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

## II. $^1$H NMR SPECTRA

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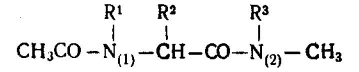
In the course of an investigation of the laws of the formation of the spatial structures of linear [1-4] and cyclic [5-12] peptides, the synthesis [13] and an all-sided physicochemical investigation [14-17] of a series of amides of N-acetyl amino acids, which are convenient models of the corresponding dipeptides, have been performed.

The present paper gives the results of an investigation of the $^1$H NMR spectra of compounds (I)-(X), which enables the position of the equilibrium between the forms with the cis and trans configurations of the amide bonds to be determined and the rotational states of the $NH-C^{\alpha}H$ and $C^{\alpha}H-C^{\beta}H$ fragments to be characterized.



$$CH_3CO-\underset{(1)}{\overset{R^1}{N}}-\overset{R^2}{CH}-CO-\underset{(2)}{\overset{R^3}{N}}-CH_3$$

| | | |
|---|---|---|
| I. | AcAlaNHMe | $R^1=R^3=H,\ R^2=CH_3;$ |
| II. | $AcAlaNMe_2$ | $R^1=H,\ R^2=R^3=CH_3;$ |
| III. | AcMeAlaNHMe | $R^1=R^2=CH_3;\ R^3=H;$ |
| IV. | $AcMeAlaNMe_2$ | $R^1=R^2=R^3=CH_3;$ |
| V. | AcValNHMe | $R^1=R^3=H,\ R^2=CH(CH_3)_2;$ |
| VI. | $AcValNMe_2$ | $R^1=H, R^2=CH(CH_3)_2,\ R^3=CH_3;$ |
| VII. | AcMeValNHMe | $R^1=CH_3,\ R^2=CH(CH_3)_2, R^3=H;$ |
| VIII. | $AcMeValNMe_2$ | $R^1=R^3=CH_3,\ R^2=CH(CH_3)_2;$ |
| IX. | AcProNHMe | $R^1,\ R^2=(CH_2)_3,\ R^3=H;$ |
| X. | $AcProNMe_2$ | $R^1,\ R^2=(CH_2)_3,\ R^3=CH_3.$ |

NMR spectroscopy is widely used to study the cis–trans isomerism of amides [18, 19] and also of derivatives of N-methyl amino acids [20, 21, 27-29] and of proline [22-26, 30-32]. Since, as a rule, the energy barriers of cis–trans transitions in amides are extremely high (15-20 kcal/mole), corresponding to coalescence temperatures of 40-100°C, with the participation of both forms in the conformational equilibrium the observed spectrum is the result of the superposition of two spectra, the intensities of the corresponding signals of which are proportional to the proportions of the respective forms.

Literature information shows that the trans forms of secondary peptide groups are advantageous as compared with the cis forms by approximately 2 kcal/mole [33, 34]. Consequently, in linear and unstrained cyclic peptides the trans conformation of the peptide groups is realized. For N-methylated peptide bonds [28] and proline derivatives, the energy barrier between the trans and cis forms decreases (for example, by 0.6 kcal/mole in the case of derivatives of N-methylalanine), which leads to the appearance of considerable amounts of conformers with the cis configuration of the tertiary amide bonds.

The results of an investigation of compounds (I)-(X) (Tables 1 and 2, Figs. 1-4) agree well with the facts given above. Thus, in the spectra of the diamides (I) (see Fig. 1), (II), (V), and (VI) no additional sig-

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TABLE 1. Chemical Shifts of the Protons (ppm) and Amounts of the Cis Isomers with Respect to the CO–$N_{(1)}H$ Bond in Compounds (I-VIII)

