CONFORMATIONAL STATES OF METHYLAMIDES OF N-ACETYL α-AMINO ACIDS AND THEIR N-METHYL DERIVATIVES

III. DIPOLE MOMENTS

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We have previously [1, 2] considered the NMR and IR spectra of the following methylamides of N-acetyl α-amino acids:

Ac-L-Ala-NHMe (I), Ac-L-Ala-NMe_2 (II), Ac-L-MeAla-NHMe (III), Ac-L-MeAla-NMe_2 (IV), Ac-L-Val-NHMe (V), Ac-L-Val-NMe_2 (VI), Ac-L-MeVal-NHMe (VII), Ac-L-MeVal-NMe_2 (VIII), Ac-L-Pro-NHMe (IX), Ac-L-Pro-NMe_2 (X).

It follows from an analysis of the NMR spectra that the amide groups in compounds (I), (II), (V), and (VI) in both polar and nonpolar media have the trans configuration. The diamides (III), (IV), and (VII-X) exist in the form of equilibrium mixtures of forms with the trans and cis configurations of the tertiary amide groups, the position of the equilibrium (particularly in a nonpolar medium) being shifted in the direction of the conformations with the trans amide groups. By means of IR spectra a study has been made of the equilibrium between the two types of conformations of compounds (I), (III), (V), (VII), and (IX) – folded (with an intramolecular H bond of the 3 → 1 type closing a seven-membered ring) and extended. The present paper is a continuation of investigations of the spatial structure of compounds (I-X) by the dipole-moment method.

The dipole moments of the methylamides of N-acetyl α-amino acids with aliphatic side chains can be represented in the form of the vector sum of the moments of the amide groups. According to the literature [3, 6], the dipole moments of amides are insensitive to alkyl substituents and amount to ~ 3.7 D. They also remain practically constant on passing from solutions in CCl_4 to those in $CHCl_3$.* Further, it may be considered that the vector of the dipole moment is directed at an angle of 40° to the C–N bond. This direction follows from the microwave spectrum of formamide [7], an analysis of the intensities of the absorption bands in the IR spectrum of this compound [8], and from quantum-chemical calculations of a series of amides [9]. In addition, the results of experimental [10, 11] and theoretical investigations of amides and lactams show the close values and directions of the dipole moments of the trans and cis amide groups. Thus, in interpreting the experimental dipole moments of compounds (I-X) we assumed that the differences between them are determined only by the conformational parameters of the main chain – the angles Φ, Ψ, and $C^{\alpha}C'N$ [12]. Figures 1 and 2 give maps of the dipole moments in the coordinates Φ, Ψ for the trans and cis configurations of a N-terminal amide group. They coincide with the corresponding conformational maps of the molecules of (I) and (III) on which the points corresponding to the optimum forms have been plotted [13-16].

* The dipole moments of N-methylacetamide in CCl_4 and $CHCl_3$ that we have measured are, respectively, 3.65 and 3.68 D, and those of N,N-dimethylacetamide are 3.63 and 3.74 D.

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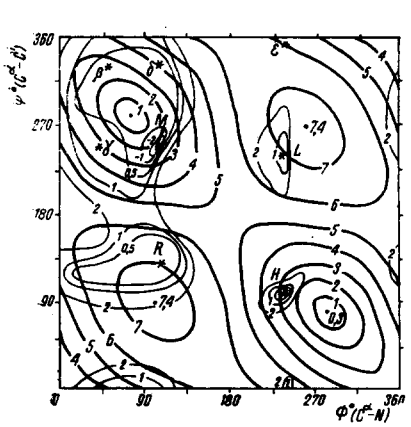

Fig. 1

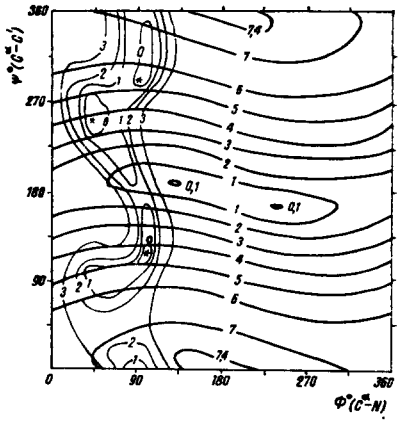

Fig. 2

Fig. 1. Map of the dipole moments and conformational map [13] of the methylamide of N-acetyl-L-alanine (I) with the trans configuration of the amide groups. (Contours given in D and kcal/mole, respectively. The asterisks mark the positions of the optimum conformations.)

Fig. 2. Map of the dipole moments and conformational map [15] of the methylamide of N-acetyl-N-methyl-L-alanine (III) with the cis configuration of the $-CONCH_3-$ group (Notes as in Fig. 1.)

