Macrodipole Moment of Polypeptides in β-Sheet and Its Prediction from Dipole Moments of Amino Acid Residues as Building Blocks: Alanine and Glycine in β-Strand

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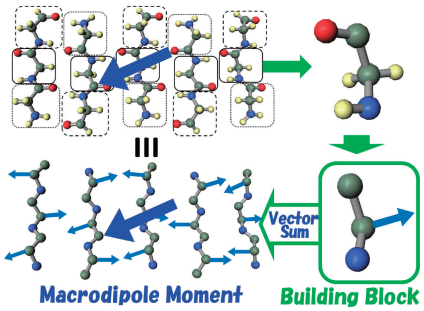

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Macrodipole Moment of Polypeptides in β-Sheet and Its Prediction from Dipole Moments of Amino Acid Residues as Building Blocks: Alanine and Glycine in β-Strand

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The macrodipole moment of a β-sheet depends on the number and length of β-strands, as well as whether it is parallel or antiparallel. Here, we propose the VSHBβ model, in which the dipole moments of amino acid residues are used as building blocks to predict the macrodipole moment of a β-sheet. Once a set of VSHBβ models is available, large-scale MO calculations will not be needed to obtain local dipole moments or macrodipole moments of large polypeptides in β-sheets.

Antiparallel and parallel β-sheet structures are ubiquitous in proteins. It is also known that several diseases such as Alzheimer's disease[1] and mad-cow disease[2] are associated with the aggregation of fibers containing misfolded proteins with the β-sheet conformation.[3] In the β-sheet structure, N–H and C=O groups of a backbone are oriented approximately perpendicular to the direction of a β-strand, and therefore, are available for interstrand hydrogen bonding. The interstrand hydrogen bonds mold several β-strands into an antiparallel or a parallel form.

Although many properties such as the structural parameters, hydrogen-bond energies, and cooperativity of β-sheets have been explored in detail,[4–6] only a few computations of the dipole moments of β-sheets have been carried out to date.[7,8] Owing to the alternate directions of amino acid residues in a β-sheet, it is often speculated that the dipole moments of individual residues in a β-sheet might be almost canceled out and that the macrodipole moment of the β-sheet might be small.[7] In this letter, we show that this is not the case, especially for parallel β-sheets.

We prepared several kinds of model polypeptides in β-sheet structures and calculated their geometries, dipole moments, and atomic charges. All ab initio molecular orbital (MO) calculations in this letter were performed using Gaussian 03.[9] The natural population analysis (NPA)[10] was used to calculate the atomic charges of the amino acid residues, since it is generally accepted that NPA gives reasonable values for atomic charges.[11]

We use the following notation for a β-sheet composed of homo-polypeptides: $(R_m)_n$ap and $(R_m)_n$p, for antiparallel and parallel β-sheet structures, respectively. Here, R is an amino acid residue (alanine or glycine, in this letter), *m* indicates the number of amino acid residues in a β-strand, and *n* indicates the number of β-strands in the β-sheet. Each polypeptide is capped with –H for both N- and C-termini. The geometry of the β-strand was optimized at the HF/6-311G(d,p) level with the dihedral angles fixed to keep the β-strand conformation.[12] The interstrand structural parameters of the β-sheet were optimized at the theoretical level of B3LYP/6-311G(d,p) with the intrastrand structural parameters fixed. The dipole moments of the β-sheets were calculated as the expectation values of the dipole moment operator, applying the ab initio MO method.

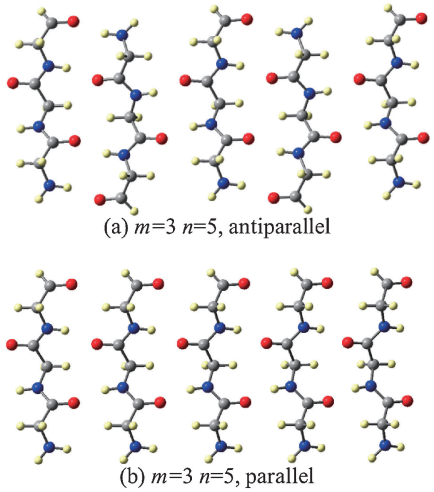

Figure 1. β-Sheet structures: (a) quintuple antiparallel β-strands, $(Gly_3)_5$ap, and (b) quintuple parallel β-strands, $(Gly_3)_5$p.

