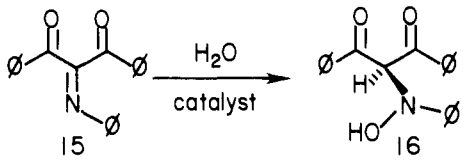
unreacted **1**, plus 1% dimer **4a**). The conversion **1** → **14** (Scheme II) may reflect oxidation of the initially formed adduct **11** upon exposure to the atmosphere and further tautomerization (**12** → **13**) of **12** in the presence of excess morpholine. Upon exposure to water and oxygen, **13** would readily give the observed 8-formylated product **14**.[15] The stability of the imidazole adduct **10** to similar workup conditions may reflect the lower basicity of imidazole as compared to morpholine.[16]

The tautomerization **1** → **2** likely proceeds directly by 8α-proton abstraction from **1** (general base catalysis) by the bases of Table I. The rate of flavin dimerization is base dependent (**8b** ≃ **8a** > **7** > **6a** ≃ **6b** > **6c**), paralleling the basicity of the catalysts in organic solvent (see Figure 1).[17] We had considered that an N(5) covalent adduct of **1** with some bases might form competitively with the tautomerization **1** → **2** or alternatively as an intermediate preceding tautomerization. Such an adduct would be stabilized by delocalization of the N(1) dihydroflavin anion (pK_a at N(1) ≃ 6–7).[18] We have examined the reactivity of imine **15** toward the bases of Table I. As a simple model[19] for the flavin N(5)–C(4α) unsaturation, **15** might add bases at nitrogen, at least reversibly, giving a stabilized dibenzoylmethane anion. No adduct formation of **15** with bases was noted; rather hydration of the imine (**15** → **16**[20]) in moist acetonitrile is accelerated by the same



catalysts responsible for flavin dimerization (Table I). A Brønsted plot (Figure 1)[17] for the hydration of **15**, catalyzed by the six bases of Table I, is a straight line indicative of general base catalysis. A striking smilarity of both absolute and relative catalyst activity for imine hydration and flavin dimerization[21] suggests that general base catalysis is a sufficient condition for tautomerization **1** → **2**.

The mild in vitro generation and interception of the flavin quinone methide (**2**) suggests a critical biological role for this long-ignored tautomer. Bases present in vivo may catalyze tautomerization of flavins at flavoenzyme active sites, resulting in the covalent attachment of enzyme and coenzyme. For example, the substrates for monoamine oxidase may play a role in the known attachment of the flavin cofactor to an active-site cysteine residue.[3] Our continuing study of tautomer **2** will focus on the susceptibility of the quinone methide to other nucleophiles from the family of amino acids.

Acknowledgment. This work was generously supported by National Institutes of Health Grant No. CA 20574. We thank Professor Chris Walsh and his research collaborators for stimulating discussions, and Dr. C. Costello for field-desorption mass spectra.

Supplementary Material Available: Brønsted plot for hydration of imine **15** (Figure 1) (1 page). Ordering information is given on any current masthead page.

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(15) An alternative mechanism might proceed by addition of the *N*-oxide to tautomer **2** followed by base-mediated 8α-proton abstraction with N–O bond cleavage. This mechanism is unlikely as substitution of the tertiary amine, *N*-methylpyrrolidine, for morpholine (see Scheme II) results in only dimer (**4**) formation with no **14** observable.

(16) Imidazole in the absence of *N*-oxide **6b** does not catalyze flavin dimerization or production of adduct **10**.

(17) Supplementary material.

(18) For a general discussion of flavin covalent adducts, see: Bruice, T. C. *Acc. Chem. Res.* **1980**, *13*, 256.

(19) Use of a similar imine model compound has proven to be useful in studies of flavin-mediated thiol oxidations: Sayer, J. M.; Conlon, P.; Hupp, J.; Fancher, J.; Belanger, R.; White, E. J. *J. Am. Chem. Soc.* **1979**, *101*, 1890.

(20) Scheinbaum, M. L. *Tetrahedron Lett.* **1969**, 4221.