| Compound | Solvent | Configuration of the CO–$N_{(1)}CH_3$ bond | Protons of the side chain |  | $CH_3CO$ | $N_{(1)}CH_3$ | $N_{(2)}CH_3$ | $C^{\alpha}H$ | $N_{(1)}H$ | $N_{(2)}H$ | Amt. of cis isomer, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | $CH_3$ | CH |  |  |  |  |  |  |  |
| I | $CDCl_3$ | — | 1,39 | — | 2,00 | — | 2,79 | 4,59 | 6,96 | 7,05 | 0 |
|  | $(CD_3)_2SO$ | — | 1,16 | — | 1,83 | — | 2,57 | 4,20 | 8,02 | 7,77 | 0 |
| II | $CCl_4$ | — | 1,26 | — | 1,87 | — | 2,93; 3,15 | 4,86 | 7,40 | — | 0 |
|  | $CDCl_3$ | — | 1,35 | — | 2,03 | — | 3,01; 3,12 | 4,95 | 6,86 | — | 0 |
|  | $(CD_3)_2SO$ | — | 1,14 | — | 1,82 | — | 2,83; 3,01 | 4,72 | 8,08 | — | 0 |
| III | $CCl_4$ | trans | 1,28 | — | 2,07 | 2,97 | 2,73 | 5,04 | — | 7,03 |  |
|  |  | cis | 1,41 | — | 2,08 | 2,78 | 2,75 | —* | — | —* | 15 |
|  | $(CD_3)_2SO$ | trans | 1,20 | — | 2,03 | 2,84 | 2,59 | 4,96† | — | 7,65† |  |
|  |  | cis | 1,29 | — | 2,03 | 2,86 | 2,62 | 4,41 | — | 7,88 | 26 |
| IV | $CCl_4$ | trans | 1,16 | — | 2,02† | 2,89; 2,88; 2,98 |  | 5,42 | — | — |  |
|  |  | cis | 1,28 | — | 2,07 | —* —* —* |  | 4,58 | — | — | 4 |
|  | $(CD_3)_2SO$ | trans | 1,10 | — | 2,03† | 2,79; 2,84; 2,89 |  | 5,33 | — | — |  |
|  |  | cis | 1,24 | — | 2,06 | 2,65; 2,88; 2,98 |  | 4,86 | — | — | 14 |
| V | $CDCl_3$ | — | 0,96 | 1,60 | 2,02 | — | 2,82 | 4,19 | Under signal of $CHCl_3$ |  | 0 |
|  | $(CD_3)_2SO$ | — | 0,83 | 1,95 | 1,87 | — | 2,58 | 4,05 | 7,84 | 7,83 | 0 |
| VI | $CCl_4$ | — | 0,90 | 2,00 | 1,88 | — | 2,95; 3,19 | 4,64 | 7,65 | — | 0 |
|  | $CDCl_3$ | — | 0,92<br>0,96 | 2,15 | 2,01 | — | 2,97; 3,14 | 4,84 | 6,59 | — | 0 |
|  | $(CD_3)_2SO$ | — | 0,84<br>0,86 | 1,97 | 1,85 | — | 2,84; 3,08 | 4,56 | 8,03 | — | 0 |
| VII | $CCl_4$ | trans | 0,80<br>0,93 | 2,20 | 2,06 | 2,99 | 2,71 | 4,54 | — | 7,17 | 0 |
|  | $CDCl_3$ | trans | 0,84<br>0,96 | 2,20 | 2,12 | 3,00 | 2,77 | 4,54 | — | 6,44 | 0 |
|  | $(CD_3)_2SO$ | trans | 0,75<br>0,85 | 2,40 | 2,03† | 2,95† | 2,56 | 4,57† | — | 7,86 |  |
|  |  | cis | 0,81<br>0,87 | — | 2,10 | 2,77 | 2,62 | 3,72 | — | 8,08 | 35 |
| VIII | $CCl_4$ | trans | 0,80<br>0,87 | 2,20 | 2,02 | 3,08; 2,88; 2,87 |  | 5,04 | — | — | 0 |
|  | $CDCl_3$ | trans | 0,85<br>0,92 | 2,23 | 2,11 | 3,13; 2,94: 2,97 |  | 5,17 | — | — | 0 |
|  | $(CD_3)_2SO$ | trans | 0,75 | 2,20 | 2,04 | 2.83†; 2.84†; 2,98† |  | 4,98 | — | — |  |
|  |  | cis | 0,82 |  | 2,13 | 2,70; 2,88; 3,07 |  |  |  |  | 7 |

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* The chemical shifts of the signals from the cis form of the CO–$N_{(1)}$ fragment could not be observed in the spectrum.

† Signals used for the determination of the amount of cis isomers.

nals whatever are observed, which shows the presence of amide bonds in only a single conformation – trans-amide bonds. In the spectra of compounds (III), (IV), (see Fig. 3), and (VII-X), however, signals from the cis and the trans forms clearly appear. For example, in the diamide (VII) (Fig. 2b), in $(CD_3)_2SO$ solution, each signal from the trans form is accompanied by a signal from the cis form with a similar shape but a lower intensity.

