, when he came to the Harvard Medical School during 1951–52, to spend a year in the laboratory of Professor Edwin J. Cohn in the Department of Biological Chemistry. It soon became apparent that, besides our common interest in peptides, we had many attitudes in common—including those relating to hard work, to scientific understanding, and to more personal attributes. This initial meeting was followed by several scientific exchanges and was heightened by a scientific collaboration which started when Ephraim spent another year at Harvard, 1957–58, with Paul Doty and with me. Our mutual interest in polypeptides and polyamino acids resulted in a number of papers published from The Weizmann Institute and Harvard, and in the years 1958–1960, at least three papers appeared which were the joint efforts of our two laboratories.

Ephraim was a pioneer in the field of synthetic polypeptides and polyamino acids and made many original contributions to this area. Among them is the first synthesis of polylysine (1947), followed soon by reports of the preparation of poly-DL-arginine and poly-L-aspartic acid (1951). A trigger for work in this field was his review article, "Poly-α-Amino Acids" which appeared in *Advances in Protein Chemistry* in 1951 and was followed by a spate of synthetic work from Israel which culminated in the synthesis of poly-L-proline in 1954.

Research on polyproline stimulated consideration of polypeptides in a variety of areas, both of biochemical and physical-chemical interest. Perhaps one of the most interesting investigations of this nature was that carried out by the late Arieh Berger and Ephraim on the mutarotation of polyproline reported in *Nature* in 1956. Ephraim was an evangelist, a supporter, and a protagonist for those who would argue the importance or lack thereof of polypeptides and polyamino acids. I still have in my desk at the Harvard Medical School a sample of polylysine which Ephraim gave me in the early 50's. This chapter of Ephraim's scientific career cannot close without mention also of his long-time association with Michael Sela, which culminated in the publication of a great review article, "Biological Properties of Poly α-Amino Acids," in *Advances in Protein Chemistry* in 1959. The collaborations with Arieh Berger and Michael Sela represent special and highly predictive associations. The untimely death of Berger was a major loss to Ephraim and to peptide chemistry. It is gratifying that Michael Sela's relationship with Ephraim on a scientific, personal, and political level has deepened and strengthened over the last three decades.

In the early 1960's, work on synthetic peptides, polypeptides, and polyamino acids, began to attract the attention of an increasing number of laboratories, and the first conference on the subject was held in Madison, Wisconsin, in 1961. Ephraim was not only an organizer and participant, but a spark plug and advocate for the field. Since then, he has participated in the succeeding conferences held in Israel in 1974 and in Italy in 1983, always being counted on to deliver lectures containing new material *and* thoughtful analysis of older observations.

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During this time, our own friendship deepened both because of our common scientific interests and because we enjoyed visiting each other's homes in Israel and in Boston. This close personal tie was strengthened by a continuing exchange of students and postdoctoral fellows between our laboratories, which increased when I officially joined the Department of Biological Chemistry at Harvard Medical School, in 1962, occupying the laboratories and offices Ephraim had visited with Professors Cohn, Edsal, and Oncley in the early 1950's. Many were the "lab seminars" we enjoyed during the 1960's when Ephraim's travels brought him to the Boston-Cambridge area.

During this period, Ephraim's scientific contributions were being recognized nationally and internationally. In 1961, he became a Scientific Advisor to the Israel Ministry of Defense, and in 1966, he accepted an invitation to be the Dunham Lecturer at the Harvard Medical School, where he joined that distinguished list of foreign scientists called over the last 50 years to give this lecture series. I don't know which honor Ephraim enjoyed more, but I do know that as Dunham Lecturer, he was superb.

While at times Ephraim has said that he shies away from administrative work, and there is no doubt that his first love is science, there is also no doubt that he is an excellent administrator, having lead the Department of Biophysics at The Weizmann Institute for many years, building it into a world-renowned department with the special attributes that only a man of Ephraim's talents can give to an organization.

Ephraim is a man who likes challenges—be they scientific, administrative, or political. His abilities in the latter area were tested and found formidable following his election as the fourth President of Israel. In his dramatic Inaugural Address in May, 1973, he looked both backwards and forwards and said in a moving statement, "Let us look more deeply at the history of our people and let us learn from the past to know ourselves." He discharged his duties as President of Israel with aplomb and graciousness; aided by his witty and imaginative wife, Nina, he entertained at the President's Mansion with dignity and warmth. In addition, Ephraim's eminence as both a scholar and a statesman is attested to by the more than 200 scientific publications, of which he is author or coauthor, by the numerous honorary degrees granted to him, including those from Harvard University and Brandeis University, and by his honorary membership in a host of scientific societies, including both the Royal Society and the National Academy of Sciences.