(21) Only some *N*-oxides (e.g., **6a–c**) display catalytic activity for flavin dimerization and imine hydration (**15** → **16**). Inactive catalysts include *N,N*-dimethylaniline *N*-oxide, trimethylamine *N*-oxide, and pyridine *N*-oxide.

(22) Firmenich Assistant Professor of Natural Products Chemistry, Alfred P. Sloan Fellow, 1980–1982.

Induced α Helix in a Peptide System by Introduction of a Nucleus

Sir:

The recent successful estimation of protein structure[1] demonstrates that protein structure is principally determined by the sequence of amino acids with the intrinsic conformational preference. Studies on conformations of model peptide systems having specific sequences of various amino acids are of much interest on this standpoint. We are specially interested in a simple peptide system having the alternating glycine–L-leucine. Glycine is known to be an amino acid which prevents formation of the α helix.[2] On the other hand, L-leucine is classified as an amino acid which strongly tends to form the α helix and thus stabilizes this conformation.[3] Therefore, the conformation of the peptide consisting of L-Leu-Gly sequence should be formed by a counterbalance between opposite conformational preference of these amino acids. We have synthesized a series of peptides shown by Nps-(L-Leu-Gly)$_n$-OEt (n = 1–10)[4] and examined their conformations in the solid state. Because of the strong tendency of L-leucine to form the α helix, we expected to find the α-helical conformation in this peptide system. The conformational study, however, demonstrated that the peptides do not form the α helix but assume the β structure. This result led us to the speculation that if the β structure observed in this series of peptides results actually from the counterbalance of the local conformations of these amino acids, introduction of a nucleus favoring, locally, the α-helical conformation into this peptide chain should induce an α-helical conformation over the peptide chain. In order to develop the nucleus in this peptide system, it may be most effective to insert an additional amino acid sequence having a strong tendency to form the α helix into the original amino acid sequence. We have introduced L-alanyl residues into the peptide chain consisting of the L-Leu-Gly sequence and synthesized Nps-(L-Leu-Gly)$_4$-(L-Ala)$_n$-(L-Leu-Gly)$_4$-OEt (n = 1 and 2).[5] The original and modified sequences of amino acids are shown by

LeuGlyLeuGlyLeuGlyLeuGlyLeuGlyLeuGlyLeuGly-
LeuGlyLeuGlyLeuGly

and

LeuGlyLeuGlyLeuGlyLeuGly*Ala*(*Ala*)LeuGlyLeuGly-
LeuGlyLeuGly

The conformmations in the solid state were examined by infrared (IR) spectroscopy and X-ray powder diffraction measurement. Figure 1 shows the IR spectra of these peptides.[6] The

(1) Chou, P. Y.; Fasman, G. D. *Annu. Rev. Biochem.* **1978**, *47*, 251–276.

(2) Fasman, G. D. "Poly-α-Amino Acids"; Marcel Dekker: New York, 1976; pp 499–604.

(3) Chou, P. Y.; Fasman, G. D. *Biochemistry* **1974**, *13*, 222–245.

(4) Peptide synthesis was done by the fragment condensation method using the active esters Nps-L-Leu-Gly-ONSu and Nps-(L-Leu-Gly)$_2$-ONSu.

(5) These peptides were synthesized from the intermediate peptides Nps-(L-Leu-Gly)$_n$-OEt by the reaction with Nps-L-Ala-L-Leu-Gly-ONSu and Nps-L-Ala-L-Ala-L-Leu-Gly-ONSu.

(6) The amide II band resulting from a deformational vibration of the N–H bonding is also sensitive to the conformational change of peptides and can be used to identify the conformations. However, since the peptides protected by the Nps group show strong bands in the amide II region, the amide II band cannot be used for assignment of the conformation of the Nps peptides.