In the plotting of the maps, no account was taken of the change in the dipole moments of the amide groups with the formation of intramolecular hydrogen bonds in the M and H conformations. However, as will be shown below, a H bond has no substantial influence on the resulting dipole moment.

The dipole moments of compounds (I-X) were measured in CCl_4 and $CHCl_3$ solutions at concentrations excluding the formation of intermolecular H bonds [17] (Table 1). For the majority of compounds in the table the calculated dipole moments for the optimum conformations, the geometric parameters of which were found by a minimization of the energy on varying the dihedral and valence angles [13-16], are also given.

By comparing the experimental results with the calculated figures, two conclusions can be drawn relating to all the compounds investigated.

1. In the conformational equilibria of compounds (I-X) in CCl_4 and $CHCl_3$ the forms with the trans configuration of the amide groups are the dominating ones. For example, let us consider compounds (III), (IV), and (VII-IX) with tertiary N-terminal amide groups, where the realization of the cis configuration is most probable [1]. With this configuration, to the dipole moments of compounds (III), (IV), and (VII-IX) (1.99-2.90 D) correspond conformational regions in the range $140° < \Psi < 240°$, in which there are no minima of the potential energy (see Fig. 2). The dipole moments of the majority of the optimum conformations with trans amide groups, on the other hand, agree well with the experimental values (see Fig. 1 and Table 1). So far as concerns the dimethylamide of N-acetyl-L-proline (X) with dipole moments of 4.17 D (in CCl_4) and 4.30 D (in $CHCl_3$), for this, according to the results of semiempirical [15, 16, 18] and quantum-chemical [19] calculations, the most favorable conformations, both with the trans and with the cis configurations of the amide group, are found in the $\Psi = 280-360°$ region (δ form) and have dipole moments of ~ 4.0 and ~ 7.0 D, respectively. This unambiguously indicates the realization in the diamide (X) in CCl_4 and $CHCl_3$ of the δ conformation with the trans configuration of the amide group (see also [22]).

Madison and Schellman [18] ascribe to the conformations of (X) with trans and cis amide groups dipole moments of 3.0 and 4.2 D, respectively. However, these values were obtained by using an inadequately based distribution of the charges on the atoms [20, 21], which, for example, leads to a considerable discrepancy between the calculated (2.4 D) and experimental (3.8 D [10, 11]) values of the dipole moments of cis amides.

2. In the conformational equilibrium of compounds (I-X) in nonpolar and weakly polar media, only a small proportion of forms of the R and L type is possible. This is shown by the considerable difference between the calculated moments of these forms (~ 7.0 D) and the experimental moments of compounds (I-X) (1.99-4.17 D in CCl_4 and 2.01-4.30 D in $CHCl_3$). In addition to this, the experimental results agree quite satisfactorily with the calculated dipole moments of other optimum conformations of the molecules of (I-X).

TABLE 1. Dipole Moments of the Methylamides of N-Acetyl-L-alanine, N-Acetyl-L-valine, N-Acetyl-L-proline, and Their N-Methyl Derivatives

No.	Compound	Dipole moment (D)								
		exptl. solvent		calc. optimum conformation [13-16]						
		CCl_4	$CHCl_3$	R	L	γ	δ	ε	H	M
I	Ac-L-Ala-NHMe	3,12	3,20	7,0	6,9	3,2	3,9	5,7	2,7	2,3
II	Ac-L-Ala-NMe_2	2,80	3,56	6,8	7,0	2,8	2,9	6,6		
III	Ac-L-MeAla-NHMe	2,85	2,92	7,2	6,8	3,2	3,8	5,6	2,8	2,5
IV	Ac-L-MeAla-NMe_2	2,90	2,93		6,8	2,9	3,1	3,8		
V	Ac-L-Val-NHMe	2,80	2,70	7,1	7,2	3,1	3,8		2,6	2,2
VI	Ac-L-Val-NMe_2	2,53	2,49	6,7	6,9	2,5	2,8			
VII	Ac-L-MeVal-NHMe	1,99	2,01		7,2	2,3	3,7		2,5	2,0
VIII	Ac-L-MeVal-NMe_2	2,57	2,62		7,1	2,5				
IX	Ac-L-Pro-NHMe	2,96	3,44	6,8			4,3			2,7
X	Ac-L-Pro-NMe_2	4,17	4,30	7,0 4,4*			4,0 7,0*			

* Dipole moment with the cis configuration of the amide group; in all other cases, the calculated values of μ for the conformation with trans amide groups are given.

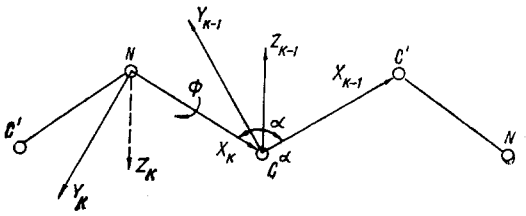

Fig. 3. System of rectangular coordinates of the main chain of a dipeptide fragment.

