Fully Extended Poly(*β*-amino acid) Chains: Translational Helices with Unusual Theoretical *π*−*π** Absorption and Circular Dichroic Spectra

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Calculations of ultraviolet absorption and circular dichroic (CD) spectra in the $\pi-\pi^*$ band for fully extended chains of poly(*β*-amino acids) yield simple spectra dominated by a single normal mode, using our classical dipole interaction theory with parameters developed previously for peptides and proteins. These molecules represent the unusual case of a purely translational helix, in which the array of amide chromophores is achiral. The CD spectra are thus unusual in deriving all of their rotational strength by "borrowing" from the nonchromophoric atoms in the molecule. Calculations are presented also for parallel and antiparallel sheet structures, whose existence is known, and for both single chains and sheets in the presence of solvent, using a lattice-filled cavity model for the surrounding medium. The molecules treated are poly(*β*-alanine), poly(*β*-aminobutyric acid), poly(*β*-aminoisobutyric acid), poly(3-amino-2-methylbutanoic acid), and poly(2-aminocyclohexanecarboxylic acid).

Introduction

Recent interest in poly(*β*-amino acids) has been stimulated by a number of discoveries of novel conformations that are analogous to the ordered helical and sheet structures in poly(α-amino acids) and proteins. The reviews by DeGrado *et al.*[1] and Gademann *et al.*[2] document the extensive progress on this subject. The ultraviolet circular dichroic (CD) spectra have been among the tools used to characterize the structures in solution, and we have been interested in these studies in connection with our efforts to develop a theory relating peptide structures to CD spectra and the related ultraviolet absorption spectra.[3−8]

A special case of a helical structure is the fully extended chain, in which the backbone torsion angles ϕ, ξ, ψ, and ω are all 180°. This structure was first found in the solid state for long-chain poly[(*S*)-*β*-aminobutyric acid],[9,10] where the extended chains are arranged in antiparallel fashion with interchain hydrogen bonding between amide groups (Figure 1). Similar antiparallel structures have been identified in solution in small *β*-peptides which form hairpin conformations.[11,12] Parallel sheet structures have been found recently in intermolecularly hydrogen-bonded *β*-tripeptides in the solid state.[12,13] The observed structures are thus analogous to the pleated *β*-sheets found in poly(α-amino acids), though there are at least two important distinctions: (i) The pleated *β*-sheets have chiral backbone structures even in the idealized two-dimensional lattices originally proposed by Pauling and Corey,[14] while the fully extended poly(*β*-amino acid) backbone atoms, including the NC′O chromophores, all lie in a plane, so that the backbone itself is achiral. (ii) The individual chains of the idealized pleated *β*-sheets are 2-fold helices generated by translation and 180° rotation of a residue with respect to the helix axis, while the fully extended poly(*β*-amino acid) chain is a purely translational helix, involving no rotation of successive residues.

The purpose of this study is to explore the predictions of our theory of absorption and CD spectra for the fully extended poly(*β*-amino acid) chains, both as isolated chains and as intermolecularly hydrogen-bonded sheets. We wish to see what special effects occur due to the properties of the fully extended backbone noted above. Possibly these findings will provide new tools for identifying the structures in solution, and they suggest new tests of the theoretical model.

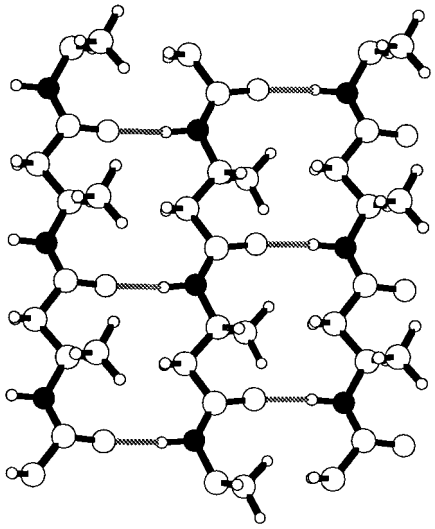

Figure 1. Poly[(*R*)-*β*-aminobutryic acid] in an antiparallel sheet structure.[9,10] Nitrogen atoms are black. Produced with the MacMolplt program, courtesy Dr. Brett Bode.