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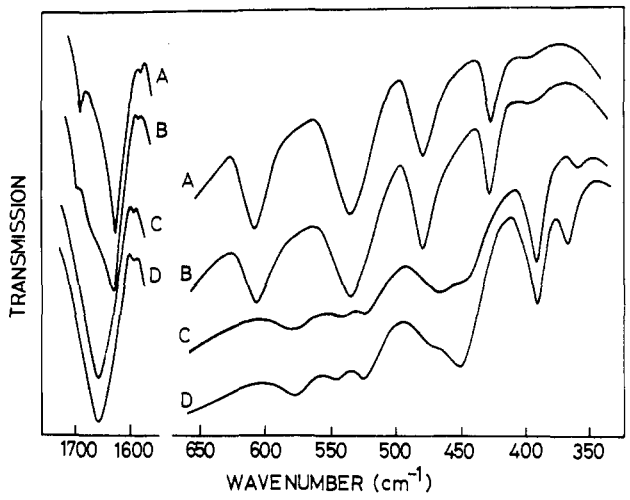

Figure 1. IR spectra in the amide I and far-IR regions of oligopeptides in the solid state: (A) Nps-(L-Leu-Gly)$_5$-OEt, (B) Nps-(L-Leu-Gly)$_{10}$-OEt, (C) Nps-(L-Leu-Gly)$_4$-L-Ala-(L-Leu-Gly)$_4$-OEt, (D) Nps-(L-Leu-Gly)$_4$-(L-Ala)$_2$-(L-Leu-Gly)$_4$-OEt.

peptide Nps-(L-Leu-Gly)$_5$-OEt is shown as a standard sample of the peptides with the original sequence.[7] This peptide showed very sharp bands at 1695 and 1630 cm^{-1} in the amide I region and bands at 613, 540, 483, and 435 cm^{-1} in the far-IR region. The amide I bands at 1695 and 1630 cm^{-1} are characteristic of the antiparallel β structure,[8] and the band at 613 cm^{-1} is that observed for copolypeptides containing glycine with the β structure.[9] The band at 483 cm^{-1} is characteristic of L-leucine with the β structure.[10] A solid sample of Nps-(L-Leu-Gly)$_{10}$-OEt obtained by reprecipitation from a solution of 1,1,1,3,3,3-hexafluoropropan-2-ol by addition of diethyl ether[11] showed a spectrum very similar to that of Nps-(L-Leu-Gly)$_5$-OEt except for a very weak shoulder near 1650 cm^{-1} which suggests the presence of the α helix or random coil as a minor component. Since the far-IR spectrum of this sample has no bands characteristic of the α helix, the shoulder can be assigned to the random coil. These IR results suggest that the peptides consisting of L-Leu-Gly sequence assume predominantly the β structure. On the contrary, the peptides Nps-(L-Leu-Gly)$_4$-(L-Ala)$_n$-(L-Leu-Gly)$_4$-OEt after the reprecipitation from solutions showed different spectra from those of Nps-(L-Leu-Gly)$_n$-OEt. All bands characteristic of the β structure disappeared in these spectra. The peptide Nps-(L-Leu-Gly)$_4$-L-Ala-(L-Leu-Gly)$_4$-OEt showed a band at 1655 cm^{-1} in the amide I region and bands at 585, 548, 527, 474, 449, 394, and 366 cm^{-1} in the far-IR region. The band at 1655 cm^{-1} can be assigned to the α helix and/or the random coil. The bands at 527 and 366 cm^{-1} are characteristic of L-alanine with the α-helical conformation,[12] and the strong band at 394 cm^{-1} is of L-leucine with the α-helical conformation.[13] The peptide Nps-(L-Leu-Gly)$_4$-(L-Ala)$_2$-(L-Leu-Gly)$_4$-OEt showed a spectrum almost identical with that of Nps-(L-Leu-Gly)$_4$-L-Ala-(L-Leu-Gly)$_4$-OEt except for a moderate band at 371 cm^{-1} resulting from L-Ala-L-Ala sequence with the α-helical conformation.[14] These IR spectra suggest that the modified peptides take the α-helical conformation. It should be noted that these IR spectra have bands at 527 and