On the basis of calculation [15], the γ conformation may be predicted as the most favorable for compounds (IV) and (VIII); after this, the L conformation has an energy greater by 1.5 kcal/mole for (IV) and by 2.0 kcal/mole for (VIII). The results of a comparison of the experimental and calculated values of the dipole moments show the existence of both compounds in the γ form. The considerable difference in the energies of the γ and L forms gives grounds for assuming that the γ conformation will be stable in polar and nonpolar media. This hypothesis is confirmed completely by the CD and ORD spectra obtained for (IV) and (VIII) in heptane and in water [22], and also by the constancy of the dipole moments of these compounds in CCl_4 and $CHCl_3$. A somewhat different situation must be observed according to [15] for compounds (II) and (VI). Although, as before, the most preferred conformation is the γ conformation, nevertheless the difference between the energy of this form and two others (δ and L) is not so great as in the preceding case. According to calculation [15], the experimental values of the dipole moments of (II) and (VI) in CCl_4 practically coincide with the calculated moments for compounds (IV) and (VIII), respectively, and, consequently, correspond to the γ conformation. Passage from solution in CCl_4 to $CHCl_3$ considerably raises the dipole moment of (II), which can be explained only by the partial displacement of the conformational equilibrium to the L form. In the case of compound (VI) the dipole moment in the two media remains unchanged and, as can be seen from Table 1, corresponds to the γ and δ conformations. As will be shown in a subsequent paper [22], these conclusions are also in full harmony with the CD and ORD spectra.

In an investigation of the IR spectra [2], we established that compounds (I), (III), (V), (VII), and (IX) exist in CCl_4 solution to the extent of 60-90% as the folded forms (M, H), stabilized by an intramolecular H bond. The calculated moments of these forms (2.3-2.7 D) in the compounds listed are very close to the experimental values (2.8-3.22 D). The somewhat higher values of the latter are connected with the presence of the extended forms which, on an average, have greater dipole moments than the H and M forms; this has been shown for compound (I) by summing the contributions of the moments of the optimum conformations, taking into account their relative energies and population densities over the whole of the conformational map [14]. On passing from solution in CCl_4 to $CHCl_3$, the amount of the folded forms (I), (III), (V), (VII), and (IX) decreases approximately twofold [2, 14]. Nevertheless, with such a sharp change in the conformational equilibrium the dipole moments rise only slightly (2.85-3.44 D). This fact additionally confirms that among the extended forms of the compounds mentioned those most preferred in CCl_4 and $CHCl_3$ are the conformations present on the map in the B region (γ, δ). Subsequently [17] the dependence of the dipole moments of (I) and (V) on the concentration and the conformational features of these compounds following from them will be considered.

The dipole moment of compound (IX) (2.96 D in CCl_4), which, under the conditions of measurement, adopts conformation M to the extent of 90% [2], is close to the calculated value (2.7 D). It follows directly from this that the extremely substantial redistribution of the electron density in the amide groups that takes place with the formation of a H bond has little effect on the magnitude of the resulting dipole moment of the molecule. A similar conclusion can be drawn by comparing the experimental and calculated moments of compound (III), which is present in CCl_4 solution to the extent of 70% in the folded M for [2, 22].

Maigret et al. [26] give the calculated value of the dipole moments of the M and H conformations as 4.5 D. They differ from our values mainly by the noncoincidence of the potential minima of these forms on the Φ and Ψ maps obtained by quantum-chemical (for example, M, $\Phi = 90°$, $\Psi = 210°$) [26] and semiempirical (M, $\Phi = 108°$, $\Psi = 250°$) [13] methods. With the geometrical parameters of M and H given by Maigret et al. [26], the moments of the folded conformations, according to the dipole-moment map (see Fig. 1) are about 4.0 D, which also shows the small influence of a H bond on the dipole moment of the molecule.

In a comparison of the experimental values of the dipole moments of the alanine derivatives (I and V) and (II and VI), and so on, attention is attracted by the fact that the moments of (I-IV) are in all cases greater than the moments of (V-VIII). Nevertheless, as shown above, the members of each pair of corresponding compounds in CCl_4 solution are present in extremely close conformational states. The observed effective dipole moments differ, in the first place, by the noncoincidence of the geometric parameters (particularly the angles Φ and Ψ and the valence angle $NC^{\alpha}C'$ [17]) in the monotypical optimum conformations of the alanine and valine diamides and, in the second place, by the different positions of the conformational equilibria. In actual fact, as follows from Table 1, the calculated moments of identical forms of these compounds have different values, and in the case of the valine derivatives the moments of the R and L conformations (which scarcely exist in CCl_4) are somewhat greater and, conversely, those of the γ, δ, H, and M conformations (dominating under the same conditions) are smaller than the moments of the corresponding forms of the alanine derivatives. The increase in the dipole moments of (III) and (IV) as compared with (VII) and (VIII) may also be partially connected with the greater proportion, in the alanine derivatives, of the more polar forms with the cis configuration of the tertiary amide groups.