Theory

The dipole interaction model provides a means of calculating optical properties of molecules on the basis of the polarizabilities of atoms and chromophores which interact solely by way of induced dipole fields when in the presence of an electric field.[15−17] Solvent effects are taken into account by means of the lattice-filled cavity model described previously.[8] Details of the theory and its application to the prediction of absorption and circular dichroic spectra and other spectral properties are provided elsewhere.[3] Briefly, the NC′O chromophores have anisotropic polarizabilities consisting of a complex, frequency-

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dependent contribution from the $\pi-\pi^*$ transition and a nondispersive contribution from higher energy transitions, while all other atoms behave as nondispersive, isotropic units. All atoms and chromophoric groups mutually interact via induced dipole moments, and the response of the entire molecule to light is expressed in terms of normal mode electric dipole moments, $\boldsymbol{\mu}^{(k)}$, normal mode magnetic dipole moments, $\mathbf{m}^{(k)}$, and the wavenumber $\bar{\nu}_k$ of light whose frequency $c\bar{\nu}_k$ is equal to the resonant frequency of the normal mode. Spectral properties are obtained as sums over normal mode bands expressed in terms of a normal mode dipole strength $D_k = \boldsymbol{\mu}^{(k)}\cdot\boldsymbol{\mu}^{(k)}$ and a normal mode rotational strength $R_k = \mathbf{m}^{(k)}\cdot\boldsymbol{\mu}^{(k)}$. The quantities of primary interest are the molar absorption coefficient ϵ and the circular dichroism $\Delta\epsilon$, both on a residue-molar basis, in an isotropic medium of refractive index n_r (or optical dielectric constant n_r^2). These are given by[18−22]

$$\epsilon = \left(\frac{3n_r}{2n_r^2+1}\right)\frac{8\pi^2\bar{\nu}^2 N_A \Gamma}{6909 N_p}\sum_{k=1}^{q}\frac{D_k}{(\bar{\nu}_k^2-\bar{\nu}^2)^2+\Gamma^2\bar{\nu}^2} \quad (1)$$

$$\Delta\epsilon = \left(\frac{5n_r^2+1}{4n_r^2+2}\right)\frac{32\pi^3\bar{\nu}^3 N_A \Gamma}{6909 N_p}\sum_{k=1}^{q}\frac{R_k}{(\bar{\nu}_k^2-\bar{\nu}^2)^2+\Gamma^2\bar{\nu}^2} \quad (2)$$

where $\bar{\nu}$ is the wavenumber of the light, N_A is Avogadro's number, Γ is the half-peak bandwidth of all normal modes, q is the number of normal modes, and N_p is the number of residues in the solute molecule. We set $\Gamma = 4000\ \mathrm{cm}^{-1}$ in all calculations reported here.

Methods

The coordinates of atoms in the extended chains were generated as described previously for general β-peptide helices.[4] The backbone torsion angles ϕ, ξ, ψ, and ω (defined by the atoms $C^\alpha C^\beta NC'$, $C'C^\alpha C^\beta N$, $NC'C^\alpha C^\beta$, and $C^\beta NC'C^\alpha$, respectively) were all set at 180°. As before, the repeating unit was $-C^\alpha HX-C'O-NH-C^\beta HX'-$, where X and X′ represent H or other side chains. Methyl side chains were attached with C−C bonds in staggered conformations. No additional end groups were attached.

Sheet structures were generated by first placing a single extended chain in a right-handed Cartesian coordinate system with the z-axis coincident with the helix axis and the atoms $C^\alpha C^\beta NHC'O$ lying in the xz-plane. Subsequent chains were generated by the transformations $(x, y, z) \rightarrow (x + a, y, z + t)$ (parallel sheets) and $(x, y, z) \rightarrow (x + a', -y, -z + t')$ (antiparallel sheets), where t and t' are translations along z to produce hydrogen bonds between all NH and C′O pairs on adjacent strands with optimal NO distance 2.79 Å and optimally linear N−H···O═C groups.[4] Figure 1 shows the antiparallel structure for poly[(*R*)-β-aminobutryic acid]. For this sheet the x-axis translation is $a' = 4.65$ Å (exptl 4.8 Å[9,10]) and the z-axis repeat is 4.824 Å (exptl 4.6 Å,[9] 4.8 Å[10]). The calculated parallel structure has x-axis translation $a = 4.64$ Å and z-axis repeat 4.824 Å.