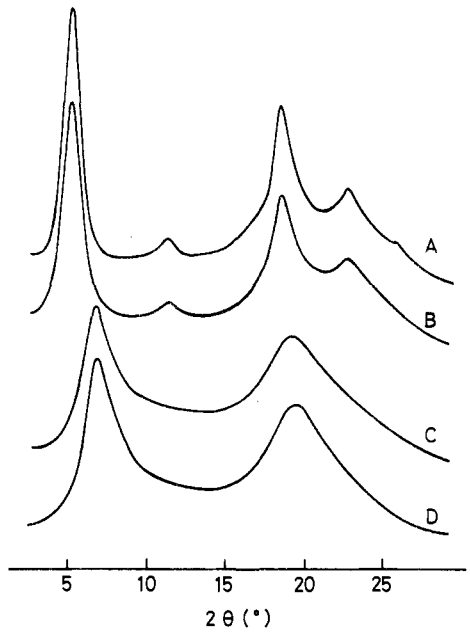

Figure 2. X-ray powder diffraction patterns of oligopeptides: (A) Nps-(L-Leu-Gly)$_5$-OEt, (B) Nps-(L-Leu-Gly)$_{10}$-OEt, (C) Nps-(L-Leu-Gly)$_4$-L-Ala-(L-Leu-Gyl)$_4$-OEt, (D) Nps-(L-Leu-Gly)$_4$-(L-Ala)$_2$-(L-Leu-Gly)$_4$-OEt.

near 370 cm^{-1} and a strong band at 394 cm^{-1}. The former suggests that the inserted L-alanyl residues form the nucleus taking the α-helical conformation, and the latter suggests that almost all L-leucyl residues are incorporated into the α-helical conformation; that is, this conformation is formed over the peptide chain.

The X-ray powder diffraction patterns shown in Figure 2 support the results by the IR study. The peptides Nps-(L-Leu-Gly)$_n$-OEt (n = 5 and 10) showed peaks at 2θ = 5.7, 11.5, 19.0, and 23.2°. The reflections at 2θ = 5.7 and 19.0° can be assigned as corresponding, respectively,[15] to the (020) and (110) planes of the orthorhombic unit cell of the peptides assuming the β structure. In comparison, the peptides Nps-(L-Leu-Gly)$_4$-(L-Ala)$_n$-(L-Leu-Gly)$_4$-OEt (n = 1 and 2) showed peaks at 2θ = 7.0 and 19.4°, the first peak of which can be assigned as corresponding to the (100) plane of the hexagonal unit cell of the peptide taking the α-helical conformation.[15]

We have found another interesting fact: all the peptides Nps-(L-Leu-Gly)$_m$-L-Ala-(L-Leu-Gly)$_n$-OEt (m = 2–6 and n = 6–2) form the α helix. This suggests that an L-alanyl residue inserted at any position far from the terminus by four amino acid residues can promote α-helix formation.

It is unexpected that the conformation of the peptide consisting of the L-Leu-Gly sequence is easily changed from the β structure to the α helix by introduction of only one L-alanyl residue. This fact suggests that the β structure of the original peptide formed by the opposite conformational preferences of L-leucine and glycine is not so stable. In general, there may be a possiblity that secondary structures of rather small peptides consisting of amino acids with various conformational preferences could be changed to another conformation by some extent of perturbation such as introduction of an amino acid in this study.

In conclusion, this study has shown a novel induced conformational change from the β structure to the α helix of a peptide having the L-leucylglycyl sequence. The L-alanyl residues inserted into the peptide chain form the nucleus, assuming an α-helical conformation with an adjacent L-leucyl residue in the original sequence to promote an α-helical conformation over the peptide chain. Amino acids other than L-alanine could form the nucleus of the α helix. It will be interesting to study the helix-forming

(7) The solid samples were prepared by dissolving the peptides as synthesized in a solvent at a concentration 1 g/50 mL followed by reprecipitation by addition of diethyl ether to the solution. The resulting precipitate was collected on a glass filter, washed with diethyl ether, and dried in a vacuum desiccator over P_2O_5.

(8) Miyazawa, T. "Poly-α-Amino Acids"; Marcel Dekker: New York, 1976; pp 69–104.