All the above honors, scientific achievements, and the influence he has had on colleagues, students, and citizens does not mean that Ephraim has not had his share of sorrows. This brief account must include telling Ephraim how much we share in the tragedies that have befallen him, including the murder of his brilliant brother, Aharon, in 1972, the untimely death of his beloved daughter, Nurith in 1964, and most recently, the terrible loss of his wife, Nina. We share your sorrows as well as your achievements.

To close these remarks without stressing Ephraim's contributions to international science—including his founding editorship of *Biopolymers*—would not be appropriate. We salute you, Ephraim Katachalski-Katzir, as a man of science, a man of political accomplishments, and—above all—as a superb human being who has left his mark on several generations of scientists and countrymen.

Elkan Blout

Ephraim Katzir—My Mentor and Friend

It is a great privilege for me to have been asked to join in these congratulations to one whose life has been one of continuous and totally committed achievement on behalf of his country, of science and of humanity.

Ephraim Katchalski-Katzir, born in Kiev on May 16, 1916, arrived in Palestine at the age of six. His family settled initially in Tel Aviv, where Ephraim and his older brother, Aharon, attended the Herzlia Gymnasium and then moved to Jerusalem where both boys went to Rehavia's prestigious High School. Ephraim's fascination with the world of science began in early childhood, and flowered in high school. In 1932 he enrolled at the Hebrew University in Jerusalem—itself then only seven years old. Since chemistry was not yet taught as a major subject, he chose botany, zoology and bacteriology, receiving his M.Sc. degree in 1937 and his Ph.D. in 1941.

From the outset, Ephraim's academic life intertwined with his contribution towards building the new Israeli society. In the 1930's, with his brother, he was already an active member of the *Haganah*, the precursor of the Israel Defense forces.

Ephraim remained in Jerusalem until 1946 as assistant in the Hebrew University's Department of Theoretical and Macromolecular Chemistry, and during this period I met him and attended his lectures and seminars. In 1947–1948, he was a research fellow at the Polytechnic Institute of Brooklyn and Columbia University. Professor Herman Mark, then serving as Chairman of the Pioneering Scientific Committee charged with planning the about-to-be-born Weizmann Institute of Science, was Ephraim's host.

In 1948, the Katchalski brothers moved to Rehovot at the special and pressing invitation of Dr. Chaim Weizmann, first President of the Institute and soon to become President of the State of Israel. At the Weizmann Institute, Ephraim established the Department of Biophysics, which he headed until 1973 when he himself became President of the State, and Aharon, founded the Institute's Department of Polymer Research and headed it until his murder by terrorists in May 1972.

Earlier, Aharon had adopted the Hebrew name Katzir. Ephraim, on becoming Israel's President, in memory of his brother, also changed *his* name to Katzir. He returned to Israel in 1978 as an Institute Professor and was also appointed Head of the new Center for Biotechnology at the Tel Aviv University, in which posts he remains to the present.

My own contact with Ephraim goes back to the summer of 1950, when I returned home from Prague, Czechoslovakia, on behalf of the State of Israel, and began working with him, first on an applied research project and then on my doctoral thesis. He was an incredible teacher; friendly, inspiring, patient, thorough—and always stimulating. The long evenings, sometimes even longer nights, spent in the laboratory, and even more often in his home, studying, analyzing, writing, talking are still vivid for me, as are the excitement of preparing the first scientific papers published in significant journals abroad, each word, sentence and paragraph polished to perfection. And what stands

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out in my memory is Ephraim's friendship, his caring, his humanity. Looking back with the perspective of 35 years, I realize now that the difference in our ages was not really tremendous, but I was always the pupil; he will be for me forever, always the mentor.

Ephraim's scientific work started with preparing synthetic model compounds of proteins, the polyamino acids with which his name is so intimately connected. The first important breakthrough (published in 1947), was the synthesis of polylysine, a macromolecule which showed amazing biological properties, and continued with many other polyamino acids including polyarginine, polyaspartic acid, polytyrosine, polyhistidine, polytryptophan, polyproline, polyhydroxyproline, and polyserine. These studies opened the way to a wholly new approach to the study of proteins, and won him almost immediately international recognition.