The structures of $(Gly_3)_5$ap and $(Gly_3)_5$p are shown in Figure 1. The coordinates of all the calculated homo-polypeptides are given in the Supporting Information.[13]

The calculated dipole moments for polypeptides with different strand numbers and lengths are listed in Table 1. For an antiparallel β-sheet, the macrodipole moment of the β-sheet is almost canceled out when the number of β-strands is even. For a parallel β-sheet, it is not canceled out: the macrodipole moment of the β-sheet depends on the number and length of β-strands.

The dipole–dipole interaction is important to account for the specificity between structural motifs of biological molecules.[14] Therefore, quantitative estimation of dipole moments for individual amino acid residues in proteins plays a significant role in the field of bioscience. The dipole moment of an amino acid monomer or a polypeptide can be calculated as the expectation value of the dipole moment operator by applying the MO method. However, such a method cannot be applied to calculate a dipole moment of an amino acid *residue* as a building block of a polypeptide or protein, since the building block itself is not a complete molecule to which the MO method can be applied. Instead of obtaining the expectation value, the dipole moment of an amino acid residue can be calculated as the vector sum of the atomic charges and atomic positions that compose the amino acid residue. Recently, we reported the residue dipole moments of alanine and glycine in an α-helix, and showed that

Table 1. Dipole moments (in Debye) of polyalanine and polyglycine in antiparallel (ap) and parallel (p) β-sheets: $(R_m)_n$ap and $(R_m)_n$p ($m = 3$, $n = 3$, 4, 5) and ($m = 4$, 5, $n = 3$) (R = Ala and Gly)

			Polyalanine β-sheet		Polyglycine β-sheet	
	m	n	B3LYP/ 6-311G(d,p)	MP2/ 6-31G(d)	B3LYP/ 6-311G(d,p)	MP2/ 6-311G(d,p)
ap	3	3	2.51	2.35	2.60	2.44
	3	4	0.64	0.63	1.11	0.96
	3	5	2.94	2.84	2.89	2.72
	4	3	4.82	4.86	5.81	5.94
	5	3	2.96	2.87	3.60	3.59
p	3	3	8.73	8.19	8.88	8.37
	3	4	12.01	11.24	12.18	11.46
	3	5	15.29	14.28	15.43	14.51
	4	3	6.47	6.73	7.99	8.44
	5	3	11.04	10.81	11.65	11.62

the vector summation of the residue dipole moments can express the macrodipole moment of a long peptide in the α-helix structure.[15] We called the method "VSHBα." Here, we present the dipole moment of an amino acid residue in the circumstance of a β-sheet as a building block, which can be used to calculate the macrodipole moment of any longer polypeptides in a β-sheet through the vectorial sum of the component residual dipole moments. We call this model "VSHBβ."

We examined the influence of interstrand hydrogen bonding and the influence of the neighboring residues in the same strand on the atomic charges of amino acid residues, and found an appropriate system for calculation of the residual dipole moments for the VSHBβ model. Our recipe to create the VSHBβ model for the dipole moments of amino acid residues in a β-sheet is shown in Figure 2. We define the origin and the axes of the dipole moment of an amino acid residue in a β-sheet (Figure 3) in the same way as for the dipole moments in an α-helix.[15]

