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Ab initio conformational analysis of N- and C-terminally-protected valyl-alanine dipeptide model

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Abstract

Ab initio conformational analysis of the dipeptide Ac-Valine-Alanine-NHMe was performed and optimized at the RHF/3-21g level of theory in an attempt to characterize the folding of short peptides. A topological scan of alanine's (Ala) ψ and ϕ rotors was carried out with valine (Val) in the β_L geometry to construct a Ramachandran surface in two- and three-dimensions. It was observed that Val sterically dominates the conformations of Ala. Of the 243 possible conformers in this study, 202 were found. Those that were not found had converged to a different geometry of lower energy and greater stability. The γ_L and ε_L conformers of Ala were favoured, and 47 of the found conformers can be classified as potential β-turns according to the traditional backbone torsional definitions. However, the potentially most stable conformer, $\alpha^a_D\gamma_L$, was not in one of these regions of the Ramachandran surface. Thus, β-turns may not be inherent conformations of the Val-Ala dipeptide, but may arise preferentially within protein structures due to certain steric effects from the surrounding environment.

Keywords: Dipeptide model; Ac-Valine-Alanine-NHMe; Ab initio; RHF/3-21G; β-Turn

1. Introduction

Dipeptide models are increasingly used in peptide folding studies as they represent the smallest possible structural unit for the study of typical triamide conformations, such as β-turns, in protein folding [1]. Protein folding has received intense study due to its fundamental importance in living organisms, the growing availability of protein sequences, and the increasing recognition that some diseases are a result of misfolded proteins [2,3]. Reported dipeptide models include Ac-Ala-Ala-NHMe [4], For-Ala-Ala-NH_2 [5], Ac-Pro-Ala-NH_2 [6], and Ac-Pro-Ala-NH_2 [6]. The large volume of work on dipeptide models demonstrates their relevance to elucidating the mechanism of protein folding.

The dipeptide valyl alanine is formed by the amidic linkage of the chiral, non-polar, hydrophobic amino acids valine and alanine. Val and Ala both have aliphatic sidechains, methyl on Ala and isopropyl on Val. As individual residues, both play important structural roles in soluble protein cores and transmembrane helices due to their hydrophobicity. In this study, conformations of the Ac-Valine-Alanine-NHMe were optimized using ab initio calculations. Our Ac-Val-Ala-NHMe dipeptide model has all peptide bonds in the trans isomeric state, and both chiral α-carbons in the L enantiomeric states (see Fig. 1), matching the predominant, physiological forms.

Val-Ala is isomeric to Ala-Val. The two dipeptides have identical backbones, but their sidechains have been interchanged. Comparisons between the $\beta_L\beta_L$ conformations of Val-Ala and Ala-Val have been completed using molecular orbital computations [7].

Zwitterionic forms of Val-Ala and Ala-Val have also been analyzed theoretically and spectroscopically [8]. Our

Abbreviations *g*+, *gauche*+ (60°); *a*, *anti* (180°); *g*−, *gauche*− (−60°); Ala, L-alanine; Val, L-valine; Ac, acetyl; NHMe, methyl amide; RHF/3-21G, restricted Hartree Fock/3-21G.

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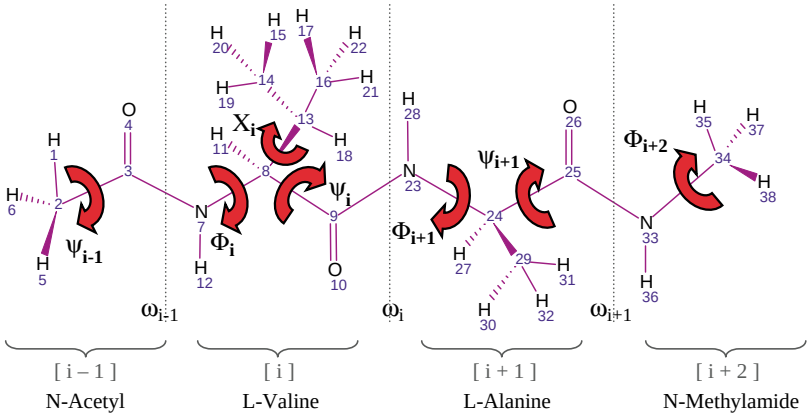

Fig. 1. N-Ac-Val-Ala-NHMe dipeptide model. The dipeptide was divided into four sections: the N-terminal protecting group, the Val residue, the Ala residue and the C-terminal protecting group, and numbered separately according to a standardized modular numbering system [3].

conformational analysis differs from the zwitterion study in that we attempt to mimic the dipeptide's environment within a protein. Our model simulates the inductive and through-space interactions of neighbouring amino acid residues with Val-Ala by introducing 'protector groups' of acetyl at the N-terminus and NH-methyl at the C-terminus, forming amide bonds at the termini.