Scientists, who know the story well, know that Ephraim's contributions have literally been seminal in every aspect—physical, chemical, and biological. The knowledge of the physical and chemical properties of synthetic polyamino acids played a decisive role in the work that led, in 1961, to cracking the genetic code. For me, it was the initial studies with Ephraim on the extension of the use of polyamino acids into immunology, that brought me, 30 years ago, into this exciting and still expanding area of medical research.

I shall mention just a few of Ephraim's important contributions including polymers as chemical reagents, conformational fluctuations in synthetic and native oligomers and polymers, and his interest in the structure and function of living cells. I would like to stress another great area of his research, leading to important discoveries both in basic and applied research, to a revolution in industry. I refer to the "immobilized" enzymes, a pivotal step in modern technology and enzyme engineering. Ephraim was among the first to prepare a well-characterized insoluble enzyme derivative in which trypsin was conjugated, appropriately enough, to an insoluble synthetic polyamino acid, to yield an insoluble conjugate with high catalytic activity. In his first paper on the subject, he made clear that even then, in 1960, he was aware of the biotechnological potential of the insoluble derivative of preparing an enzyme column and investigating the combined enzymatic flow kinetics. Following was a series of innovative studies including preparation of insoluble papain and its use in studies on the structure of immunoglobulin, investigation of the effect of polyelectrolyte field on enzyme activity using trypsin linked to a charged polymer, and preparation of a collodion-papain membrane—the first example of a synthetic membrane-enzyme conjugate.

I cannot talk about Ephraim's life without recalling his tragic losses—his lovely daughter Nurith, his brother Aharon, and recently, Nina, his wife and partner for 47 years. I want to take this opportunity Ephraim to tell you again that we grieve for and with you. Their memories will live on.

Science, society and humanism. In Ephraim, I believe they are inseparable, different aspects of an ultimate truth, and contained within this unique personality radiating warmth and humanity, creating an ambiance of harmony and enthusiasm.

Michael Sela

BIOPOLYMERS

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CONTENTS

Conformation of Human Little Gastrin and Minigastrin Analogs in Surfactant Solution*†

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Synopsis

The conformational properties of the two gastrin analogs, Nle[15]-human little gastrin and des-Trp[1], Nle[12]-human minigastrin, have been investigated in aqueous solution in the presence of increasing amounts of sodium dodecylsulfate (SDS). Both analogs at acidic pH form a β-structure when the detergent concentration is below the CMC. Above the CMC the hormones assume an ordered conformation characterized by a far-uv CD pattern with the same shape of that previously observed in trifluoroethanol. Thus, both media support the same structure. CD and fluorescence data suggest that the little gastrin analog is completely solubilized in the interior of the micelles, while the minigastrin analog is only partially solubilized because of the presence of a positive charge at the N-terminus.

INTRODUCTION

The determination of structure–function relationship for linear, bioactive peptides is in general a very difficult problem. Linear peptides in fact are usually very flexible molecules, and in solution they exist as an ensemble of conformers. This situation makes it more difficult to establish a proper correlation between structural parameters and biological activity. Recently, upon examination of a number of bioactive peptides in terms of conformational preference, sequence, and biological potency, Chipens[1] elaborated a general theory for peptide–receptor interactions. The model proposed by Chipens involves a cyclic conformation of the peptide factor at the receptor binding site. This proposal follows the development of cyclic analogs of biologically active peptides that are as potent as the natural molecules. This is the case, for instance, of the cyclic analogs of bradykinin,[1,2] enkephalins,[3] somatostatin,[4] LH-RH,[5] etc. These results support the hypothesis that the cyclic analogs adopt a conformation in solution similar to that of the natural molecules when bound to the receptors.

An alternative and complementary approach to the problem of structure–function relationships of bioactive linear peptides is a conformational investigation in solvent systems mimicking the environment of the peptide

*A preliminary account of this work has been presented at the 19th European Peptide Symposium in Porto Carras, Greece, August 31–September 5, 1986.

†Dedicated to Professor Ephraim Katzir on the occasion of his 70th birthday.