The assignments of the individual signals to the cis and trans forms of compound (III), (VI), and (VII-X) given in Tables 1 and 2 do not follow directly from the spectrum obtained, although it is extremely probable on the basis of literature information [28, 29]. However, the preferred nature of the trans form in solutions in nonpolar solvents has been shown in a recent paper on the dipole moments of diamides [15]; the preferred nature of the trans form in the case of compounds (III), (VII), and (IX) also follows from the presence of large amounts of folded conformations stabilized by intramolecular H bonds and excluding cis-amide bonds [14].

While in the regions corresponding to isopropyl (0.75-0.87 ppm), acetyl (2.03-2.10 ppm), N-methyl (2.95 and 2.77 ppm), and NH (7.86 and 8.08 ppm) groups the differences in the chemical shifts of the signals from the trans and cis forms are comparatively small (0.22 ppm), the signals from the $C^{\alpha}H$ protons are considerably more sensitive to a change in the configuration of the amide group ($\Delta\delta = 0.85$ ppm) (see Table 1). This difference, which also appears for other compounds [for example, (III) and (IV), see Table 1], is con-

TABLE 2. Chemical Shifts of the Protons (ppm) and Amounts of Cis Isomers in the $N_{(2)}$-Methylamides and $N_{(2)},N_{(2)}$-Dimethylamides of $N_1$-Acetylproline (IX) and (X)

| Compound | Solvent | Configuration of the bond $O{=}C{-}N_{(1)}CH_3$ | β– and γ–$CH_2$ | $CH_3CO$ | δ–$CH_2$ | $O{=}C{-}N_{(2)}CH_3$ | $C^{\alpha}H$ | $N_{(2)}{-}H$ | Amt. of the cis isomer, % |
|---|---|---|---|---|---|---|---|---|---|
| IX | $CDCl_3$ | trans | 1,72–2,31 | 2,11 | 3,21–3,71 | 2,77 | 4,57* | 7,22 | |
| | | cis | | 2,03 | | 2,86 | 4,34 | under $CHCl_3$ | 19 |
| | $(CD_3)_2SO$ | trans | 1,60–2,10 | 1,97* | 3,27–3,68 | 2,56 | 4,20* | 7,72* | |
| | | cis | | 1,81 | | 2,63 | 4,30 | 8,00 | 30 |
| X | $CCl_4$ | trans | 1,70–2,16 | 1,96 | 3,36–3,81 | 2,87* 3,11* | 4,60–4,88 | – | |
| | | cis | | 1,74 | | 2,91 3,07 | 4,60–4,95 | – | 10 |
| | $(CD_3)_2SO$ | trans | 1,70–2,02 | 1,95 | 3,30–3,67 | 2,80* 3,03* | 4,72 | – | |
| | | cis | | 1,75 | | 2,86 3,05 | 4,88 | – | 31 |
| | $D_2O$ | trans | 0,61–1,25 | 0,87 | 2,43 | 1,70* 1,90* | | – | |
| | | cis | | 0,68 | 2,30 | 1,75 1,91 | | – | 23 |

* Signals used for the determination of the amounts of the cis isomers.

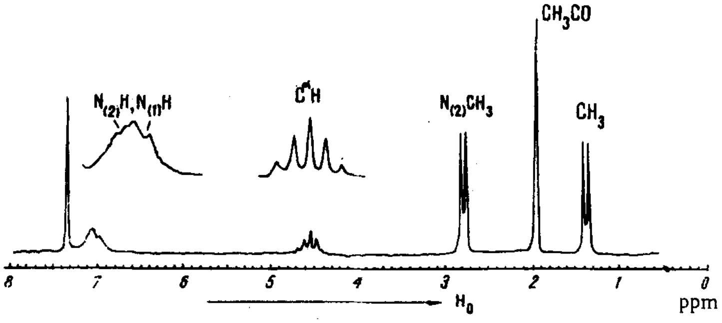

Fig. 1. NMR spectrum of AcAlaNHMe (I) in $CDCl_3$. The top part of the figure shows fragments of the spectrum taken in an expanded sweep.

