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Induced Axial Chirality in the Biphenyl Core of the C^{α}-Tetrasubstituted α-Amino Acid Residue Bip and Subsequent Propagation of Chirality in $(Bip)_n$/Val Oligopeptides

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Abstract: In the dipeptides Boc-Bip-L-Val-OMe and Boc-Bip-D-Val-OMe, an induced axial chirality in the biphenyl core of the Bip residue, a conformationally labile, proatropoisomeric $C^{\alpha,\alpha}$-disubstituted glycine, was observed by electronic CD and ^{1}H NMR. Chiral induction is significantly higher when the Val residue is located at the C-terminal position of Bip. An outstanding phenomenon of propagation of chirality was demonstrated to occur in the related 3_{10}-helical -$(Bip)_n$-L-Val ($n = 2-6$) oligopeptides by CD and vibrational CD techniques.

Introduction

In the past few years, several investigations have reported on induction of axial chirality in conformationally flexible biphenyl systems. Interactions of the proatropoisomeric biphenyl core with chiral auxiliaries linked either by covalent bonds, mostly through metal complexes,[1] or even by hydrogen bonding,[2] have been characterized and exploited in molecular recognition studies as well as in asymmetric catalysis. Central-to-axial transfer of chirality results in an induced circular dichroism (ICD)[3] of the biphenyl chromophore, which has been observed in biphenyldioxolanes from chiral 1,2- and 1,3-diols[4] and in dinitrodiphenic esters[5] from chiral secondary alcohols. These approaches constitute novel tools for the determination of the absolute configuration of these classes of compounds. ICD has been also reported for diphenimides[6] and a concomitant, induced homohelicity has been recently demonstrated in diphenimide bis-propellers.[6b] The biphenyl core is also the special feature of the 2′,1′:1,2;1″,2″:3,4-dibenzcyclohepta-1,3-diene-6-amino-6-carboxylic acid (Bip) residue, a new proatropoisomeric, conformationally labile $C^{\alpha,\alpha}$-disubstituted glycine with interconverting, nonisolable *(R)* and *(S)* enantiomers (Figure 1),[7] selected peptides of which have been investigated by our groups.[8] The rotational energy barrier of Bip has been evaluated[7b,8] to be ca. 14 kcal mol^{-1}, as expected from previous reports relative to seven-membered 2,2′-bridged biphenyl derivatives.[4,9]

Stimulated by the above literature reports, we have been interested in the search for a central-to-axial transfer of chirality in peptides of the type X-Bip-Y (Figure 1) (X or Y = amino acid residue), which could possibly result in an observable ICD. In the present paper, on the basis of results from ^{1}H NMR, CD, and VCD (vibrational CD) techniques, we describe examples of induced axial chirality in the Bip residue in terminally protected Bip/Val dipeptides (Figure 2),[10] as well as a novel process of propagation of chirality in three $(Bip)_n$/Val series of 3_{10}-helical[11] oligopeptides.

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(1) (a) Fabris, F.; De Lucchi, O.; Lucchini, V. *J. Org. Chem.* **1997**, *62*, 7156−7164. (b) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1997**, *38*, 2681−2684. (c) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Pardillos-Guindet, J.; Vallée, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3889−3894. (d) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 495−497.
(2) (a) Mizutani, T.; Takagi, H.; Hara, O.; Horiguchi, T.; Ogoshi, H. *Tetrahedron Lett.* **1997**, *38*, 1991−1994. (b) Freedman, T. B.; Cao, X.; Nafie, L. A.; Kalbermatter, M.; Linden, A.; Rippert, A. J. *Helv. Chim. Acta* **2003**, *86*, 3141−3155.
(3) Allenmark, S. *Chirality* **2003**, *15*, 409−422.
(4) Superchi, S.; Casarini, D.; Laurita, A.; Bavoso, A.; Rosini, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 451−454.
(5) Hosoi, S.; Kamiya, M.; Kiuchi, F.; Ohta, T. *Tetrahedron Lett.* **2001**, *42*, 6315−6317.
(6) (a) Eyer, M.; Schlögl, K.; Schölm, R. *Tetrahedron* **1981**, *37*, 4239−4244. (b) Kwit, M.; Rychlewska, U.; Gawronski, J. *New J. Chem.* **2002**, *26*, 1714−1717.
(7) (a) Mazaleyrat, J.-P.; Gaucher, A.; Wakselman, M.; Tchertanov, L.; Guilhem, J. *Tetrahędron Lett.* **1996**, *37*, 2971−2974. (b) Mazaleyrat, J.- P.; Gaucher, A.; Savrda, J.; Wakselman, M. *Tetrahedron: Asymmetry* **1997**, *8*, 619−631.
(8) (a) Mazaleyrat, J.-P.; Gaucher, A.; Wakselman, M.; Toniolo, C.; Crisma, M.; Formaggio, F. In *Peptides 1996*; Ramage, R., Epton, R., Eds.; Mayflower Scientific: Kingswinford, U.K., 1998; pp 623−624. (b) Formaggio, F.; Crisma, M.; Toniolo, C.; Mazaleyrat, J.-P.; Wakselman, M. In *Peptides 1998*; Bajusz, S., Hudecz, F., Eds.; Akadémiai Kiadó: Budapest, Hungary, 1999; pp 352−353. (c) Formaggio, F.; Crisma, M.; Toniolo, C.; Tchertanov, L.; Guilhem, J.; Mazaleyrat, J. P.; Gaucher, A.; Wakselman, M. *Tetrahedron* **2000**, *56*, 8721−8734.
(9) Carter, R. E.; Dahlqvist, K.-I.; Berntsson, P. *Org. Magn. Reson.* **1997**, *9*, 44−48.