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factor at the receptor binding site. This implies that a medium should be found in which the conformer population is shifted towards the "bioactive structure." In this connection we should recall Schwyzer's proposal[6] that membrane-mediated peptide–receptor interactions involve at least two consecutive steps, namely, binding of the peptide factor to the membrane, followed by binding of the peptide to the receptor in the membrane. Recently we observed that linear gastrin peptides adopt ordered conformations in trifluoroethanol (TFE).[7,8] In the case of little gastrin, the conformation assumed in this medium is similar to that observed in aqueous solution in the presence of phospholipids or micelles of detergent.[9,10] We have recently carried out conformational studies and biological activity tests on a series of gastrin analogs in which the $(Glu)_5$ sequence has been systematically elongated from 1 to 5 residues.[8] A correlation was observed between increase of conformational order in TFE and increase of biological potency *in vivo* upon chain elongation. On the basis of these results, we reconsidered the importance of the structure assumed by gastrin hormones in TFE with respect to biological activity.[8] The correlation between amount of ordered conformation in TFE and biological potency led to the hypothesis that the conformation assumed by gastrin peptides in this medium might be of biological importance. Since little gastrin in aqueous media containing micelles of detergent assumes a structure similar to that observed in TFE, we decided to extend our conformational studies on gastrin peptides in the aqueous solvent system. In the present paper we report some results of conformational studies on Nle^{15}-little gastrin and des-Trp^1, Nle^{12}-minigastrin in aqueous solution containing increasing amounts of sodium dodecylsulfate (SDS).

EXPERIMENTAL

Materials

Nle^{15}-little gastrin I and des-Trp^1, Nle^{12}-minigastrin I were synthesized and characterized as previously described.[11,12] Nle^{15}-little gastrin:

*p*Glu-Gly-Pro-Trp-Leu-$(Glu)_5$-Ala-Tyr-Gly-Nle-Trp-Asp-Phe-NH_2

des-Trp^1, Nle^{12}-minigastrin:

H-Leu-$(Glu)_5$-Ala-Tyr-Gly-Nle-Trp-Asp-Phe-NH_2

sodium dodecylsulfate (SDS) was high purity grade Fluka AG product, and was used without further purification.

N-acetyl-L-tryptophan amide (Ac-Trp-NH_2) was a Sigma product and was used as received. N-acetyl-L-tyrosyl-L-tryptophan amide (Ac-Tyr-Trp-NH_2) was prepared according to standard literature procedures.

Methods

Peptide concentrations were determined by weight and peptide content of the samples (as determined by quantitative amino acid analysis) and by absorption measurements in the near-uv as previously reported.[8] Agreement

between concentration values determined by weight and by uv absorption measurements was always within 3%.

Absorption measurements were performed using a Perkin-Elmer Lambda 5 double-beam spectrophotometer.

CD measurements were performed using a Jasco model J-500 automatic recording spectropolarimeter equipped with a Jasco DP-501 data processor. All spectra were recorded at room temperature. The signal-to-noise ratio was improved by accumulating the 2–128 scans, depending on the intensity of the CD signal. The dichrograph was equipped with a sample alternator, which allowed the recording of the air baseline immediately after each scan. As described in our previous work,[7,8] this procedure prevents errors due to possible drifts of the baseline. Addition or subtraction of the spectra were performed by the data processor. All spectra reported in this paper are original, computer-drawn CD curves. In the peptide absorption region, the spectra are reported in terms of molar ellipticity units per peptide residue ($[\vartheta]_R$), while in the aromatic absorption region the spectra are reported in terms of molar ellipticity per mole of hormone ($[\vartheta]_M$). Hellma 0.1- and 5-cm optical pathlength cells (in the far- and near-uv, respectively) with Suprasil windows were used. The concentration of the peptide solutions for CD measurements never exceeded $2 \times 10^{-5} M$.

Measurements for pH were performed using a Metrohm Herisau pH meter equipped with Metrohm glass microelectrodes.

Fluorescence measurements were performed with a Perkin-Elmer model MPF 66 fluorescence spectrophotometer equipped with a Perkin-Elmer 7300 data station.

