Journal of Peptide Science
J. Peptide Sci. **11**: 250–253 (2005)
Published online 8 February 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/psc.648

JOURNAL OF PEPTIDE SCIENCE

From coded to non-coded α-amino acids: a journey in oligopeptide stereochemistry‡

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Received 23 November 2004; *Accepted 30 November 2004*

Keywords: α-amino acids; backbone modification; conformation; peptides; peptidomimetic

OLIGOPEPTIDES FROM C^{α}-TRISUBSTITUTED α-AMINO ACIDS

On 20 October 1959, Murray Goodman, then a young Assistant Professor at the prestigious Polytechnic Institute of Brooklyn, New York, NY, published his fundamental contribution (with his student E.E. Schmitt) (Figure 1A) on the preferred conformation of well-characterized, strictly monodisperse oligopeptides [1]. In this pioneering work fully protected $[$L-Glu(OMe)$]_n$ (OMe, methoxy) homo-oligomers of different main-chain lengths were studied using optical rotation (first example of the *Goodman plot*) as a function of a variety of parameters, such as the nature of the solvent, peptide concentration and temperature. Unordered conformations and ordered secondary structures (α-helix and β-pleated sheet) were all discussed in that paper. The onset of the helical structure in this series was assessed at the level of the 5-/6-mer in the structure-supporting solvent 1,4-dioxane. Conversely, no indication for ordered secondary structure formation was found in the structure-disrupting solvent dichloroacetic acid.

Murray was the first to realize that detailed experimental investigations on monodisperse oligopeptides might have greatly helped to establish the type and stability of their conformations, such as the α-helix and the β-pleated sheet structures, which, for polydisperse polypeptides, the exclusive target of conformational studies in the 1950s, have only a statistical significance. The Goodman and Schmitt communication [1] paved the way to the extremely productive field of conformational analysis of linear peptides, not restricted to model compounds, but, from the early 1970s, extended to bioactive molecules as well.

When I joined Murray's group in Brooklyn (November 1967) I was asked to apply two newly available techniques, CD and high-resolution (220 MHz) ^{1}H NMR, to detect sensitive criteria for the critical size for α-helix formation in $[$L-Glu(OEt)$]_n$ (OEt, ethoxy) oligopeptides (Figure 1B) [2]. In particular, we recognized immediately the potential of NMR for elucidating details of *local* conformations in oligopeptide systems. In TFE we were able to observe six separated resonances for the NH protons of the conformationally unordered hexamer. Commencing with the heptamer, coalescence of most of the NH proton resonances indicated the onset of the helical structure. The first CD spectrum of a partially α-helical, monodisperse peptide was reported.

My collaborative efforts with Murray and his associates, in particular Fred Naider, continued even after my return to Padova. More specifically, Fred and I focused our attention on protein amino acids with aliphatic side chains (L-Ala and L-Ile). The most relevant result obtained was the discovery that $($L-Ile$)_n$ homo-oligomers form a β-sheet conformation beginning at the heptamer (Figure 1C) [3]. The stability of this β-sheet conformation was found to be greater than that formed by $($L-Ala$)_n$ homo-oligomers. The first CD spectrum of a monodisperse peptide in the β-sheet conformation was published. Subsequently, additional series of protected homo-oligopeptides were synthesized, all having the general formula Boc-$($L-Xxx$)_n$-OMe, where $n = 2$–7. The amino acids selected for this investigation were those with linear hydrocarbon (Abu, Nva, Nle), β-branched (Val, *a*lle), γ-branched (Leu, Cha, Phe) and sulphur-containing side chains [Cys(Me), Met]. A number of physico-chemical techniques were employed including vacuum-UV CD, x-ray diffraction (films), ^{1}H NMR, vapor-pressure osmometry, IR absorption and laser Raman. In the solid state the intermolecularly H-bonded β-sheet structure is first seen at the tetrapeptide level. In contrast to other series, the β-branched Val, Ile, and *a*lle and γ-branched, aromatic Phe series adopt the unusual parallel-type β-sheet structure. In chloroform solution folded or (associated) extended conformations are formed depending upon peptide concentration. In TFE solution the $($L-Val$)_6$, $($L-Val$)_7$, $($L-Ile$)_7$, $($D-*a*lle$)_7$, $($L-Ala$)_7$ and $[$L-Cys(Me]$_7$ homo-peptides assume β-associated structures, which can be disrupted either by dilution, heating or addition of more acidic fluoroalcohols (HFIP, HFA hydrate). A rank order for the tendency of these peptides to form β-sheet structures was established.