10.1021/ja040100v CCC: $27.50

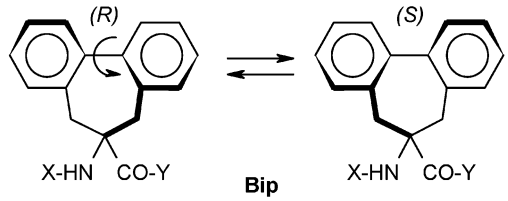

Figure 1. Conformational equilibrium (proatropoisomerism) of the X-Bip-Y peptides.

Experimental Section

Synthesis of Peptides. Synthesis and characterization of the amino acid derivatives and peptides Boc-Bip-OH (Boc, *tert*-butyloxycarbonyl),[7b] Z-Bip-OH (Z, benzyloxycarbonyl),[7b] H-Bip-O*t*Bu (O*t*Bu, *tert*-butoxy),[7b] Z-(Bip)$_3$-O*t*Bu,[8c] Z-(Bip)$_4$-O*t*Bu,[8c] Z-(Bip)$_5$-O*t*Bu,[8c] Z-(Bip)$_2$-OXL [OXL, 5(4*H*)-oxazolone],[8c] Z-(Bip)$_3$-OXL,[8c] and Z-(Bip)$_4$-OXL[8c] have already been published, while those of all new peptides discussed in this work are reported in the Supporting Information.

IR Absorption. The FT-IR absorption spectra were recorded using a Perkin-Elmer model 1720X FT-IR spectrophotometer, nitrogen-flushed, equipped with a sample-shuttle device, at 2 cm^{-1} nominal resolution, averaging 100 scans. Cells with path lengths of 0.1, 1.0, and 10 mm (with CaF_2 windows) were used. Spectrograde deuteriochloroform (99.8% *d*) was purchased from Aldrich. Solvent (baseline) spectra were recorded under the same conditions.

Nuclear Magnetic Resonance. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM300 spectrometer operating at 300 and 77 MHz, respectively, the solvent $CDCl_3$ (^{1}H: $\delta = 7.27$ ppm; ^{13}C: $\delta = 77.00$ ppm) or CD_3OD (^{1}H: $\delta = 3.31$ ppm) being used as internal standard. Spectrograde deuteriochloroform (99.5% *d*) and methyl alcohol D4 (99.8% *d*) were purchased from Euriso-top (Saclay, France).

Circular Dichroism. The CD spectra were obtained on a Jasco (Tokyo) J-715 spectropolarimeter. Cylindral fused quartz cells (Hellma) of 0.1-mm path length were used. The values are expressed in terms of $[\theta]_T$, total molar ellipticity (deg.cm^2.dmol^{-1}). Spectrograde methanol (Fluka) was used as solvent.

Vibrational Circular Dichroism. Samples for VCD and IR absorption measurements in the 1775−1475 cm^{-1} region were prepared by dissolving Ac-(Bip)$_3$-L-Val-OMe (**L3′C**) and Boc-L-Val-(Bip)$_4$-O*t*Bu (**L4N**) in a 46:11 (v/v) $CDCl_3$/TFE (2,2,2-trifluoroethanol) solvent mixture and in $CDCl_3$ solution, respectively. The solutions were placed in a demountable cell (Specac) constructed of two CaF_2 windows separated by a 500-μm Teflon spacer. The concentrations used were 9.5 and 8.6 mg/mL for Ac-(Bip)$_3$-L-Val-OMe and Boc-L-Val-(Bip)$_4$-O*t*Bu, respectively. Some additional experiments were also performed under the same conditions in the mixed solvent 46:11 (v/v) $CDCl_3$/TFE, *d* (deuterated 2,2,2-trifluoroethanol). VCD spectra were measured in the mid-IR region on a UIC dispersive VCD spectrometer, the design and use of which have been previously described in detail.[12] The VCD spectra were obtained as an average of 10 scans and recorded at 10 cm^{-1} resolution and 10-s time constant. An identical number of scans of the solvents, collected under the same experimental conditions, were averaged for baseline correction and subsequently subtracted from the averaged sample spectra. Mid-IR absorption spectra were recorded at UIC on a Digilab FTS-60a FT-IR absorption spectrometer and obtained by averaging of 940 scans measured at 4 cm^{-1} resolution with a zero-filling factor of 8.