Polarizabilities of atoms and NC′O groups were those of parameter set H_y, as in previous calculations.[4]

The calculations of spectra in the presence of solvent were carried out as described previously,[8] using the same parameters for the lattice and cavity dimensions.

Calculations were performed using double-precision Fortran programs on either a DEC 3000/300L workstation with 64 MB of memory or a cluster of six DEC 600 Alpha workstations, the largest of which had 512 GB of memory. The programs are available at www.public.iastate.edu/~jba/CaPPS.

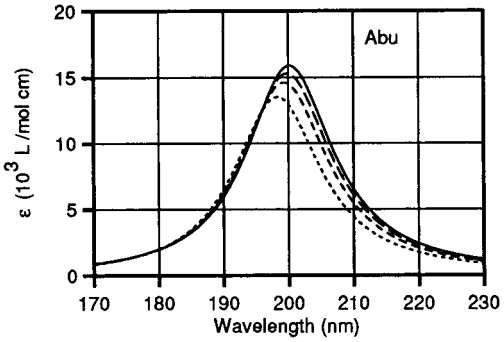

Figure 2. Absorption spectra of $(\beta\mathrm{Abu})_N$: (- - -) $N = 6$; (— — —) $N = 12$; (— —) $N = 24$; (—) $N = 100$.

Results

Calculations are reported here for the achiral molecule poly(β-alanine) $[(\beta\mathrm{Ala})_N]$ and the following chiral β-peptides with methyl side chains: poly(β-aminobutyric acid) $[(\beta\mathrm{Abu})_N]$, poly(β-aminoisobutyric acid) $[(\beta\mathrm{Aib})_N]$, and poly(3-amino-2-methylbutanoic acid) $[(\beta\mathrm{Amb})_N]$. In addition we include poly(2-aminocyclohexanecarboxylic acid) $[(\beta\mathrm{Chc})_N$, formerly abbreviated $(\beta\mathrm{Acc})_N$[4]], in which the backbone conformation is constrained by the chair form of the cyclohexane ring with its NH and C′O substituents in the axial positions, corresponding to $\xi = 180°$. The *R* configuration at chiral C^α and C^β is implied in all cases unless stated otherwise. Sheet structures are designated by formulas such as $(\beta\mathrm{Abu})_{N\times M}$, indicating a sheet of M chains with N residues each.

Figure 2 shows the calculated absorption spectra of $(\beta\mathrm{Abu})_N$ for chain lengths 6−100. The corresponding spectra for the other polymers are practically identical to these (not shown). A notable feature of these spectra is that there is a single strong normal mode, which is the longest wavelength mode. For the longer chain lengths 87% of the oscillator strength is in this mode. Thus, the band shape is essentially that of a single Lorentzian function. This mode is polarized at an angle of 13.9° with respect to the chain axis. As expected for a translational helix, the polarization is not exactly parallel or perpendicular to the axis. If only the NC′O $\pi-\pi^*$ oscillator contributed to the mode, its orientation would be that of the isolated chromophore, namely, 37.6° with respect to the axis. The calculated orientation is quite different due to the participation of the nonchromophoric atoms in the normal mode.

Figure 3 shows the calculated CD spectra of the four chiral β-peptides for chain lengths 6−100. For $(\beta\mathrm{Abu})_N$, $(\beta\mathrm{Amb})_N$, and $(\beta\mathrm{Chc})_N$ the CD spectra, like the absorption spectra, are dominated by the longest wavelength normal mode, particularly for the longer chains. Thus, the positions and band shapes of the CD and absorption spectra are very similar. $(\beta\mathrm{Aib})_N$ behaves rather differently in that the rotational strength is widely distributed among many modes, most of which occur in closely spaced pairs of equal and opposite strength. The net negative band is primarily the contribution of two closely spaced negative modes, one of which dominates the absorption spectrum as well. The CD spectra are all highly nonconservative; i.e., there is no cancellation of the total rotational strength by bands of opposite sign. This is because the array of $\pi-\pi^*$ chromophores is planar, so that its rotational strength is entirely borrowed from the nonchromophoric subsystem; under these conditions a nonconservative spectrum is expected,[20] though the dominance of a single normal mode is a surprise.