For the methylamides of N-acetyl α-amino acids, Tsuboi et al. [23] and, later, Avignon et al. [24, 25] postulated the conformation $\Phi = \Psi = 0°$ with an intramolecular H bond of the $1 \rightarrow 1$ type. The results that we have obtained on dipole moments have not confirmed the existence of such a form in the compounds investigated. Thus, the dipole moments of the diamides (II) and (VI) in CCl_4 (2.80 and 2.53 D) are considerably lower than the moment of the conformation with $\Phi = \Psi = 0°$ (3.5 D). In a preceding paper [2] we have already reported the noncorrespondence of this conformation with features of the IR spectra and the results of a theoretical analysis.

EXPERIMENTAL

The dipole moments of compounds (I-X) were determined at 25°C in CCl_4 and $CHCl_3$ solutions in a range of concentrations excluding intermolecular association ($1.0 \cdot 10^{-4}$ to $5.0 \cdot 10^{-4}$ M in CCl_4 and $1.0 \cdot 10^{-3}$ to $4.0 \cdot 10^{-3}$ M in $CHCl_3$ [17]).

The dielectric constants were measured on a Dipol' instrument produced by the Angarsk OKBA [Experimental Design Bureau for Automation]. The densities of the solutions were determined pycnometrically. The refractive indices were obtained on an IRF-23 refractometer.

The experimental values of the dipole moments in CCl_4 were calculated by Debye's method using Hedestrand's extrapolation formulas [27], and those in $CHCl_3$ by Onsager's method [28, 29]. In both cases, the values of the atomic polarization were left out of account. The values of the dipole moments are given with an accuracy of ± 0.05 D.

To construct the dipole-moment maps and to calculate the values of the moments of the optimum conformations (which are given in Table 1), a special program was drawn up for a computer which permitted the calculation of the resulting dipole moment of a molecule by the vector combination of the moments of the individual bonds or groups. The method of calculation will be understood by taking as example a dipeptide fragment (Fig. 3).

Local right-handed rectangular systems of coordinates are associated with each atom of the main chain. The X axis of each system is directed along the bond of the given atom with the preceding atom, the Y axis forms an acute angle with the neighboring bond (direction taken as right to left). The angles between the vectors of the dipole moments of the bonds at a particular atom of the main chain are given in the local

system, and then the combination of the vectors is carried out taking their modular values into account. The resultant vector in the given system of coordinates (K−1) is transferred to another one (K) by successive rotations first by an angle of $180°-\alpha$ (where α is the valence angle) around the Z axis and then by the angle of rotation Φ. In the matrix expression, these operations appear as follows:

$$\begin{vmatrix} X_K \\ Y_K \\ Z_K \end{vmatrix} = \begin{vmatrix} -\cos\alpha & -\sin\alpha & 0 \\ -\cos\Phi\cdot\sin\alpha & \cos\Phi\cdot\cos\alpha & \sin\Phi \\ -\sin\Phi\cdot\sin\alpha & \cos\Phi\cdot\cos\alpha & -\cos\Phi \end{vmatrix} \begin{vmatrix} X_{K-1} \\ Y_{K-1} \\ Z_{K-1} \end{vmatrix},$$

After the transference to the new system (K), the combination of the resultant vectors of the (K−1) and (K) systems is performed. For a molecule with n atoms in the chain it is obviously necessary to perform n−1 such successive transformations. In calculating the value of the dipole moment of the amide group, a value of 3.7 D and a direction of 40° to the C−N axis were adopted [7] both for the trans and for the cis configurations. The contribution to the dipole moment from the side chain was not taken into account, since it appears implicitly in the value of the group moment. The dipole-moment maps (Figs. 1 and 2) were plotted for the following values of the valence angles: for the trans form – $C'NC^{\alpha}=124°$, $NC^{\alpha}C'=109°$, $C^{\alpha}C'N=118°$, and for the cis form – $C'NC^{\alpha}=125.5°$, $NC^{\alpha}C'=110°$, $C^{\alpha}C'N=118.6°$. The moments of the individual conformations (see Table 1) were calculated in the light of their geometrical parameters as given in the literature [13-16].

SUMMARY

1. The dipole moments of methylamides of N-acetyl α-amino acids and their N-methyl derivatives in CCl_4 and $CHCl_3$ solutions have been measured.

2. The preferred conformational states of the compounds investigated have been determined from a comparison of the experimental and calculated values of the dipole moments.

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