Results and Discussion

Synthesis. Access to the Bip residue as its α-amino ester H-Bip-O*t*Bu, by phase-transfer bis-alkylation of a glycine *tert*-butyl ester Schiff base, has been previously reported.[7b] From the readily obtained derivatives Boc-Bip-OH[7b] and H-Bip-OMe (OMe, methoxy), the terminally protected dipeptides Boc-L-Val-Bip-OMe (**L1N**), Boc-D-Val-Bip-OMe (**D1N**), Boc-Bip-L-Val-OMe (**L1C**), and Boc-Bip-D-Val-OMe (**D1C**) were prepared in solution by using symmetrical anhydride activation[13] for coupling at the N-terminus of Bip and EDC [*N*-ethyl, N′-(3-dimethylaminopropyl)-carbodiimide]/HOAt (7-aza-1-hydroxy-1,2,3-benzotriazole) activation[14] for coupling at its C-terminus. These methods are effective even in peptide bond formation with sterically demanding $C^{\alpha,\alpha}$-disubstituted glycines.[15] These Bip/Val dipeptides are members of a much larger series of Boc or Z/OMe terminally protected X-Bip-Y di- and tripeptides with X,Y = protecting groups or N- and C-protected L- or D-α-amino acids [Ala, Val, Leu, Phe] which have been investigated by our groups.[16]

As for the synthesis of the -(Bip)$_n$/L-Val- peptide series, we took advantage of the previously prepared N^{α}-protected homopeptide esters Z-(Bip)$_n$-O*t*Bu ($n = 2-5$) and 5(4*H*)-oxazolones Z-(Bip)$_n$-OXL ($n = 2-4$).[8c] N^{α}-Deprotection of Z-(Bip)$_n$-O*t*Bu ($n = 2-5$) by hydrogenolysis on Pd/C catalyst in methanol, and subsequent acylation of the resulting aminoesters using a large excess of the N^{α}-protected *N*-carboxyanhydride Boc-L-Val-NCA[17] in the presence of diisopropylethylamine in tetrahydrofuran at 60 °C for 3−4 days, led to the desired peptides Boc-L-Val-(Bip)$_n$-O*t*Bu ($n = 2-5$) (**L2N**−**L5N**) in 48−72% yield. As for the second series of peptides with a C-terminal Val residue, Z-(Bip)$_n$-OXL ($n = 2-4$) was treated with a very large excess of H-L-Val-OMe in acetonitrile at 80 °C for 5−6 days to afford Z-(Bip)$_n$-L-Val-OMe ($n = 2-4$) (**L2C**−**L4C**) in 52−80% yield. Finally, a third series of the corresponding *N*-acetyl peptides was also prepared to avoid a possible misinterpretation in the CD analysis of the **L2C**−**L4C** peptides associated with the presence of the aromatic chromophore of the Z protecting group. Hydrogenolysis of Z-(Bip)$_n$-L-Val-OMe ($n = 2-4$), followed by acetylation of the free amino group, afforded Ac-(Bip)$_n$-L-Val-OMe (Ac, acetyl) ($n = 2-4$) (**L2′C**−**L4′C**). The hexapeptide Z-(Bip)$_6$-O*t*Bu was also prepared [from Z-(Bip)$_5$-O*t*Bu[8c] through the oxazolone Z-(Bip)$_5$-OXL] and then directly converted to the higher homologue Ac-(Bip)$_6$-L-Val-OMe (**L6′C**) via the intermediates H-(Bip)$_6$-O*t*Bu, Ac-(Bip)$_6$-O*t*Bu, Ac-(Bip)$_6$-OH, and Ac-(Bip)$_6$-OXL.

Chirality Transfer in the Bip/Val Dipeptides. The absorption spectrum of the biphenyl chromophore shows an intense

(10) Preliminary reports of this work have been published: (a) Oancea, S.; Formaggio, F.; Gaucher, A.; Wright, K.; Toulemonde, N.; Wakselman, M.; Mazaleyrat, J.-P.; Toniolo, C. In *Peptides 2002*; Benedetti, E., Pedone, C., Eds.; Edizioni Ziino: Naples, Italy, 2002; pp 392−393. (b) Mazaleyrat, J.-P.; Wright, K.; Toulemonde, N.; Gaucher, A.; Wakselman, M.; Broxterman, Q. B.; Formaggio, F.; Oancea, S.; Crisma, M.; Toniolo, C. In *Peptide Revolution: Genomics, Proteomics and Therapeutics*; Chorev, M., Sawyer, T. K., Eds.; American Peptide Society: San Diego, CA, 2004; in press.

(11) Toniolo, C.; Benedetti, E. *Trends Biochem. Sci.* **1991**, *16*, 350−353.

(12) (a) Keiderling, T. A. In *Infrared and Raman Spectroscopy of Biological Materials*; Gremlich, H. U., Yan, B., Eds.; Dekker: New York, 2001; Vol. 24, pp 55−100. (b) Keiderling, T. A. In *Practical Fourier Transform Infrared Spectroscopy*; Krishnan, K., Ferraro, J. R., Eds.; Academic Press: San Diego, CA, 1990; pp 203−284.

(13) Wieland, T.; Kern, W.; Sehring, R. *Liebigs Ann. Chem.* **1950**, *569*, 117−129.

(14) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(15) For a recent review article on the coupling methods used with $C^{\alpha,\alpha}$-disubstituted glycines, see Formaggio, F.; Broxterman, Q. B.; Toniolo, C. In *Synthesis of Peptides and Peptidomimetics;* Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; *Houben-Weyl: Methods of Organic Chemistry*, Vol. E 22c; Thieme: Stuttgart, 2003; pp 292−310.