nected with the diamagnetic anisotropy of the N-terminal amide group [18, 35, 36], which is apparently spatially close to the $C^{\alpha}H$ group, which changes its orientation by 180° relative to the carbonyl group in cis–trans transitions. It must be noted that for the proline derivatives (IX) and (X) (see Fig. 4 and Table 2), the differences in the chemical shifts for the $N-CH_3$ groups are considerably smaller than for the linear diamides, amounting to only 0.04-0.09 ppm; the values of $\Delta\delta$ for the $C^{\alpha}H$ signals are also smaller than for compounds (III), (IV), and (VII) [$< 0.2$ ppm in nonpolar solvents and 0.10-0.16 ppm in $(CD_3)_2SO$]. It is possible that this equalization of the signals of the cis and trans isomers is connected with the rapid transformation of the pyrrolidine ring and with the participation in the conformational equilibrium of at least two forms with similar thermodynamic parameters [37].

The proportion of the cis forms of the diamides (III), (IV), and (VII-X) have been determined from the ratios of the areas of the corresponding signals in the NMR spectra. The region of the N-methyl signals, which have a high intensity and a simple shape (singlet), proved to be the most convenient for this purpose. As can be seen from Tables 1 and 2, the proportions of the cis forms are higher in $(CD_3)_2SO$ (8-35%) than in $CCl_4$ or $CHCl_3$ (4-20%). This characteristic feature appears most clearly for compound (VII) the solution of which in $CCl_4$ shows no signals of the cis isomer (see Fig. 2a), while in $(CD_3)_2SO$ (see Fig. 2b) the proportion of cis isomer is 35%. The high proportion of cis isomers in polar solvents is apparently connected with the fact that the most preferred conformations of the molecules of the diamides with the cis configuration of the amide groups have, according to [15], higher dipole moments than the conformations with the trans-amide groups. Furthermore, for compounds (III), (VII), and (IX) the relative stabilization of the trans forms in nonpolar solvents can be partly explained by the formation of intramolecular H bonds of the $3 \rightarrow 1$ type which are broken by $(CD_3)_2SO$; in the cis forms the formation of such bonds is impossible.

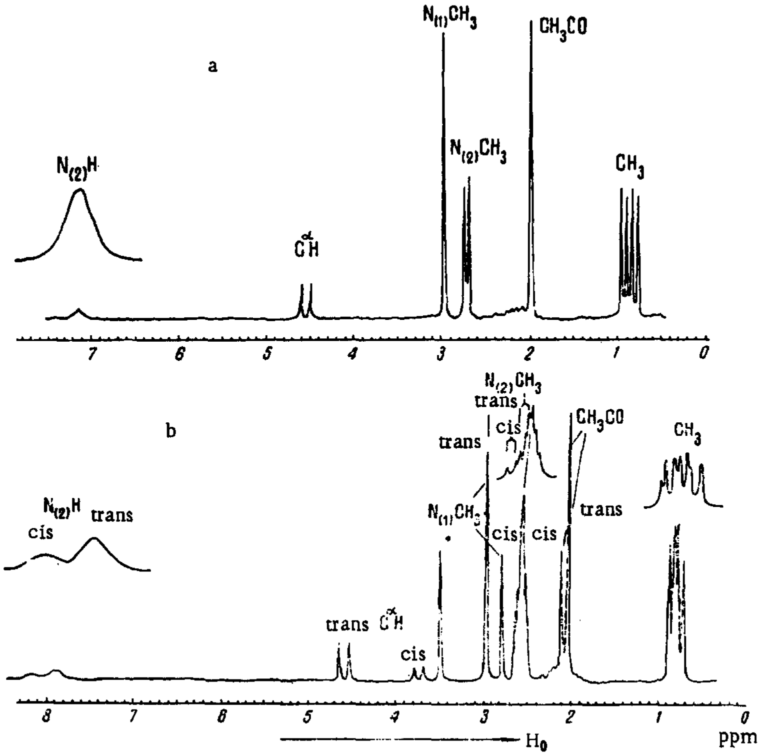

Fig. 2. NMR spectra of $AcMeValNHCH_3$ (VII): a) in $CCl_4$; b) in $(CD_3)_2SO$.*

