A THEORETICAL CONFORMATIONAL ANALYSIS OF THE METHYLAMIDE OF N-ACETYL-α-METHYLALANINE

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UDC 547.962

In the present work we have studied the results of a calculation of the potential surface of the methylamide of N-acetyl-α-methylalanine [$CH_3CONH-C(CH_3)_2-CONHCH_3$, Fig. 1]. A knowledge of all the possible conformations of this molecule is of interest in the investigation of the spatial structure of the antibiotic alamethicin [1, 2] and a number of other natural compounds the peptide chains of which include an α-methylalanine residue [3].

The calculation was performed with the inclusion of the nonvalent interactions of the atoms (U_{nv}), the deformations of the valence angles (U_{ang}), the electrostatic interactions (U_{el}), the torsional energies (U_{tor}), and the hydrogen-bond energies (U_{HB}).

The potential functions describing these relationships were taken as in a previous paper [4]. The only exception is the dependence of the torsional energy on the angle of rotation around the $C^{\alpha}-N$ bond (Φ), which we took in the form $U_{tor}^{\Phi}=0.5\cdot U_0^{\Phi}(1+\cos\Phi)$, and not $U_{tor}^{\Phi}=0.5\cdot V_0^{\Phi}(1-\cos\Phi)$. The choice was based on the results of quantum-chemical calculations of N-methylamides [5]. This form of the potential corresponds, according to the 1966 notation [6], to positions of the minima in U_{tor} at $\Phi=\pm 180, \pm 60°$. Crossed positions of the bonds at the C^{α} and $C^{\beta 1}$ ($C^{\beta 1}$) atoms correspond to the minimum value of U_{tor} in the rotation of the methyl side chains.

The values of the barriers to rotation (U_0) around $C^{\alpha}-N$, $C^{\alpha}-C'$ and $C^{\alpha}-C^{\beta 1}$ ($C^{\alpha}-C^{\beta 2}$) bonds were taken as 0.6, 0.2 [7], and 2.8 kcal/mole, respectively.

The interactions between the terminal $O_{(1)}$ and $H_{(2)}$ atoms were taken into account in the potential of a hydrogen bond [4]. In the calculation of the energy of interaction between the $H_{(1)}$ and $O_{(2)}$ atoms only the electrostatic component was taken into account. The formation of a $H_{(1)}\ldots O_{(2)}$ hydrogen bond could be assumed only in the planar extended form of the molecule ($\Phi=\Psi=\pm 180°$, see Fig. 1). However, in this conformation the distance between the $H_{(1)}$ and $O_{(2)}$ atoms ($\sim$2.15 Å) exceeds the optimum value ($\sim$1.8 Å), and the $N_{(1)}-H_{(1)}$ and $C'_{(2)}=O_{(2)}$ bonds have an orientation unfavorable for the formation of a hydrogen bond.

The values of the charges on the atoms were taken from the literature [8] for the low-energy states ($\Phi=-80°$ and $\Psi=\pm 60°$) of the amino-acid residues in peptide compounds in the absence of hydrogen bonds (the values of the charges on the atoms, the bond length, and the valence angles used in the calculation are given in caption to Fig. 1).

An idea of the potential-energy surface of the methylamide of N-acetyl-α-methylalanine was obtained from $\Phi-\Psi$ conformational maps with a variation of the angles at 20° intervals. Values of 109° and 108° were taken for the $N-C^{\alpha}-C'$ and $C^{\beta 1}-C^{\alpha}-C^{\beta 2}$ angles. The geometric and energetic parameters of the optimum conformations were found by minimizing the total energy over six independent geometric parameters – Φ, Ψ, X_1, X_2, $N-C^{\alpha}-C'$ (ε), $C^{\beta_1}-C^{\alpha}-C^{\beta_2}$ (ξ). The four other angles of the C^{α} atom (η) were taken to be equal and were determined from the relation $\cos\eta=-\cos\varepsilon/2\cos\xi/2$.

M. M. Shemyakin Institute of the Chemistry of Natural Compounds, Academy of Sciences of the USSR. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 224-229, March-April, 1973. Original article submitted June 22, 1972.

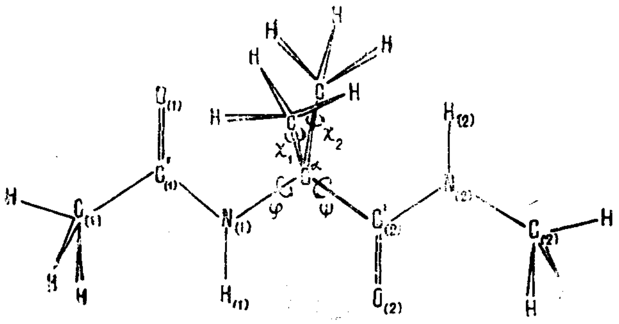

Fig. 1. Calculation model of the methylamide of N-acetyl-α-methylalanine.