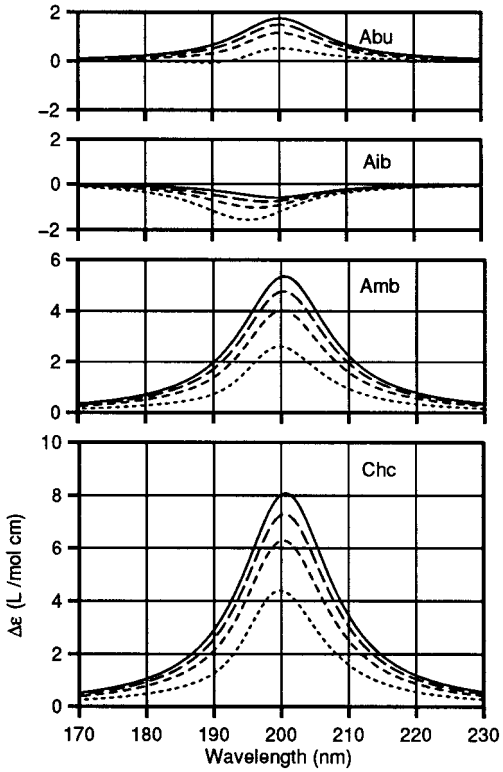

Figure 3. CD spectra of $(\beta\text{Abu})_N$, $(\beta\text{Aib})_N$, $(\beta\text{Amb})_N$, and $(\beta\text{Chc})_N$: (- - -) $N = 6$; (— — —) $N = 12$; (— —) $N = 24$; (—) $N = 100$.

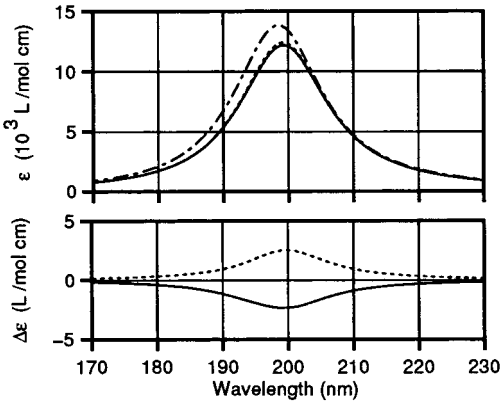

Figure 4. Absorption and CD spectra of parallel sheet structures: (—) $(\beta\text{Aib})_{6\times3}$; (- - -) $(\beta\text{Abu})_{6\times3}$; (— - —) $(\beta\text{Ala})_{6\times3}$.

Figure 4 shows the absorption and CD spectra for parallel sheets of $(\beta\text{Abu})_{6\times3}$, $(\beta\text{Aib})_{6\times3}$, and $(\beta\text{Ala})_{6\times3}$ (absorption only). Spectra could not be obtained for the corresponding sheets of βAmb or βChc due to close contacts (≤0.9 Å) between side-chain hydrogens on adjacent chains. This problem arises from the fact that the side chains throughout the structure lie on the same face of the sheet. The sheet spectra are not dominated by the long-wavelength normal mode, but show a number of significant modes in the 197−200 nm range, with the strongest mode in both absorption and CD at 200 nm. The two strongest modes in absorption are polarized nearly parallel to the chain axis. The signs of the CD bands are the same as those of the corresponding single chains.

Figure 5 shows the absorption and CD spectra for 6 × 3 antiparallel sheets of the five β-peptides. In this structure the side chains of adjacent strands are on opposite faces of the sheet (Figure 1), and no problems with close contacts were encountered. Again, the sheet spectra are not dominated by the long-wavelength normal mode, but show a strong mode in both