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‡Selected paper part of a special issue dedicated to the memory of Murray Goodman.

A

Oct. 20, 1959 Vol. 81 5507

COMMUNICATIONS TO THE EDITOR

CONFORMATIONAL TRANSITIONS IN POLYPEPTIDES

DEPARTMENT OF CHEMISTRY MURRAY GOODMAN
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, N. Y. EDWARD E. SCHMITT
RECEIVED AUGUST 14,1959

B

SENSITIVE CRITERIA FOR THE CRITICAL SIZE FOR HELIX FORMATION IN OLIGOPEPTIDES

BY MURRAY GOODMAN,* ANTONIO S. VERDINI,* CLAUDIO TONIOLO,*
WILLIAM D. PHILLIPS,† AND FRANK A. BOVEY‡

POLYTECHNIC INSTITUTE OF BROOKLYN, E. I. DU PONT DE NEMOURS & CO., AND BELL TELEPHONE LABORATORIES

Communicated by H. Mark, July 30, 1969

C

Circular Dichroism Studies of Isoleucine Oligopeptides in Solution

MURRAY GOODMAN, FRED NAIDER, *Polytechnic Institute of Brooklyn, Brooklyn, N. Y.,* and CLAUDIO TONIOLO, *Institute of Organic Chemistry, University of Padua, Padua, Italy*

Figure 1 (**A**) The 1959 Goodman and Schmitt communication (ref. [1]). (**B**) The 1969 Goodman *et al.* paper (ref. [2]). (**C**) The 1971 Goodman *et al.* paper (ref. [3]).

The results obtained indicated that branching position, aromaticity, overall bulkiness and the solvophobic character of the amino acid side chains, and configuration of the chiral atom in the lateral chain as well, are all important factors in determining the nature and stability of the ordered conformation of homo-oligopeptides. A few review articles [4–6] summarized these findings.

OLIGOPEPTIDES FROM C^{α}-TETRASUBSTITUTED α-AMINO ACIDS

During his post-doctoral experience with J.C. Sheehan at the Massachusetts Institute of Technology, Boston, MA, about 50 years ago Murray was introduced into the field of peptide synthesis and in particular into the problems connected with the activation of the α-amino acid α-carboxylic functionality in the coupling reactions. Murray's deep knowledge of this complex issue gave him the opportunity to publish (with G.W. Kenner) in 1957 the classical review article 'The Synthesis of Peptides' [7]. Subsequently (1965–1967), at the Polytechnic Institute of Brooklyn he expanded this interest to the chemistry of α-amino acid and peptide 5(4*H*)-oxazolones which allowed him to perform pioneering mechanistic studies of the racemization reaction in peptide synthesis [8]. *Inter alia*, on 5 July 1965, Goodman and McGahren described the synthesis and characterization of the L-enantiomer (and the racemate as well) of the 5(4*H*)-oxazolone from Z-Aib-Phe-OH (Figure 2A) [9,10]. Because of its extremely high optical rotation, despite the presence of the achiral Aib residue in the dipeptide sequence, the L-*Goodman oxazolone* proved to be extremely useful for kinetics studies of racemization (incidentally, Murray learned directly from Kenner and from the milestone papers of his group [11,12] of the peculiar properties of peptides based on the C^{α}-tetrasubstituted α-amino acid Aib). Many years later (1995), our group published the x-ray diffraction structures of both the L-enantiomeric and racemic forms of the *Goodman oxazolone* (Figure 2B) [13]. This was the first structural analysis of a crystalline peptide oxazolone with a chiral C^{α}-trisubstituted (protein) amino acid in the heterocyclic moiety.

Murray's interest in peptides containing backbone modified, conformationally restricted C^{α}-tetrasubstituted α-amino acids continued over the

A

3028 *Journal of the American Chemical Society / 87:13 / July 5, 1965*

Optically Active Peptide Oxazolones. Preliminary Racemization Studies under Peptide-Coupling Conditions

Murray Goodman, W. J. McGahren
Polytechnic Institute of Brooklyn
Brooklyn, New York
Received April 23, 1965

B

First 3-D Structure Determination of a Peptide Oxazol-5(4*H*)-one with a Chiral Protein Amino Acid in the Heterocyclic Moiety: An X-Ray Diffraction Analysis of the Enantiomeric and Racemic Goodman Oxazolone