(16) Mazaleyrat, J.-P.; Wright, K.; Toulemonde, N.; Gaucher, A.; Wakselman, M.; Broxterman, Q. B.; Formaggio, F.; Oancea, S.; Crisma, M.; Toniolo, C., manuscript in preparation.

(17) Fuller, W. D.; Goodman, M.; Naider, F. R.; Zhu, Y.-F. *Biopolymers* **1996**, *40*, 183−205.

Boc-L-Val-Bip-OMe (**L1N**)
Boc-D-Val-Bip-OMe (**D1N**)

Boc-Bip-L-Val-OMe (**L1C**)
Boc-Bip-D-Val-OMe (**D1C**)

Boc-L-Val-(Bip)$_2$-O*t*Bu (**L2N**)
Boc-L-Val-(Bip)$_3$-O*t*Bu (**L3N**)
Boc-L-Val-(Bip)$_4$-O*t*Bu (**L4N**)
Boc-L-Val-(Bip)$_5$-O*t*Bu (**L5N**)

Z-(Bip)$_2$-L-Val-OMe (**L2C**)
Z-(Bip)$_3$-L-Val-OMe (**L3C**)
Z-(Bip)$_4$-L-Val-OMe (**L4C**)

Ac-(Bip)$_2$-L-Val-OMe (**L2'C**)
Ac-(Bip)$_3$-L-Val-OMe (**L3'C**)
Ac-(Bip)$_4$-L-Val-OMe (**L4'C**)
Ac-(Bip)$_6$-L-Val-OMe (**L6'C**)

Figure 2. List of the Bip/Val peptides discussed in this work.

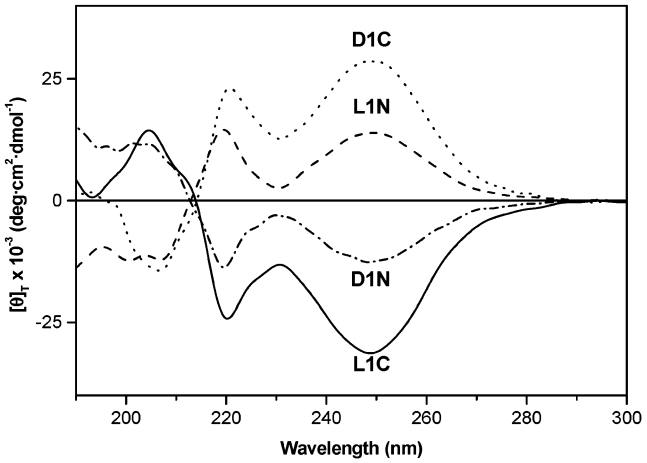

Figure 3. CD spectra of the Boc-L-Val-Bip-OMe (**L1N**), Boc-D-Val-Bip-OMe (**D1N**), Boc-Bip-L-Val-OMe (**L1C**), and Boc-Bip-D-Val-OMe (**D1C**) dipeptides in MeOH solution.

($\epsilon \cong 15\,000$) band at 250 nm (A band) accompanied by an extremely intense ($\epsilon \cong 30\,000$) band at 215 nm (C band).[18a] The A band is very sensitive to the biphenyl axial torsion angle.[18b,c] In the related CD spectrum of biphenyl-containing optically active molecules, a negative Cotton effect arising from the A band is related to a *P* torsion of the $C_{Ar}-C_{Ar}$ bond.[18b,c]

We performed a CD investigation of the Bip/Val dipeptides **L1N**, **D1N**, **L1C**, and **D1C** in MeOH solution (Figure 3). A strong negative Cotton effect is seen at 250 nm in the spectrum of **L1C**, followed by a couplet feature, negative at longer wavelengths, centered near 215 nm. Obviously, this CD spectrum is the mirror image of that of the enantiomeric **D1C**. Interestingly, if the Val residue is positioned at the N-terminus of the dipeptide sequence (dipeptides **L1N** and **D1N**), the ellipticity is significantly lower. Furthermore, the relationship between Val configuration and signs of the CD bands is reversed as compared to that characterizing dipeptides **L1C** and **D1C**.

In conclusion, our CD analysis of the Bip/Val dipeptides demonstrated the occurrence of a *chirality transfer* from L- or D-Val to the proatropoisomeric Bip, occurring more efficiently when the Val residue is at the C-terminal position (i.e. in the -Bip-Val- dipeptides). In this sequence, a *P* torsion of the Bip biphenyl axial bond is preferentially induced by an L-Val residue (and an *M* torsion by a D-Val residue).

The chirality transfer phenomenon of the Bip/Val dipeptides was also observed by ^{1}H NMR. Indeed, two sets of signals, each corresponding to the presence of one diastereomeric conformer, exchanging slowly on the NMR time scale, are present at low temperature (233 K) with unequal populations, while a single signal was observed at 333 K under fast-interconverting conditions. The diastereomeric ratio (*d.r.*) was determined at 233 K by integration of the best separated sets of signals. The singlet corresponding to the carboxylic ester methyl group appears at different chemical shifts for the two stereoisomers of **L1C** (3.80 and 3.69 ppm in CD_3OD; 3.79 and 3.70 ppm in $CDCl_3$) while separated Boc methyl singlets were observed for the two **L1N** stereoisomers (1.53 and 1.47 ppm in CD_3OD; 1.46 and 1.38 ppm in $CDCl_3$). Separation of the amide NH or Boc-urethane NH signals of the two stereoisomers in $CDCl_3$ also occurs. The *d.r.* is dependent on the nature of the solvent, $CDCl_3$ and CD_3OD, in particular with relatively high values observed in CD_3OD (see Supporting Information). In that solvent, the same as in our CD experiments (vide supra), *d.r.* of 77:23 for **L1C** and of 58:42 for **L1N** were observed, confirming the paramount role played by the C-terminal rather than the N-terminal position of the Val residue for the occurrence of a significant central-to-axial transfer of chirality in the present series of compounds.