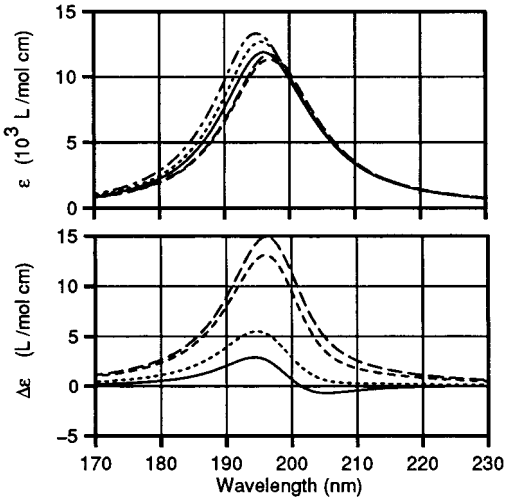

Figure 5. Absorption and CD spectra of antiparallel sheet structures: (—) $(\beta\text{Aib})_{6\times3}$; (- - -) $(\beta\text{Abu})_{6\times3}$; (— — —) $(\beta\text{Amb})_{6\times3}$; (— —) $(\beta\text{Chc})_{6\times3}$; (— - —) $(\beta\text{Ala})_{6\times3}$.

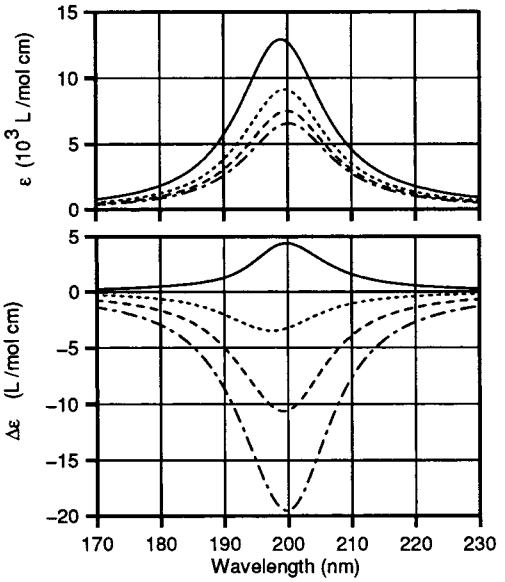

Figure 6. Absorption and CD spectra of single-chain $(\beta\text{Chc})_6$ in solvent with refractive index n_r: (—) $n_r^2 = 1.0$; (- - -) $n_r^2 = 2.0$; (— — —) $n_r^2 = 3.0$; (— - —) $n_r^2 = 4.0$.

absorption and CD at 196 ± 1 nm and a weaker, but significant, mode at 202 ± 1 nm. The absorption spectrum of the shorter wavelength mode is polarized nearly parallel to the chain axis, while the long-wavelength mode is polarized in the plane of the sheet nearly perpendicular to the chain axis. Thus, the nature of the normal modes is quite different from that in the single chains, and the dependence on side chain structure is different as well.

Figure 6 shows the absorption and CD spectra for $(\beta\text{Chc})_6$ single chains in the presence of solvent with $n_r^2 = 2.0$, 3.0, and 4.0. The curves for $n_r^2 = 1.0$ correspond to the molecule in a vacuum. The molecule is centered in a spherical cavity of radius 18.0 Å, and 661 solvent molecules are placed on a simple cubic lattice, filling the void region. The most striking effect is the reversal of the sign of the CD band in the presence of solvent. This effect is also found in $(\beta\text{Abu})_6$ and $(\beta\text{Amb})_6$ in the presence of solvent (data not shown), while $(\beta\text{Aib})_6$ shows a negative CD band with or without solvent. To learn whether the sign reversal is an artifact due to close contacts between the solvent lattice and the solute, the calculation for $(\beta\text{Chc})_6$ was repeated

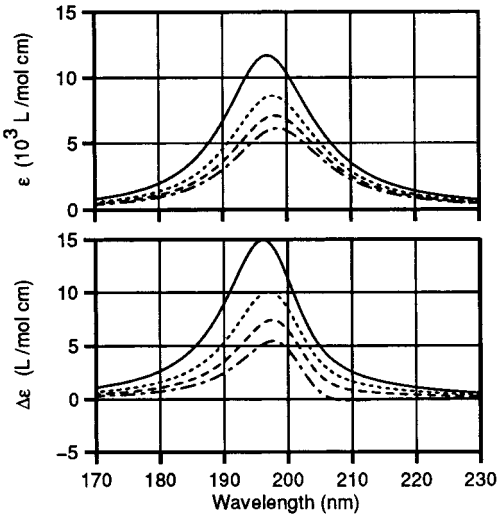

Figure 7. Absorption and CD spectra of antiparallel $(\beta\text{Chc})_{6\times3}$ in solvent with refractive index n_r: (—) $n_r^2 = 1.0$; (- - -) $n_r^2 = 2.0$; (— — —) $n_r^2 = 3.0$; (— - —) $n_r^2 = 4.0$.