RESULTS AND DISCUSSION

CD Properties in the Far uv

The CD spectra of little gastrin in the far-uv absorption region, in aqueous solution and in the presence of increasing amounts of SDS, are shown in Fig. 1. All spectra are recorded at pH ~ 2.1, i.e., in absence of negative charges on the peptide side chains. At neutral pH, in fact, no interaction is observed between the hormone and the detergent. It is clear from Fig. 1 that the effect of the surfactant on the peptide conformation depends strongly upon its concentration. In absence of detergent, little gastrin exhibits a strong tendency to precipitate even at very low concentrations. The spectrum of Fig. 1 was quickly recorded immediately after adjusting the pH to 2.1, and is typical of a random structure. No hormone precipitation was observed in the presence of small amounts of detergent. Under these conditions, an ordered conformation begins to form. In 1 mM SDS, the CD pattern of little gastrin is characterized by a broad negative band at $\simeq$ 220 nm ($[\vartheta]_R \simeq -6{,}000$) and a strong positive band at $\simeq$ 195 nm ($[\vartheta]_R \simeq -17{,}000$). These spectral features are typical of a β-structure.

All spectra recorded at SDS concentrations between 0 and 1 mM fit an isodichroic point indicating the presence of a two-component equilibrium system, the random form and the β-structure. When the detergent concentration is increased to 1.6 mM, i.e., just in the range of the CMC, a sharp

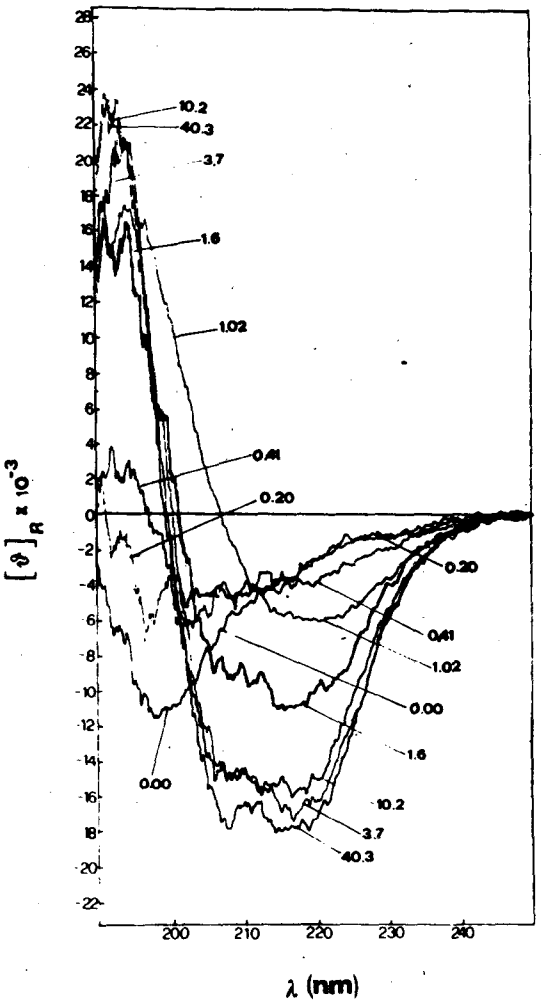

Fig. 1. Far-uv CD spectra of Nle[15]-little gastrin in aqueous solution at pH 2.1 at the SDS concentration indicated, expressed in mmol/L. In this and in the following spectra in the far uv, ellipticity values are expressed in molar ellipticity units per peptide residue.

conformational change takes place, as indicated by the appearance of two negative bands around 218 and 208 nm. The CD spectrum does not fit the same isodichroic point as those recorded at low SDS concentration, and reaches its final form in 40 m*M* SDS, well above the CMC. Under these conditions the CD properties of little gastrin are very similar to those observed in TFE,[7] except for the intensities of the two negative bands, which are higher in the micellar system. The CD spectra of the hormone in 40 m*M* SDS and in TFE are reported in Fig. 2 for comparison. Our results are consistent with those reported by Wu and Yang,[9] except for the position of the long-wavelength negative band, which is below 220 nm, i.e., blue shifted with respect to that reported by these authors. These features indicate an increased amount of ordered conformation in the surfactant solution with respect to TFE.