M. Crisma, G .Valle,
V. Moretto, F. Formaggio
and C. Toniolo
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C

Solid-State and Solution Conformation of Homo Oligo(α-aminoisobutyric acids) from Tripeptide to Pentapeptide: Evidence for a 3_{10} Helix[1a]

Ettore Benedetti,[*1b] Alfonso Bavoso,[1b] Benedetto Di Blasio,[1b] Vincenzo Pavone,[1b] Carlo Pedone,[1b] Marco Crisma,[1c] Gian Maria Bonora,[1c] and Claudio Toniolo[*1c]

Contribution from the Istituto Chimico, University of Naples, 80134 Naples, Italy, and the Biopolymer Research Centre, C.N.R., Institute of Organic Chemistry, University of Padua, 35100 Padua, Italy. Received August 11, 1981

Figure 2 (**A**) The 1965 Goodman and McGahren communication (ref. [9]). (**B**) The 1995 Crisma *et al.* paper (ref. [13]). (**C**) The 1982 Benedetti *et al.* paper (ref. [28]).

years: (i) the L-Phe residue of the dipeptide ester sweetener aspartame was replaced with a series of 1-aminocycloalkane-1-carboxylic acids $Ac_nc(n = 3–8)$ [14], the first example of the 'Ac_nc scan' approach which we extended few years later to the formyl-methionyl tripeptide chemo-attractant [15], and with the $Ac_3c(\phi)$ [16] or the L-(αMe)Phe residue [17]. (ii) L-(αMe)Val, L- and D-(αMe)Phe, and Ac_5c were incorporated in somatostatin-related cyclic hexapeptides [18–20]. (iii) The mechanism of an unusual acid cleavage reaction was investigated for MeAib-Xxx peptide bonds [21]. (iv) Asymmetric syntheses were developed for the preparation of chiral (αMe)Cys, a building block which was incorporated into cyclic enkephalin analogs [22,23]. (v) The conformational and spectroscopic properties of Ac-(αMe)Pro-NHMe were studied thoroughly [24].

In 1978, with my student Marco Crisma, I decided to enter the field of oligopeptides from C^{α}-tetrasubstituted α-amino acids [25] based on the following stimulating published information: (i) The extraordinary optical rotatory properties of the *Goodman oxazolone* [8–10]. (ii) The classical strategy of synthesis of $(Aib)_n$ homo-oligomers *via* 5(4*H*)-oxazolone intermediates proposed by Kenner and his associates [11,12]. (iii) The helical conformational region strongly preferred by Ac-Aib-NHMe, as calculated by Marshall [26]. (iv) The first unambiguous example of a 3_{10}-helix reported by Balaram and coworkers for Tos-$(Aib)_5$-OMe in the crystal state [27]. (v) The emerging field of backbone-modified peptides for drug design.

After our first publication (1982) on the 3D-structure of a complete set of $(Aib)_n$ homo-oligomers [28], part of an extremely productive collaboration with the crystallographic group of E. Benedetti and his colleagues at the University of Naples, we concentrated on the investigation of the preferred conformations of peptides heavily based on a variety of achiral and (DSM Research, Geleen, The Netherlands) chiral C^{α}-tetrasubstituted α-amino acids, as determined by conformational energy computations, crystal-state (x-ray diffraction) analyses and solution (^{1}H NMR and spectroscopic) techniques. We found that $3_{10}/\alpha$-helical structures [29] and the fully extended (C_5) conformation [30] are preferentially adopted by peptide sequences characterized by this family of amino acids, depending upon overall bulkiness and nature (e.g. whether acyclic or $C^{\alpha}_i \leftrightarrow C^{\alpha}_i$ cyclized) of their side chains.

Intriguing relationships between α-carbon chirality and bend/helix handedness were also unraveled. γ-Bends and *semi*-extended conformations are rarely observed. Formation of β-sheet structures, including those formed by β-amyloid peptide sequences, is prevented. The huge amount of theoretical and experimental results collected in this field has recently been reviewed [31].

I am deeply grateful to Murray for his inspiration on various areas of peptide research over the years and for his constant encouragement to follow his approach to find a well defined niche in our always evolving field. As an example, from one of his letters to this author, dated 27 October 1977, I quote: 'It has always been very important for me to present a unified body of work on themes that can clearly be attributed to my group'. I am always trying to keep in my mind also this part of his broad intellectual and scientific legacy.

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