for values of the minimum contact distance CMOL = 3.0, 3.5, and 4.0 Å. The CD band for $n_r^2 = 2.0$ remained negative throughout, indicating that this feature is insensitive to the immediate solvent structure. The reversal of sign of the CD band indicates a major participation of the solvent in the normal mode. The absorption spectra in the presence of solvent are similar to those of the isolated molecule in that they are dominated by the long-wavelength normal mode, which is polarized nearly along the chain axis. However, the intensities are quite sensitive to n_r. The spectra for $n_r^2 = 2.0$ represent predictions for typical measurements in solution, since this is in the range of typical solvent refractive indices.

Figure 7 shows the absorption and CD spectra for $(\beta\text{Chc})_{6\times3}$ antiparallel sheets in the presence of solvent with $n_r^2 = 2.0$, 3.0, and 4.0. The curves for $n_r^2 = 1.0$ correspond to the molecule in a vacuum. The sheet is centered in a spherical cavity of radius 19.4 Å, and 751 solvent molecules are placed on a simple cubic lattice, filling the void region. It is seen that the primary effect of the solvent is to reduce overall intensities of both the absorption and CD spectra. The dominant normal modes and their polarizations are shifted only slightly from those of the isolated sheet. The dominant CD band in the sheet, unlike that of the single chain, does not reverse sign in the presence of solvent.

Discussion

The fully extended poly(β-amino acid) chains represent a particularly simple ordered structure, a purely translational helix. The predicted $\pi-\pi^*$ absorption and CD spectra of the single chains show the following features that are related to the unique nature of this structure: (i) for three of the four chiral molecules the spectra are dominated by a single normal mode, which is the same mode in both absorption and CD; (ii) the CD spectra are highly nonconservative due to the fact that the achiral array of chromophores derives all of its rotational strength from the interaction of the chromophores with the nondispersive atoms; (iii) some of the polymers are predicted to show a reversal of sign of the CD band in solution relative to the isolated molecule.

As far as we know, there are no experimental data on these systems to test the present theory. Efforts such as those in the laboratories of Gellman[11] and Seebach[12] to prepare sheet structures of β-peptides in solution could eventually lead to spectral measurements that would test our sheet calculations. As the single chains best exhibit the unusual properties of the translational helix, a means of preparing such structures in solution would be very desirable. This might be done by introducing ionized side chains, which would favor extended structures in long polymers by polyelectrolyte expansion.

In our model the $\pi-\pi^*$ normal modes are split by dipole interaction into N modes in the range 191−200 nm. The dominant mode is the longest wavelength mode for the fully extended poly(β-amino acids). The remaining modes have small, but nonvanishing, dipole and rotational strengths. It is worth noting that an earlier calculation[21] of absorption and CD spectra of fully extended poly(α-L-alanine) chains produced results similar in some respects to those reported here. The absorption and CD spectra for the chain with $\phi = \psi = \omega = 180°$ were each dominated by single normal modes, but the absorption was in the long-wavelength mode, while the CD was at the opposite end of the $\pi-\pi^*$ band in the short-wavelength mode. Like the present systems, the structure consisted of a planar, achiral array of NC′O chromophores which derived all of its chirality from the presence of the methyl side chains. However, the fully extended poly(α-amino acid) chain is a 2-fold helix, not a translational helix, and the spectra are thus a degree more complicated. Interestingly, Krimm and Tiffany[22] proposed that the strongly nonconservative CD spectrum observed for ionized poly(α-amino acids) does in fact correspond to a highly extended helix, though they favored a 3-fold helix rather than a 2-fold helix on energetic grounds.

The origin of the unusual spectral features found here for poly(β-amino acids) remains to be clarified. The following paper in this issue examines this matter in an analysis of the normal mode method.[23] Briefly, it is shown that the normal modes are described by sinusoidal standing waves in the electronic polarization of the molecule, and that the dominant mode is a wave of low wavenumber whose relative strength in both absorption and CD arises from the manner in which mutual cancellation of dipole moments occurs within the wave.

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