Lengths of the valence bonds [9]:
$b\,(C'-O)=1.24\,\text{Å}$; $b\,(N-H)=1.02\,\text{Å}$; $b\,(N-C^{\alpha})=1.47\,\text{Å}$;
$b\,(C^{\alpha}-C')=1.52\,\text{Å}$; $b\,(C'-N)=1.35\,\text{Å}$; $b\,(C^{\alpha}-C^{3})=1.54\,\text{Å}$;
Valence angles [10]:
$\tau\,(H-C_{(1)}-C'_{(1)})=\tau(H-C_{(2)})-N_{(2)})=\tau\,(H-C^{\beta}-C^{\alpha})=111.1°$,
$\tau\,(C^{\alpha}-N_{(1)}-H_{(1)})=\tau\,(C_{(2)}-N_{(2)})-H_{(2)}=115.9°$,
$\tau\,(C^{\alpha}-N_{(1)}-C'_{(1)})=\tau\,(C_{(2)}-N_{(2)}-C'_{(2)})=123.6°$,
$\tau\,(N_{(1)}-C'_{(1)}-O_{(1)})=\tau\,(N_{(2)}-C'_{(2)}-O_{(2)})=122.4°$,
$\tau\,(N_{(1)}-C'_{(1)}-C_{(1)})=\tau\,(N_{(2)}-C'_{(2)}-C^{\alpha})=118.6°$.
Charges on the atoms [8] (in e units):
$q\,(C_{(1)})=-0.173$; $q\,(C'_{(1)})=+0.469$; $q\,(O_{(1)})=-0.410$;
$q\,(N_{(1)})=-0.356$, $q\,(H_{(1)})=+0.175$, $q\,(C^{\alpha})=+0.041$;
$q\,(C^{3}H_{3})=+0.034$, $q\,(C'_{(2)})=+0.447$;
$q\,(O_{(2)})=-0.386$, $q\,(N_{(2)})=-0.360$;
$q\,(H_{(2)})=+0.193$, $q\,(C_{(2)})=+0.048$.
Charges on the terminal H atoms at the $C_{(1)}$ atom:
$q(H')=+0.040$;
$q\,(H)=+0.060$.
Charges on the terminal H atoms at the $C_{(2)}$ atom:
$q\,(H')=0.050$;
$q\,(H)=0.017$.

To evaluate the role of the various types of interactions in the structural organization of the methylamide of N-acetyl-α-methylalanine, conformational charts were obtained (Fig. 2a, b) with the inclusion of the individual components of the total energy. Figure 2a shows the potential surface obtained by taking U_{nv} and U_{tor} into account (because of the existence of planar symmetry of the bonds at the C^{α} atom only half the chart is shown in the figure). The energy contours are drawn at various values of the energies: 1, 2, 3, 5, 7, and 10 kcal/mole. Because of the small value of the barriers to rotation around the $C^{\alpha}-N$ and the $C^{\alpha}-C'$ bonds, the contribution from U_{tor} is small and the chart reflects mainly the nonvalence interactions of the atoms. The lines of the equipotential sections of the permitted regions extend along the verticals $\Phi=-180°$ and $-60°$. Among the permitted conformations, the R conformation possesses the lowest engergy. The regions delimited by the 1 kcal/mole contour occupy less than 2% of the total area of the conformational chart of the methylamide of N-acetyl-α-methylalanine. In the case of the methylamides of N-acetylglycine and L-alanine, such regions amount to ~60% and ~13%, respectively [11]. In comparison with glycine diamide, the value of the barrier between the R and B regions also rises, from ~1.5 to 6 kcal/mole.

Figure 2b shows the levels of the electrostatic energy obtained at a value of the effective dielectric constant $\varepsilon_{eff}=4$. The state of lowest energy from the point of view of electrostatic interactions corresponds to the planar extended form ($\Phi=\Psi\pm 180°$), which is stabilized mainly by the interactions of the $H_{(1)}$ and $O_{(2)}$ atoms. Figure 3a, b shows the potential surfaces of the methylamide of N-acetyl-α-methylalanine with the inclusion of all forms of interaction as applied to nonpolar ($\varepsilon_{eff}=4$) and polar ($\varepsilon_{eff}=10$ [12]) media.

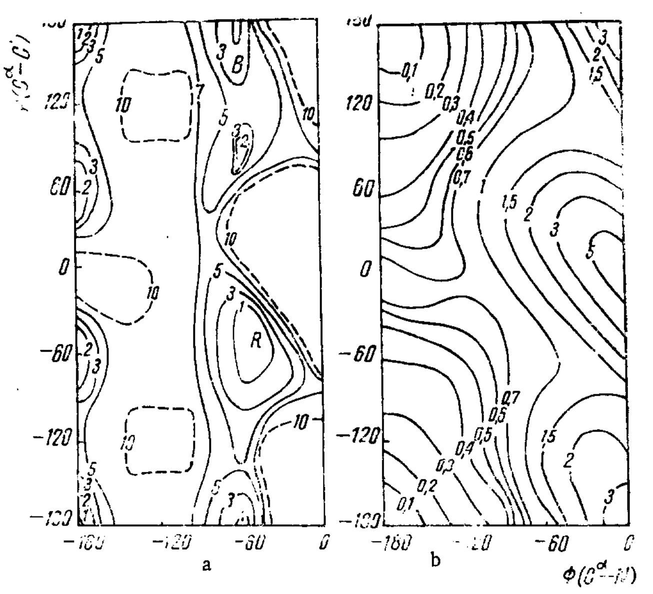

Fig. 2. Conformational map of the methylamide of N-acetyl-α-methylalanine taking into account U_{nv} and U_{tor} (a) and U_{el} (b).