(9) Itoh, K.; Katabuchi H. *Biopolymers* **1972**, *11*, 1593–1605.

(10) Katakai, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1193–1196.

(11) Oligopeptides potentially capable of forming α helices assume the α-helical conformation in the solid state obtained by reprecipitation from solutions: Katakai, R. *J. Am. Chem. Soc.* **1977**, *99*, 232–234.

(12) Katakai, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 905–909.

(13) Itoh, K.; Katabuchi, H. *Biopolymers* **1973**, *12*, 921–929.

(14) Katakai, R. *J. Chem. Soc., Chem. Commun.* **1978**, 692–693.

(15) Komoto, T.; Kim, K. Y.; Oya, M.; Kawai, T. *Makromol. Chem.* **1974**, *175*, 283–299.

power of various amino acids using this peptide system and to examine whether the tendency of the amino acids to promote α-helix formation is consistent with that in protein.[3] At this stage of the study, we have found that L-leucine (a strong α-helix former) and L-phenylalanine (an α-helix former) can promote α-helix formation but L-valine (an α-helix former) cannot.

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*Book Reviews**

The Peptides. Analysis, Synthesis, Biology. Volume I. Major Methods of Peptide Bond Formation. Edited by Erhard Gross and Johannes Meienhofer. Academic Press, New York. 1979. xvii + 435 pp. $39.50.

The recent explosive interest in the synthesis of biologically active peptides has led to the publication of several series of books on the topic, most of which are the result of recent symposia. The present editors are to be congratulated on the publication of a really superior first volume of a new series. This book gives the reader a thorough and critical review of the most useful methods presently used in the synthesis of peptide bonds. The first chapter, written by the editors, gives an overview of the structure, reactions, and synthesis of amide linkages while the last chapter carefully describes the omnipresent racemization problem encountered in peptide synthesis.

If the quality of the present volume can be maintained in those that follow, we can anticipate publication of a very excellent and useful series. The chapter titles (authors) are: 1. The Peptide Bond (E. Gross and J. Meienhofer); 2. The Formation of Peptide Bonds (J. J. Jones); 3. Active Esters in Peptide Synthesis (M. Bodanszky); 4. The Azide Method in Peptide Synthesis (J. Meienhofer); 5. The Carbodiimide Method (D. H. Rich and J. Singh); 6. The Mixed Carbonic Anhydride Method of Peptide Synthesis (J. Meienhofer); 7. Racemization in Peptide Synthesis (D. S. Kemp). This is clearly a book written for practioners (or aspiring practitioners) by experts in the field of peptide synthesis.

While there may be some overlap between Chapters 1 and 2, this does not detract seriously because of the difference in viewpoints of the authors. Chapter 3 is written by one who can be considered the prime advocate of the active ester method in peptide synthesis. It is therefore blessed by a depth and attention to detail which would be difficult to attain by another author. The personal involvement of the authors directly in their topics shows up again in the following four chapters. Chapters 4 and 6 show an extreme attention to detail which makes these true reference works, obviating the need to search for further information on these subjects. Chapter 5 is an admirably written discussion of what is, perhaps, the most commonly used coupling method today, but also the one most likely to cause problems. Again, the chapter is very well written, thorough, and complete. The last chapter on racemization was, quite possibly, the most difficult to assemble because racemization crosses the boundaries of all peptide coupling methods and its causes are difficult to sort out and organize. The author succeeds, I believe, in describing the present "state of the art" very clearly by organizing the information beautifully and the hard data in table form.

This book is a very useful addition to the practicing peptide chemists' bookshelf, but is so well written throughout that the uninitiated will also find it useful for breaking into the art of peptide synthesis. It may serve to invite organic chemists to join the quest for the perfect amino acid coupling method and should certainly be in every science library.

Charles H. Stammer, *University of Georgia*

Synthetic Gems Production Techniques. Edited by L. H. Yaverbaum. Noyes Data Corp., Park Ridge, N.J. 1980. ix + 353 pp. $39.00.