Propagation of Chirality in the (Bip)$_n$/Val Oligopeptides. The above demonstrated central-to-axial chirality transfer Bip ← Val* led us to ask whether axial-to-axial chirality transfers would further occur in Bip ← Bip$^{(*)}$ ← Val* tripeptides, Bip ← Bip$^{(*)}$ ← Bip$^{(*)}$ ← Val* tetrapeptides, and so forth, resulting in a propagation of chirality through a covalent domino effect.[19] To address this question, the solution conformation and the chirospectroscopic properties of the oligopeptides Boc-L-Val-(Bip)$_n$-O*t*Bu (**L2N**−**L5N**), Z-(Bip)$_n$-L-Val-OMe (**L2C**-**L4C**), and Ac-(Bip)$_n$-L-Val-OMe (**L2′C**−**L4′C** and **L6′C**) were investigated by using FT-IR absorption, CD, and VCD techniques.

A solution conformational analysis of the terminally protected (Bip)$_n$/Val peptides was carried out by using FT-IR absorption in $CDCl_3$, a structure-supporting solvent (unfortunately, the extremely complex NMR spectra did not provide any valuable 3D-structural information). Figure 4a and 4b shows the FT-IR absorption spectra in the conformationally informative 3500−3250 cm^{-1} (N−H stretching) region of the Z-(Bip)$_n$-L-Val-OMe ($n = 2-4$) (**L2C**−**L4C**) and Boc-L-Val-(Bip)$_n$-O*t*Bu ($n = 2-4$) (**L2N**−**L4N**) peptide series, respectively. We assign (i) the high-frequency bands found at >3410 cm^{-1} to free, solvated NH groups [20] and (ii) the low-frequency band at 3350 ± 20 cm^{-1} to intramolecularly H-bonded NH groups of folded conformers.[20] No marked spectral changes were seen by decreasing the concentration to 0.1 mM, thus excluding any significant amount of self-associated peptide species.

(18) (a) Suzuki, H. *Electronic Absorption Spectra and Geometry of Organic Molecules*; Academic Press: New York, 1967. (b) Bunnenberg, E.; Djerassi, C.; Mislow, K.; Moscowitz, A. *J. Am. Chem. Soc.* **1962**, *84*, 2823−2826. (c) Borecka, B.; Cameron, T. S.; Linden, A.; Rashidi-Ranjbar, P.; Sandström, J. *J. Am. Chem. Soc.* **1990**, *112*, 1185−1190.

(19) (a) Inai, Y.; Tagawa, K.; Takasu, A.; Hirabayashi, T.; Oshikawa, T.; Yamashita, M. *J. Am. Chem. Soc.* **2000**, *122*, 11731−11732. (b) Inai, Y.; Ishida, Y.; Tagawa, K.; Takasu, A.; Hirabayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 2466−2473.

(20) (a) Mizushima, S.; Shimanouchi, T.; Tsuboi, M.; Souda, R. *J. Am. Chem. Soc.* **1952**, *74*, 270−271. (b) Cung, M. T.; Marraud, M.; Néel, J. *Ann. Chim. (France)* **1972**, 183−209. (c) Bonora, G. M.; Mapelli, C.; Toniolo, C.; Wilkening, R. R.; Stevens, E. S. *Int. J. Biol. Macromol.* **1984**, *6*, 179−188.

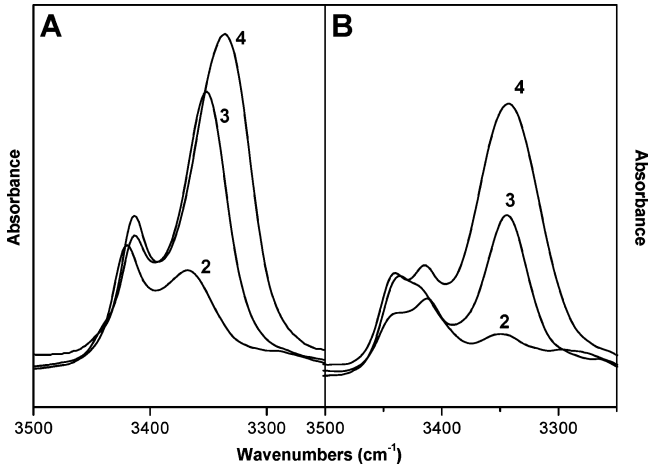

Figure 4. FT-IR absorption spectra (3500−3250 cm^{-1} region) in $CDCl_3$ solution of (A): Z-(Bip)$_n$-L-Val-OMe (n = 2−4) (**L2C**−**L4C**) and (B) Boc-L-Val-(Bip)$_n$-O*t*Bu (n = 2−4) (**L2N**−**L4N**). Peptide concentration: 1 mM.

