A CONFORMATIONAL ANALYSIS OF THE METHYL ESTER OF O-ACETYL-L-LACTYL-L-ALANINE AND THE METHYLAMIDE OF N-ACETYL-L-ALANYL-L-LACTIC ACID

E. M. Popov, V. Z. Pletnev,
G. M. Lipkind, and S. F. Arkhipova

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In the preceding paper [1] we reported a study of the methyl esters of α-acetylamino acids and of the methylamides of α-acetylamino acids. It was shown that the conformational states of such molecules are described by a small number of canonical forms – R, B, L, P (see also [2]). The results of a conformational analysis for chain fragments with one residue are insufficient for understanding close interactions. Thus, it follows from the calculation of the methylamides of N-acetyldipeptides [3] that the conformational states of adjacent residues are not completely independent because of the interaction of the terminal peptide groups. Furthermore, in a fragment of three units of a depsipeptide, as also of a peptide chain, the appearance of new conformations with an intramolecular hydrogen bond closing a ten-membered ring is possible. In order to determine the interactions existing between neighboring amino acid and hydroxy acid residues in a depsipeptide chain, we have performed a conformational analysis of the methyl ester of O-acetyl-L-lactyl-L-alanine (Ac-L-Lac-L-Ala-OMe, I) and of the methylamide of N-acetyl-L-alanyl-L-lactic acid (Ac-L-Ala-L-Lac-NHMe, II, see Fig. 1). The extended conformations and the convoluted conformations with a hydrogen bond are considered separately in the corresponding sections of the paper.

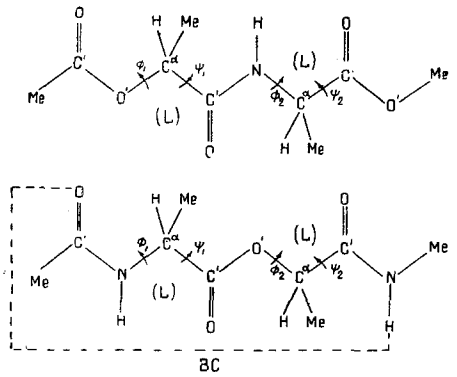

Fig. 1. Structural formulas of the methyl ester of O-acetyl-L-lactyl-L-alanine (Ac-L-Lac-L-Ala-OMe, I) and of the methylamide of N-acetyl-L-alanyl-L-lactic acid (Ac-L-Ala-L-Lac-NHMe, II).

The method of calculating the conformations has been described previously [4]. The nonvalent and electrostatic interactions of the atoms, hydrogen bonds, and the torsional contribution were taken into account in the potential energy [4]. In the calculation of the optimum forms, as the independent variables we selected the angles of rotation round the $C^{\alpha}-N$, $C^{\alpha}-C'$, and $C^{\alpha}-O'$ bonds (Φ_1, Ψ_1, Φ_2, Ψ_2, see Fig. 1). The values of the valence angles of the amide and ester groups were taken from the calculation of N-methylacetamide and methyl acetate [7]. The $N-C^{\alpha}-C'$ and $O'-C^{\alpha}-C'$ angles were taken as 110° [2].

Extended Forms. In the calculation of the extended forms of the molecules (I) and (II), as in the case of the tripeptides [3], we took as the initial zero approximations with minimization of the energy for the amino and hydroxy acid residues the optimum forms of Ac-L-Ala-OMe and Ac-L-Lac-NHMe [1]. The conformations of the molecules considered are denoted by R–R, R–B, and so on. The geometrical parameters and the relative energies of the most preferred forms are given in Table 1.

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TABLE 1. Optimum Extended Conformations of the Molecules Ac-L-Lac-L-Ala-OMe and Ac-L-Ala-L-Lac-NHMe

Angles, degrees	Ac-*L*-*Lac*-*L*-*Ala*-OMe				Ac-*L*-*Ala*-*L*-*Lac*-NHMe			
	R–*R*	*R*–*B*	*B*–*R*	*B*–*B*	*R*–*R*	*R*–*B*	*B*–*R*	*B*–*B*
Φ_1	112	108	103	103	130	70	72	70
Ψ_1	136	168	295	295	130	126	342	338
Φ_2	82	75	65	67	103	101	105	102
Ψ_2	147	352	123	324	138	337	131	337
$U\varepsilon=\infty$	0	0,45	0,75	1,1	0	1,1	1,1	1,6
(kcal/mole) $\varepsilon=4$	0	0,10	0,05	0,20	0	0,5	0,5	1,0

TABLE 2. Optimum Conformations of Ac-L-Ala-L-Lac-NHMe

Angles, degrees	Ac-*L*-*Ala*-*L*-*Lac*-NHMe			
	R–*R*	*R*–*B*	*B*–*L*	*L*–*L*
Φ_1	125	133	130	232
Ψ_1	153	128	294	209
Φ_2	110	78	232	233
Ψ_2	152	220	218	215
U (kcal/mole) $\varepsilon = 4$	0	0,50	2,75	3,10