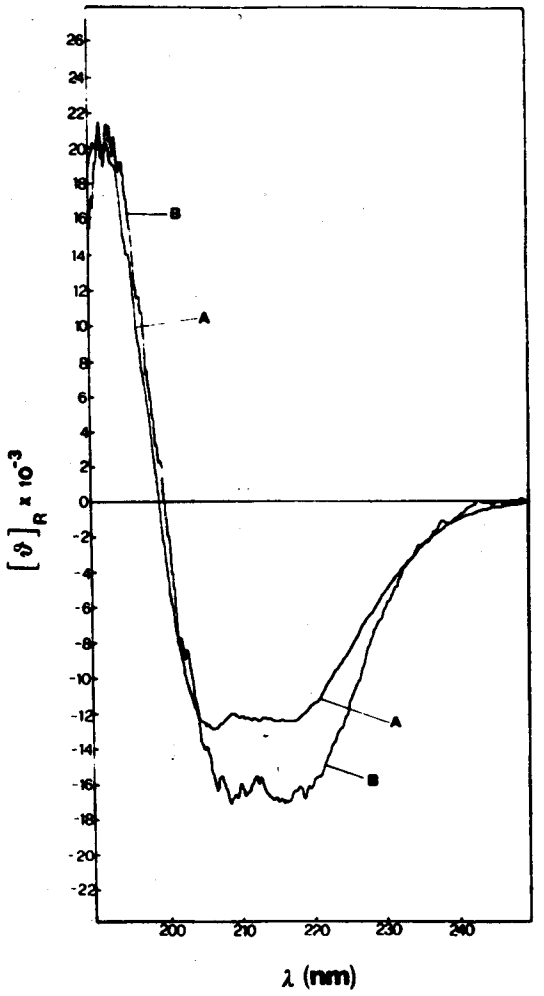

Fig. 2. Comparison of the CD spectra of Nle[15]-little gastrin in 98% TFE (curve A) and in 40.3 m*M* aqueous SDS (curve B).

The CD spectra of des-Trp[1], Nle[12]-minigastrin in surfactant solutions at pH = 2.1 are reported in Fig. 3. Also in this case, the effect of the detergent on the peptide conformation is observed only at acidic pH. At neutral pH there is no evident interaction of the hormone with the detergent in the examined concentration range.

At SDS concentrations below the CMC, the behavior of this gastrin analog is similar to that of little gastrin. In 1.02 m*M* SDS, the CD spectrum is nearly identical to that of little gastrin, with a broad negative band at ≃ 220 nm and a positive band at ≃ 195 nm. Again, we can conclude that, at low SDS concentration, the preferred conformation of the hormone is the β-structure. At SDS concentrations well above the CMC, the minigastrin analog exhibits a CD pattern characterized by two negative CD bands at 218 nm ($[\vartheta]_R \simeq -6{,}000$) and 208 nm ($[\vartheta]_R \simeq -6{,}200$), and by a positive band at ≃ 195 nm. The shape of the spectrum is the same as that observed in TFE,[7] but in this

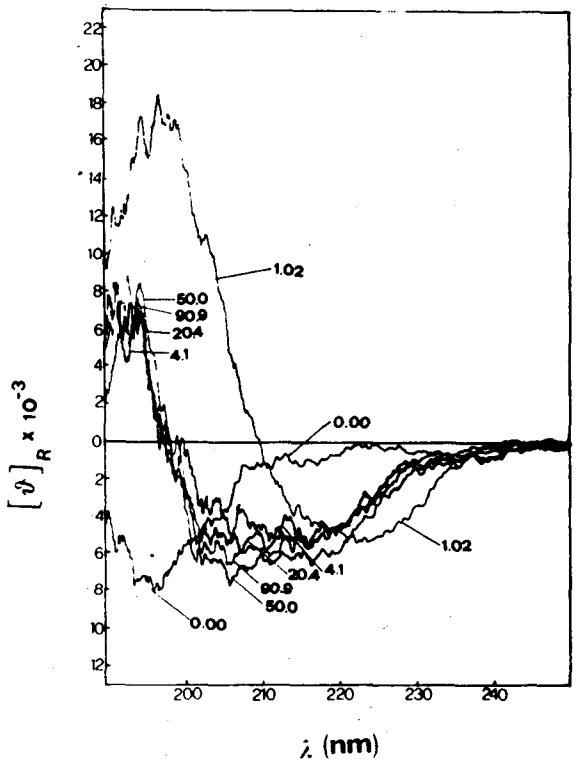

Fig. 3. Far-uv CD spectra of des-Trp[1], Nle[12]-minigastrin in aqueous solutions at pH 2.1 at the SDS concentrations indicated, expressed in mmol/L.

case the intensity of the dichroic bands is substantially reduced. This is shown in Fig. 4 where the CD spectra in the two solvent media are compared.