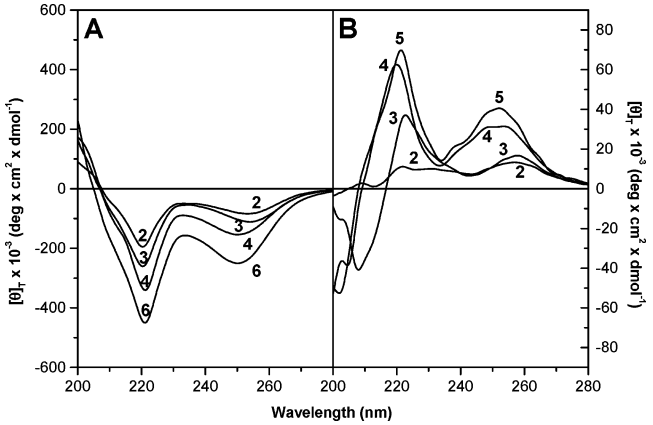

Figure 5. CD spectra in MeOH solution of (A): Ac-(Bip)$_n$-L-Val-OMe (n = 2−4, 6) (**L2′C**−**L4′C**, **L6′C**) and (B) Boc-L-Val-(Bip)$_n$-O*t*Bu (n = 2−5) (**L2N**−**L5N**).

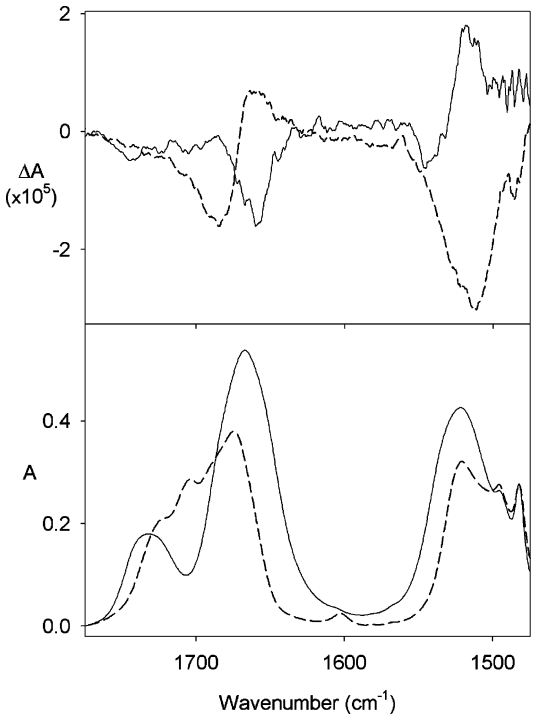

Figure 6. VCD (upper part) and IR absorption (lower part) spectra of Ac-(Bip)$_3$-L-Val-OMe (**L3′C**) (full lines) and Boc-L-Val-(Bip)$_4$-O*t*Bu (**L4N**) (dashed lines) in a 46:11 (v/v) $CDCl_3$/TFE solvent mixture and in $CDCl_3$ solution, respectively.

In both peptide series, the intensity of the low-frequency band, relative to that of the high-frequency band, tends to increase remarkably with peptide main chain lengthening. This behavior is reminiscent of that previously reported by our groups for the Z-(Bip)$_n$-O*t*Bu homopeptide series.[8c] A comparison of the spectra of the three tripeptides is indicative of the following rank order for intramolecular H-bonding: Z-(Bip)$_3$-O*t*Bu [8c] > Z-(Bip)$_2$-L-Val-OMe (**L2C**) ≫ Boc-L-Val-(Bip)$_2$-O*t*Bu (**L2N**). These findings indicate that Bip has a higher propensity for folding than Val, particularly at position 1 of the sequence. As we already published similar results for Bip/Ala peptides,[8c] it is clear that amino acid C$^\alpha$-tetrasubstitution, as in Bip, is indeed largely responsible for the observed folding enhancement.

The present FT-IR absorption study has provided convincing evidence that main chain length-dependent intramolecular H-bonding typical of folded species is a factor of paramount importance influencing the conformation of (Bip)$_n$/Val peptides in $CDCl_3$ solution. In addition, on the basis of the conclusions extracted from analogous FT-IR absorption data of a variety of other peptide series rich in C$^\alpha$-tetrasubstituted α-amino acids,[8c,21] we support the view that the type of folding preferentially adopted by the (Bip)$_n$/Val peptides is the 3_{10}-helical structure.

The far-UV CD spectra of the Ac-(Bip)$_n$-L-Val-OMe (n = 2−4,6) (**L2′C**−**L4′C**, **L6′C**) and Boc-L-Val-(Bip)$_n$-O*t*Bu (n = 2−5) (**L2N**−**L5N**) peptide series are shown in Figure 5a and 5b, respectively. All CD patterns share the common features of two Cotton effects of the same sign at about 250 and 220 nm.These curves parallel those reported in Figure 3 for the corresponding Bip/Val dipeptides. Again: (i) The absolute values of the ellipticities are much higher for the series with the N-terminal (Bip)$_n$ chain and (ii) the curves of the two series are roughly mirror images.