The central residue enclosed by a black solid line in Figure 2a is the target residue for which we calculated the structure and the atomic charges. First, we prepared a β-strand, which was a 3-mer peptide of Gly–Gly–Gly or Gly–Ala–Gly capped with –H for both the N- and C-terminal residues. The geometry of the β-strand was optimized at the theoretical level of HF/6-311G(d,p). Second, we prepared an antiparallel β-sheet with three β-strands (Figure 2a). The center residue X (Gly or Ala in this letter) of the center strand was the target residue. The interstrand structural parameters of the β-sheet were optimized at the theoretical level of B3LYP/6-311G(d,p) with the intra-strand structural parameters fixed. Third, we reduced the residues of the β-sheet and found the smallest model that gives the atomic charges of the central residue similar to that in the original β-sheet. The reduced β-sheet model is shown in Figure 2b. The geometry of the center residue in the reduced β-sheet model was optimized at the HF/6-311G(d,p) level with the dihedral angles fixed to keep the β-strand conformation.[12] After optimization, a single-point calculation was performed at the MP2/6-311G(d,p) level. Then, the NPA charges of the atoms composing the central target residue were picked up and adjusted such that the total of the atomic charges of the target residue was zero by dividing the redundant charge equally into the central residue atoms. The adjusted atomic charges were

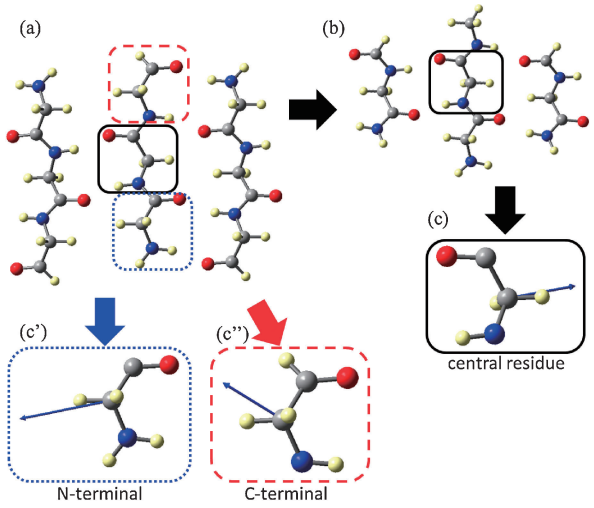

Figure 2. Scheme of VSHBβ model.

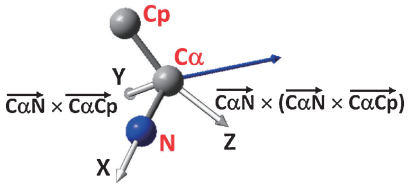

Figure 3. Definition of axes for residue dipole moment.

used to calculate the dipole moment of the target residue together with the atomic positions (Figure 2c).

The terminal residue enclosed by the blue dotted line or red broken line in Figure 2a is the target N- or C-terminal residue for which we calculate the structure and the atomic charges. The residues other than the target terminal residue are all glycine residues. After a single-point MO calculation of the β-sheet (Figure 2a) at the MP2/6-311G(d,p) level, the total of the atomic NPA charges of each terminal residue was adjusted. The adjusted atomic charges were used to calculate the dipole moment of the target terminal residue together with the atomic positions. See Figure 2c′ for N-terminal and Figure 2c″ for C-terminal residues.

The calculated residual dipole moments from the positions and atomic charges of the central, N-terminal, and C-terminal residues of alanine and glycine in the circumstance of a β-sheet are listed in Table 2.

We have found that the atomic charges of a residue in a β-sheet are affected by the surrounding residues: the residues of the neighboring β-strands through hydrogen bonds as well as the neighboring residues in the same β-strand through peptide bonds. Therefore, the dipole moments of the terminal residues are different from those in a central part of the polypeptide.

The dipole moments of amino acid *residues* are such that we can calculate the dipole moment of any longer and expanded polypeptides in a β-sheet by the vectorial sum of the component residues, which are listed in Table 2. We call this method of calculation of the dipole moment of a peptide the "VSHBβ model," which is the "vectorial sum of individual amino acid residues taking account of hydrogen bonding in a β-sheet." Previously, we presented the dipole moments of alanine and

Table 2. X, Y, and Z components and the amplitude of dipole moment (in Debye) of amino acid residue in β-sheet