TABLE 1. Optimum Conformations of the Methylamide of N-Acetyl-α-methylalanine, deg

Parameters of the molecule	M(B')	R	B	G	Q
Φ	–63,5	–53,2	–61,3	180	180
Ψ	71,0	–46,2	174,3	180	–57,7
X_1	56,9	57,4	53,6	63	64,3
X_2	58,8	60,1	60,5	63	53,6
$\angle N-C^{\alpha}-C'$	110,6	109,7	112,1	109,1	108,4
$\angle C^{\beta_1}-C^{\alpha}-C^{\beta_2}$	104,7	108,2	109,0	110,8	109,5
U_{nv}	1,7	0	0,6	1,0	1,0
U_{HB}	–3,95	0	0	0	0
U_{def}	0,11	0	0,03	0	0
U_{tor}	0,01	0,02	0,05	0	0,08
U_{el} (ε=4)	1,7	1,0	0,8	0	0,4
U_{tot} (ε-4)	0	1,5	1,9	1,5	1,9
U_{tot} (ε=10)	2,1	0	0,6	0,6	0,9
μ (D)	2,7	6,6	5,4	3,3	5,2

The symbols of the angles are in accordance with the 1970 notation [6].

Attention is attracted above all by the considerable similarity of the two maps to the map of steric interactions (see Fig. 2a), which shows the dominating role of nonvalence interactions. By taking the other energy contributions into account it is possible to evaluate the relative stabilities of the individual conformations. The low-energy regions on the charts correspond to the optimum forms: R – right-handed α-helix; B – β structure; M – twisted form with an intramolecular hydrogen bond; G – conformations with a planar structure of the main chain; and Q – crescent-like conformations. To each form in the left-hand part of the chart corresponds its mirror isoenergy analog in the right-hand part.

Table 1 gives the calculated values of the geometric parameters, energies, and dipole moments of all the nonequivalent optimum conformations of the methylamide of N-acetyl-α-methylalanine.

In the general case, for this molecule 12 spatial forms are possible (taking mirror forms into account), the conformational equilibrium between which depends fundamentally on the polarity of the medium.

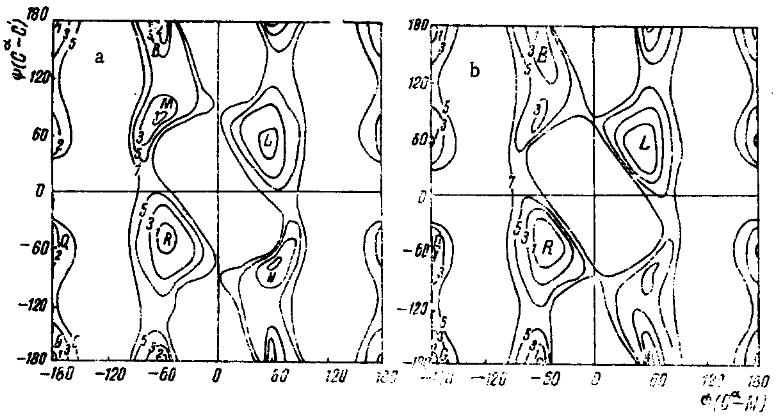

Fig. 3. Conformational chart of the methylamide of N-acetyl-α-methylalanine taking into account U_{tot} ($\varepsilon_{eff}=4$) (a) and U_{tot} ($\varepsilon_{eff}=10$) (b).

The results of the calculation show that in nonpolar solutions of low concentration the extended forms M (H) must exist predominantly. The M (H) conformations are the optimum not only from the point of view of a hydrogen bond but also from that of nonvalence interactions. In the formation of a hydrogen bond, the total reduction in the energy of the minimum B' is not accompanied by an appreciable shift in its position.

On passing to polar media, the equilibrium of the structures shifts in the direction of the sterically least-strained structures. In this case, the proportion of the R (L) form must be the highest, but together with this the B, G, and other conformations may exist.

The advantageousness of structure R (L) is determined not only by the enthalpy but also by the entropy, as can be judged from the area of the minimum (see Fig. 3b).

In the majority of cases, the deviations of the angles of rotation of the C^{α} side chains from the position corresponding to the minimum of U_T (60°) are small and average about 3°. In the M (B') form the maximum deformation of the valence angles at the C^{α} atom is observed (in comparison with the tetrahedral arrangement), amounting to about 5°. The M (H) form, which predominates in nonpolar media, has a small dipole moment – 2.7 D. The conformation predominating in polar media – R (L) – is characterized by the highest value of the dipole moment – 6.6 D.

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