The absolute values of the total molar ellipticities do not decrease with increasing peptide molecular weight in each series. Indeed, such a decrease would be expected if the only source of chirality is the asymmetric Val α-carbon atom. Therefore, these results strongly support our contention that a novel type of chirality (induced Bip ← Bip$^{(*)}$ chirality), in addition to the induced Bip ← Val$^{(*)}$ chirality discussed above, plays a significant role in the CD properties of the peptides examined. This phenomenon is particularly pronounced in the -(Bip)$_n$-L-Val- series, where the absolute values of the total molar ellipticities steadily increase with increasing peptide molecular weight. Unfortunately, no detailed information on the peptide conformation can be extracted from this far-UV CD analysis since the optically active transitions of the biphenyl chromophore overwhelmingly predominate in the spectra over the −CONH− transitions.

The IR absorption and VCD spectra of the tetrapeptide Ac-(Bip)$_3$-L-Val-OMe (**L3′C**) in a 46:11 (v/v) $CDCl_3$/TFE solvent mixture and the pentapeptide Boc-L-Val-(Bip)$_4$-O*t*Bu (**L4N**) in $CDCl_3$ solution over the spectral region 1775−1475 cm^{-1} are given in Figure 6. The longer peptide has a complex amide I (amide C═O stretch) IR absorption with a maximum at 1675

(21) (a) Toniolo, C.; Bonora, G. M.; Barone, V.; Bavoso, A.; Benedetti, E.; Di Blasio, B.; Grimaldi, P.; Lelj, P.; Pavone, V.; Pedone, C. *Macromolecules* **1985**, *18*, 895−902. (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers (Pept. Sci.)* **2001**, *60*, 396−419.

cm^{-1}. The shoulders at 1725 and 1704 cm^{-1} are assigned to the ν(C═O) ester vibration of the C-terminal group and to the ν(C═O) urethane vibration of the N-terminal group, respectively. The amide II lies at 1522 cm^{-1} and is partially overlapped by biphenyl modes at 1495 and 1482 cm^{-1}. Other much weaker biphenyl bands are localized between 1610 and 1570 cm^{-1}. The VCD spectrum of **L4N** in Figure 6 shows a weak positive couplet (positive to low frequency) in the amide I region and a strong negative amide II band with maximum at 1511 cm^{-1}. The conformationally informative VCD shape and relative intensity of the amide I and amide II bands of the **L4N** peptide are comparable to those found experimentally for right-handed 3_{10}-helical structures.[22]

The IR absorption spectrum of **L3′C** shows an amide I maximum at 1667 cm^{-1}, a separate, broad vibration at 1732 cm^{-1} for the terminal groups, and an amide II at 1522 cm^{-1}. The side-chain biphenyl vibrations reflect those noted for **L4N**. The VCD of **L3′C** in the amide I region exhibits a quite distorted, negatively biased, negative couplet, the maximum of which at 1660 cm^{-1} is clearly shifted down in frequency from the absorption maximum. The amide II VCD is a mostly positive, distorted couplet with its positive maximum also shifted to lower frequency in comparison to the position of the IR absorption band. Overall, the VCD spectral features of **L3′C** imply a left-handed helicity, but the conformation is probably distorted, since it is that of a short peptide, which would explain the less developed band shapes.

To confirm the nature of the amide II band and distinguish it from any contributions that arise from the biphenyl modes, IR absorption and VCD of both peptides in a partially deuterated form were measured in a 46:11 (v/v) $CDCl_3$/TFE, *d* solution mixture under the same conditions (data not shown). Although the amide I IR absorption and VCD spectra shift about 10 cm^{-1} to lower wavenumbers, the shape of the amide I positive couplet of **L4N** is consistent in both solvents ($CDCl_3$ and $CDCl_3$/TFE, *d*). The amide II IR absorption and VCD intensities seen in Figure 6 essentially disappear, confirming their origins to be in the amide and not in the biphenyl part of the molecule. Similar results were obtained for **L3′C**, that is, the amide I VCD signal is consistent and the amide II disappears after deuteration.

The VCD spectra thus reveal a left-handed 3_{10}-helical conformation for **L3′C**, which is probably distorted for such a small peptide, whereas a right-handed 3_{10}-helical conformation for **L4N**.

Taken together, the most significant results of the present conformational and configurational analyses on the $(Bip)_n$/Val peptides are strongly in favor of the following conclusions: (i) A single, C-terminal, C^{α}-trisubstituted L-α-amino acid (e.g., L-Val) is able to generate a preferential *P* torsion in the biphenyl moiety of the adjacent, proatropoisomeric Bip residue. (ii) The penultimate Bip residue, in turn, successfully propagates its induced *P* chirality to all of the adjacent Bip residues in the peptide chain. (iii) Although quantitatively more modest, such a phenomenon is also operative when the chiral L-amino acid is positioned at the N-terminus of the chain. In this case, however, not only is the chirality transmission less effective, but, more significantly, the screw sense of the torsion generated in the biphenyl core of the Bip residues is reversed (*M*). (iv) The homopeptide chain based on the helicogenic Bip residue[8c] is predominantly folded in a left-handed 3_{10}-helix when the single, L-residue is C-terminal, whereas the right-handed screw sense is adopted by the peptides with the N-terminal L-residue.