This book is a review of the patent literature and is "a continuation and updating" of the book "Synthetic Gem and Allied Crystal Manufacture", published in 1973. The title has been changed because of the decision to omit crystals used only in making semiconductors for the electronics industry. It is a pity that such an awkward wording for the unpunctuated title was chosen.

The largest part of the book is concerned with synthesis of diamond, but there are substantial sections on garnets, titanates, rutile, and corundum, as well as miscellaneous others. The chapters begin with a historical overview of the patent literature in some detail; these parts can be quite interesting to the general reader. One learns, for example, that the first practical synthesis of a gemstone was accomplished in 1900 by Auguste Verneuil, who grew crystals of corundum. The first patent for synthetic diamonds was issued in 1960 for a process announced in 1955.

The value of this book lies not only in the fact that patents on a single subject have been brought together, but also in the detailed information that has been extracted from the patents and presented in detail with a description of the experimental procedures. To obtain this sort of information independently would require an enormous amount of searching as well as digestion. Since in the technology of gem synthesis, most of the significant literature is in patent form, this volume is an important work of reference.

Rodd's Chemistry of Carbon Compounds. Second Edition. Volume IV. Part L. Edited by S. Coffey. Elsevier Scientific Publishing Co., Amsterdam and New York. 1980. xxii + 552 pp. $126.76.

This book completes Volume IV, Heretocyclic Compounds. It contains four chapters, each of which is largely devoted to compounds involved with the control of biochemical processes. The chapter by G. Shaw covers Purines and Related Ring Systems, including thiazolopyrimidines, pyrazolopyrimidines, and triazolopyrimidines. The chaper by D. Jones is devoted to Nucleosides, Nucleotides, and Nucleic Acids. A chapter by Ohta, Wrigglesworth, and Wood describes Pteridines, Alloxazines, Flavins and Related Compounds. Biosynthesis of Plant Alkaloids and Nitrogenous Microbial Metabolites, by R. B. Herbert, closes the text and is followed by an index of nearly 100 pages.

The style of this series and its plan, emphasizing synthesis, structure, and properties (physical and chemical) about evenly, is well known. The quality of the reviews remains high, as does the reference value. The countless citations (they are included in the text, unnumbered) include many to the patent literature. Unfortunately, the contributors still do not generally tell the reader at what date their surveys of the literature ceased, and only one chapter (Herbert) informs us of this valuable piece of information (June 1976).

The special emphasis on matters of interest to biochemists and medicinal chemists should justify consideration for purchase by individuals or libraries not subscribing to the entire series, for this volume can be used independently.

Spectres d'Absorption Ultraviolets de Composés Organiques Azotés et Correlations Spectrochimiques. Volume 2: Bases Aromatiques. By P. Grammaticakis. Technique et Documentation, Paris. 1979. 132 pp. Fr. 150 (paperbound).

The first volume of this work appeared in 1977. As in that volume, this one consists of a large number of UV spectra (over 1300) in graphic form. They are rather small (up to nine layouts per page), but they have the useful feature of showing several closely related compounds superimposed (such as ortho, meta, and para isomers), and of being reliably comparable, since they all came from the author's own laboratory. A second section is devoted to commentary, in which the author elaborates the method of "naive spectroscopy", a method he has devised for correlating the form of UV spectra with structure. The relationships that he thereby generates are very interesting and should be useful for empirical correlations. There is an alphabetical index to compounds by name.

Proteoglycans-Biological and Chemical Aspects of Human Life. By John F. Kennedy. Elsevier Scientific Publishing Co., Amsterdam, and New York, 1979. xxi + 493 pp. $80.50.

This book describes a complex class of compounds that has not been commonly recognized in the scientific community. The lack of recognition of proteoglycans has probably been due to their structural complexity and to experimental difficulties in characterizing them. Their function in mammals and other living organisms is just beginning to be understood. This book therefore addresses a need to bring together information now available for this important class of compounds.

Proteoglycans consist of polypeptide chains to which long linear chains

*Unsigned book reviews are by the Book Review Editor.