It follows from the results obtained that the two pairs of angles in (I) and (II) are in the low-energy regions on the conformational charts of the fragments with one amino acid residue (see Fig. 3b in [1]). However, the numerical values of the parameters of the optimum forms of (I) and (II) differ considerably from the values of the parameters for Ac-L-Ala-OMe and Ac-L-Lac-NHMe [1] in a number of cases. The nature of the scatter of the values of Φ, Ψ is in good agreement with the profile of the conformational charts (see Fig. 3, [1]). The parameters of the hydroxy acid residues, which are characterized by a lower conformational freedom than the amino acid residues, show a greater stability. For the amino acid residues, the forbidden Φ, Ψ regions are wider than for the hydroxy acid residues and have approximately the same extension along the Φ, Ψ axes. Because of this, the formation of a compact structure which is the optimum for higher-order interactions takes place mainly through changes in the dihedral angles of the amino acid residue.

Let us compare the optimum conformations of (I) and (II) (see Table 1) with the corresponding conformations of the tripeptides [3]. The R–R form of compound (II) is similar to the R–R form of its tripeptide analog, in which $\Phi_1 = 126°$, $\Psi_1 = 133°$, $\Phi_2 = 106°$, and $\Psi_2 = 136°$. In both cases, the angle Φ_1 is approximately 30° greater than the angle in the R conformation of the alanine dipeptide and is close to the value of the angle of rotation round the C^{α}–N bond in the standard α-helix ($\Phi = 132°$). Just as in the tripeptide, a considerable contribution to the stability of the R–R conformation in (II) is made by the dispersion attraction of the terminal amide groups. In compound (I) the ester groups are terminal, in consequence of which the dispersion effect is weakened. In the R-B conformation, the terminal amide (II) and ester (I) links are directed towards one another. Their interaction leads to a deviation of the Φ, Ψ angles of the amino and hydroxy acid residues by 30-40° from the optimum values in Ac-L-Ala-OMe and Ac-L-Lac-NHMe. Conversely, in the B–R form there is no such dispersion stabilization. The B–B conformation resembles the corresponding spatial structures of the triterpene analog. The parameters of the B–B forms in (I) and (II) prove to be close to the values of Φ and Ψ in the antiparallel β structure.

When only nonvalent interactions in the molecules of (I) and (II) are taken into account, the R–R conformation is the most favorable (see Table 1). Including the electrostatic component ($\varepsilon_{eff} = 4$) leads to a considerable equalization of the energies of the R–R, R–B, B–R, and B–B conformations (see Table 1), which is due to the stabilization of the B form. Thus, in strongly polar media with high dielectric constants [5] conformations of the R–R type in (I) and (II) will predominate.

Convoluted Forms. In the molecules of (I) and (II), two types of intramolecular hydrogen bonds are possible. Hydrogen bonds of the 1-3 type close a seven-membered ring formed by neighboring amide and ester groups (M and H forms, see [2]). However, because of the steric stress of the M and H forms, such

hydrogen bonds are hardly represented in large molecules. In the study of the structure of complex compounds, hydrogen bonds of the 1-4 type in ten-membered rings are of considerably greater interest [compound (I) does not form a hydrogen bond of the 1-4 type]. Such hydrogen bonds are encountered in linear and cyclic peptide and depsipeptide compounds [6].

Table 2 gives calculated values of the geometrical parameters of the optimum conformations with an intramolecular hydrogen bond of the 1-4 type for compound (II). The energy is a minimum in the R–R and R–B conformations. The preferential nature of these structures is due to the position of the most favorable minima of the amino and hydroxy acid residues on the conformational charts (see Fig. 3 in [1]) and is due mainly to the short-range interactions of the atoms. The energy of the hydrogen bond in all the forms calculated is ~3.9 kcal/mole, and the N...O distance is ~2.85Å. The energy difference of the R–R and the R–R forms (without taking U_{el} and U_{tors} into account) is 2.7 kcal/mole, and for R–B and R–B it is –3.1 kcal/mole, i.e. the formation of a hydrogen bond leads to a definite increase in the energy of the nonvalent interactions of these forms. Thus, the parameters of the hydroxy acid residue fall into the comparatively unfavorable region of U_{nonv} in Fig. 3, b [1].

The stability of the parameters (~10°) shows the considerable stereochemical similarity of the amide and depsipeptide groups [1].

SUMMARY

1. The most preferred extended conformations for Ac-L-Lac-L-Ala-OMe and Ac-L-Ala-L-Lac-NHMe in a polar medium are R–R, R–B, B–R, and B–B. Of the conformations with a hydrogen bond of the 1-4 type, the most stable are R–R and R–B.

2. There is an interrelationship between the conformational states of neighboring hydroxy and amino acid residues.

3. The stereochemical characteristics of the ester group are similar to those of the amide group.

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