These findings may be rationalized in terms of the following set of available X-ray diffraction and CD data: (i) A single, C-terminal, C^{α}-trisubstituted L-α-amino acid tends to induce a left-handed screw sense in a preceding homo-oligomeric peptide chain based on an achiral, 3_{10}-helicogenic C^{α}-tetrasubstituted α-amino acid (e.g., α-aminoisobutyric acid).[23] The opposite helical screw sense is found when the single L-residue is N-terminal. (ii) A C-terminal, C^{α}-trisubstituted L-α-amino acid forces the preceding Bip residue to adopt an (*S*)-configuration.[16] (iii) An (*S*)-configurated source of chirality tends to induce a *P* torsion in a biphenyl core.[4,6b] (iv) The relationship between the absolute configuration of the closely related congener of Bip, the atropoisomeric, binaphthyl residue (Bin), and the screw sense of the generated 3_{10}-helix is opposite to that exhibited by protein amino acids [i.e., (*S*)-Bin adopts ϕ, ψ backbone torsion angles typical of a left-handed helix].[24]

In summary, we believe that it is the helical secondary structure predominantly adopted by the peptides examined in this work that is the essential prerequisite for the observed propagation of chirality through a covalent domino effect on the proatropoisomeric $(Bip)_n$ chain. In our view, it remains to be established whether the experimental transmission of chirality of the same configuration in the $(Bip)_n$ chain should be associated with a predominant stereoselective interaction between the side chains of consecutive Bip residues or between each Bip residue and the 3_{10}-helix characterized by a strongly biased screw sense.

Conclusions

The present study illustrates, in particular, new and interesting features in the field of induced chirality in peptides: (i) a substantial central-to-axial induction of chirality from a C-terminal Val residue to a proatropoisomeric, helicogenic, C^{α}-tetrasubstituted α-amino acid Bip residue has been revealed in simple dipeptides, which represents a new method for the determination of the absolute configuration of α-amino acids and (ii) a novel, remarkably effective type of chiral propagation has been highlighted, involving a covalent domino effect from a C-terminal Val residue to a proatropoisomeric $(Bip)_n$ 3_{10}-helical secondary structure.

In future developments, proatropoisomeric, helicogenic $(Bip)_n$ sequences could perhaps be used as interesting new tools for (i) the study of noncovalent domino effects, as recently reported

(22) (a) Silva, R. A. G. D.; Yasui, S. C.; Kubelka, J.; Formaggio, F.; Crisma, M.; Toniolo, C.; Keiderling, T. A. *Biopolymers* **2002**, *65*, 229−243. (b) Kubelka, J.; Silva, R. A. G. D.; Keiderling, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 5325−5332. (c) Keiderling, T. A. In *Circular Dichroism: Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. A., Eds.; Wiley: New York, 2000; pp 621−666. (d) Keiderling, T. A.; Silva, R. A. G. D.; Yoder, G.; Dukor, R. K. *Bioorg. Med. Chem.* **1999**, *7*, 133−141.

(23) (a) Pengo, B.; Formaggio, F.; Crisma, M.; Toniolo, C.; Bonora, G. M.; Broxterman, Q. B.; Kamphuis, J.; Saviano, M.; Iacovino, R.; Rossi, F.; Benedetti, E. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1651−1657. (b) Benedetti, E.; Saviano, M.; Iacovino, R.; Pedone, C.; Santini, A.; Crisma, M.; Formaggio, F.; Toniolo, C.; Broxterman, Q. B.; Kamphuis, J. *Biopolymers* **1998**, *46*, 433−443. (c) Inai, Y.; Kurokawa, Y.; Hirabayashi, T. *Biopolymers* **1999**, *49*, 551−564.

(24) (a) Toniolo, C.; Formaggio, F.; Crisma, M.; Mazaleyrat, J.-P.; Wakselman, M.; George, C.; Deschamps, J. R.; Flippen-Anderson, J. L.; Pispisa, B.; Venanzi, M.; Palleschi, A. *Chem. Eur. J.* **1999**, *5*, 2254−2264. (b) Formaggio, F.; Peggion, C.; Crisma, M.; Toniolo, C.; Tchertanov, L.; Guilhem, J.; Mazaleyrat, J.-P.; Goubard, Y.; Gaucher, A.; Wakselman, M. *Helv. Chim. Acta* **2001**, *84*, 481−501.

by Inai et al.,[19] that is, in the search for interactions between N^{α}-protected, chiral α-amino acids and H-$(Bip)_n$-OR homopeptide esters, and (ii) the detection and amplification of a small enantiomeric imbalance in α-amino acids, in relation with the stimulating work of Yashima and co-workers,[25] that is, in the search for interactions between chiral α-amino acid esters and $(Bip)_n$-[crown] homopeptides. These projects are currently being explored in our groups.

(25) (a) Nonokawa, R.; Yashima, E. *J. Am. Chem. Soc.* **2003**, *125*, 1278−1283. (b) Yashima, E.; Maeda, K.; Nishimura, T. *Chem. Eur. J.* **2004**, *10*, 42−51.

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Supporting Information Available: Preparation and characterization of newly synthesized peptides, mass spectra, and temperature-dependent ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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