As a diamino acid triamide system, Ac-Val-Ala-NHMe may adopt conformations characteristic of β-turns, the third most prevalent secondary structural unit in globular proteins [9,10]. β-turns are traditionally defined by their dihedral angles, ϕ_i, ψ_i, ϕ_{i+1} and ψ_{i+1}, as specified in Fig. 2 [5]. Typically, β-turns are found to exist in types I, II and III; their conformational enantiomers and β-turns of types VIa, VIb and VIII are less common. Types IV, V and VII have not been listed in Fig. 2, as they have ambiguously assigned backbone dihedral angles, as defined through experimental data [11].

The 243 topologically possible different conformers of Ac-Val-Ala-NHMe were investigated at the RHF/3-21G level of theory. Migrations of nonexistent conformers are identified to illustrate the relative stabilities and instabilities of the different conformations. Conformers that adopt the β-turn configuration are also identified and the relative stabilizing effects are investigated.

2. Methods

The structure of Ac-Val-Ala-NHMe was numbered according to a standardized modular numbering system [12], as shown in Fig. 1. The dipeptide was divided into four sections: the N-terminal protecting group, the Val residue, the Ala residue and the C-terminal protecting group, with each numbered separately. This allows any section to be replaced by another amino acid group, thus facilitating the use of our results in future studies on oligopeptides.

In peptide residue, three backbone dihedral angles, ϕ, ψ, and ω, measure the rotation about the N–C_α, the C_α–CO, and the OC–NH bonds, respectively. The sidechain dihedrals are defined by χ. In Ac-Val-Ala-NHMe, there are 10 dihedrals angles: ψ_{i-1}, ω_{i-1}, ϕ_i, χ_i, ψ_i, ω_i, ϕ_{i+1}, ψ_{i+1}, ω_{i+1}, and ϕ_{i+2}. Five dihedrals were considered most relevant to the shape and stability of the dipeptide model: ϕ_i, ϕ_{i+1}, χ_i, ψ_i and ψ_{i+1}. The rotations for each dihedral were defined as $g+$, a and $g-$. Thus, 243 (3^5) different conformations were considered.

All calculations were carried out using the GAUSSIAN98 software package [13]. The common convergence criteria of 3.0×10^{-4}, 4.5×10^{-4}, 1.20×10^{-3}, and 1.8×10^{-3} were used for gradients of root mean square (RMS) force,

β-turn type	Backbone Torsional Angle Values				Ramanchandran Nomenclature
	Φ_i	ψ_i	Φ_{i+1}	ψ_{i+1}	
I	-60	-30	-90	0	$\alpha_L\alpha_L$, $\alpha_L\gamma_L$, $\alpha_L\delta_L$
I'	60	30	90	0	$\alpha_D\alpha_D$, $\alpha_D\gamma_D$, $\alpha_D\delta_D$
II	-60	120	80	0	$\varepsilon_L\alpha_D$, $\varepsilon_L\gamma_D$, $\varepsilon_L\delta_D$
II'	60	-120	-80	0	$\varepsilon_D\alpha_L$, $\varepsilon_D\gamma_L$, $\varepsilon_D\delta_L$
III	-60	-30	-60	-30	$\alpha_L\alpha_L$
III'	60	30	60	30	$\alpha_D\alpha_D$
VI*a*	-60	120	-90	0	$\varepsilon_L\alpha_L$, $\varepsilon_L\gamma_L$, $\varepsilon_L\delta_L$
VI*b*	-120	120	-60	0	$\beta_L\alpha_L$, $\beta_L\gamma_L$, $\beta_L\delta_L$
VIII	-60	-30	-120	120	$\alpha_L\beta_L$

Fig. 2. Torsional definitions of β-turns. Traditional criteria for β-turns are defined by their torsional angles, Φ_i, Ψ_i, Φ_{i+1} and Ψ_{i+1} [5]. The most rigidly-defined β-turns of types I, II, III, their enantiomers, VI*a*, VI*b* and VIII are listed. Types IV, V and VII are not included. The nomenclature describes the region of the Ramachandran map containing torsional angles of the *i*th and $i+1$th residues.