Thus, in contrast to the little gastrin analog, the amount of ordered conformation of minigastrin in the micellar system is much lower than in TFE. A possible explanation for this behavior could be that at acidic pH there is a positively charged H_3N^+ group at the N-terminus, while in little gastrin, the N-terminal residue is a charge-free pGlu residue. Since the interaction between the hormones and the micellar system occurs only when the negative charges in the side chains are neutralized, we conclude that the interaction occurs via solubilization of the peptide chains in the interior of the micelles. The hydrophobic environment inside the micelles is responsible for the enhanced structural order in the case of little gastrin. However, in the case of minigastrin, the presence of a positive charge at the N-terminus prevents crossing of the negatively charged micelle surface, therefore inhibiting complete solubilization of the peptide chain in the interior of the micelles. Taking into account our previous hypothesis about the conformation of minigastrin,[8] we might conclude that the N-terminal α-helical segment of the peptide chain is destabilized because of the presence of the positive charge at the N-terminus. The same conclusion was also suggested for des-Trp[1], Nle[12]-minigastrin in TFE in the presence of HCl,[8] where protonation of the N-terminal amino group leads to a CD pattern almost coincident with that observed in the

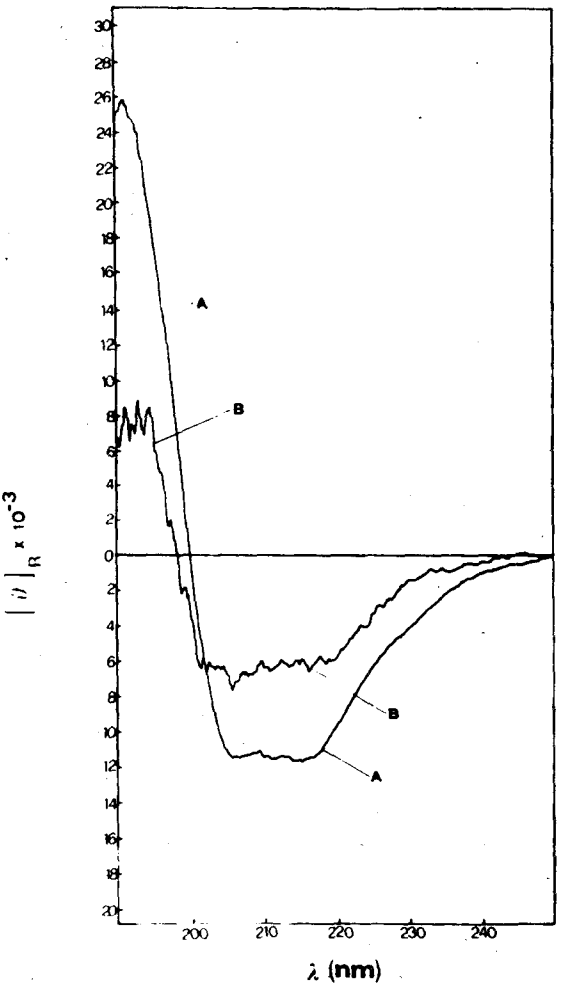

Fig. 4. Comparison of the CD spectra of des-Trp[1], Nle[12]-minigastrin in 98% TFE (curve A) and in 50.0 m*M* aqueous SDS (curve B).

micellar system at pH 2.1. Thus, according to our previous hypothesis,[8] the conformational feature responsible for the observed double-minimum CD spectrum in both media should be a type I β-turn, possibly located in the sequence Ala-Tyr-Gly-Trp.

CD properties in the near UV

The CD spectra in the near-uv absorption region of the little gastrin and minigastrin analogs at pH 2.1 and in the presence of 30 m*M* SDS are shown in Fig. 5. The spectra are very different from those previously observed in TFE. In the fluorinated solvent, the CD pattern is dominated by a strong L_a-Trp transition with a superimposed vibronic envelope of the phenyl-L_b transitions.[7] In that case, the intense CD signal was interpreted in terms of conformational rigidity of the aromatic moieties in the ordered structure of the peptide