		X	Y	Z	Amplitude
central residue	ala	−2.424	−1.219	2.510	3.696
	gly	−2.235	−1.481	2.265	3.510
N-terminal residue	ala(N)	−1.004	−2.643	3.271	4.324
	gly(N)	−0.915	−2.821	3.210	4.370
C-terminal residue	ala(C)	−2.449	−0.812	1.328	2.902
	gly(C)	−2.312	−0.948	1.134	2.744

Table 3. Dipole moments (in Debye) calculated by the VSHBβ model of polyalanine and polyglycine in antiparallel (ap) and parallel (p) β-sheets: $(R_m)_n$ap and $(R_m)_n$p, ($m = 3$, $n = 3$, 4, 5), and ($m = 4$, 5, $n = 3$), (R = Ala and Gly). The values of Δdirection are in degrees.

			Polyalanine β-sheet		Polyglycine β-sheet	
	m	n	VSHBβ model	Δdirection	VSHBβ model	Δdirection
ap	3	3	3.58	7.39	3.61	4.11
	3	4	2.06	7.20	1.85	5.10
	3	5	3.99	9.48	3.87	8.34
	4	3	6.37	3.54	6.76	1.58
	5	3	4.24	11.46	4.28	7.53
p	3	3	10.33	3.97	10.37	4.11
	3	4	13.68	3.88	13.77	1.58
	3	5	17.00	4.16	17.10	7.53
	4	3	8.52	6.47	8.69	4.42
	5	3	12.48	2.02	12.52	8.92

glycine residues in an α-helix.[15] We find that the dipole moment of an amino acid residue in a β-sheet is smaller than that in an α-helix, indicating that the polarization caused by the interstrand hydrogen bonding in a β-sheet is smaller than that in an α-helix.

For the purposes of assessment, we calculated the dipole moments of several kinds of β-sheets composed of homo-polypeptides by using the VSHBβ model; they are listed in Table 3. It should be noted that the dipole moments from the VSHBβ model compare very well with those calculated directly from ab initio MO methods, as listed in Table 1. It is noteworthy that the values from the VSHBβ model can predict the macrodipole moments of a β-sheet, not only in antiparallel but also in parallel formation, even though the VSHBβ model was created based on the antiparallel β-sheet structure.

To assess the direction of the macrodipole moment, we calculated Δdirection, which is an angle formed between macrodipole moments calculated from the VSHBβ model and directly from wave functions by MP2/6-31G(d) (for polyalanine) or MP2/6-311G(d,p) (for polyglycine). As shown in Table 3, the Δdirection values ranged from 1 to 11 degrees, which indicates that the direction of the macrodipole moment can also be predicted reasonably well by the VSHBβ model.

The VSHBβ model, which is the vector sum of residue dipole moments based on NPA charges, can predict the macrodipole moment of any longer polypeptides in antiparallel or parallel β-sheets. Once a set of VSHBβ models is available, large-scale MO calculations will not be needed to predict local dipole moments or macrodipole moments of large polypeptides in a β-sheet.

Although the computational costs of large-scale ab initio MO calculations are decreasing because of increased computer power and advanced algorithms, ab initio MO calculations require all the XYZ coordinates of the constituent atoms of the target polypeptides or proteins and still a rather large computational time. The purpose of our work is to create a "standard" set of dipole moments for all common neutral amino acid residues, which can be used to predict the properties caused by dipole–dipole interactions without full knowledge of the XYZ coordinates. The VSHBβ model requires the atomic positions of only three atoms (N, C_α, and C_p) of each residue in a polypeptide to define the origin and the axes of the residual dipole moment, and the macrodipole moment is calculated quickly by the vector summation of the component amino acid residues. If such a standard set were available, it would be very valuable for understanding characteristics and could be used to estimate the dipole–dipole interactions between building blocks of biological molecules or nanoarchitectures.

In this study, we found that the VSHBβ model is promising for the prediction of the macrodipole moments of β-sheets. Further calculations are now in progress to include the dipole moments of other amino acid residues in the β-sheet in the VSHBβ model. These dipole moments of amino acid residues will be valuable for the prediction of the macrodipole moments of protein substructures.

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