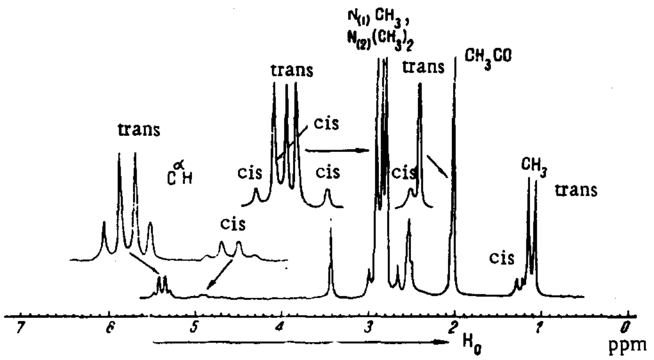

Fig. 3. NMR spectrum of $AcMeAlaN(CH_3)_2$ (IV) in $(CD_3)_2SO$.†

Madison and Schellman [24], on making a detailed study of the diamide (X) came to the conclusion that in polar media [$H_2O$, $CD_3OD$, $(CD_3)_2SO$], the compound exists predominantly (70-85%) in the trans form, and in nonpolar solvents ($CHCl_3$, $CCl_4$, $C_6H_{12}$) in the cis form. The results of measurements of the NMR spectra of compounds (X) in mixtures of $CCl_4$ and $(CD_3)_2SO$ in different proportions that we have performed, however, have shown that the trans form is the dominating one in all cases, since with the change in the solvent there is no appreciable redistribution of the intensities of the signals of the two forms (Fig. 5). The cause of the contradiction mentioned was possibly that in the determination of the ratio of the cis and trans forms of (X) in nonpolar solvents, Madison and Schellman [24] erroneously assigned the two multiplet signals observed in the $C^{\delta}H_2$ region (2.9-4.0 ppm) to the $CH_2$ groups of the cis and trans forms and did not consider the region of the signals of the N-methyl groups. This left out of account the possibility of the assignment of these multiplet signals to the two nonequivalent $C^{\delta}H_2$ protons. If such a possibility is assumed, then it is not surprising that the amount of the cis form in solutions in $CCl_4$, $C_6H_6$, and $CHCl_3$ measured by Madison

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* Signal of $H_2O$ (impurity in the solvent).

† Signal of $H_2O$ (impurity in the solvent).

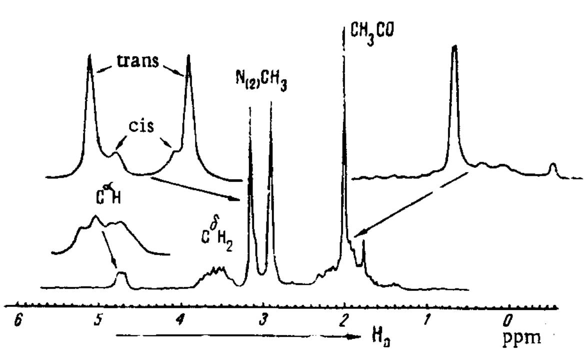

Fig. 4. NMR spectrum of AcProN$(CH_3)_2$ (X) in $CCl_4$.

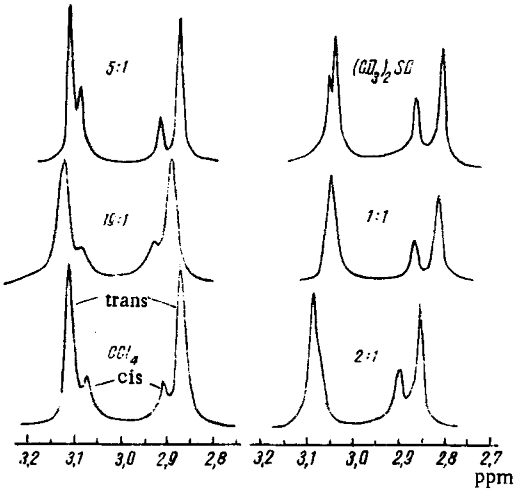

Fig. 5. Region of the signals of the $N-CH_3$ groups of compound (X) in mixtures of $CCl_4$ and $(CD_3)_2SO$ with various ratios of the components.

and Schellman [24] should prove close to 50% (52, 50, and 55%, respectively); in evaluating the results for solutions in cyclohexane (65%) the great error of measurement connected with the poor solubility of the diamide (X) in this solvent must be borne in mind.

The hypothesis put forward was confirmed by our study of the spectra of the diamide (X) in $CCl_4-C_6H_6$ (1 : 1) solution at various temperatures (Fig. 6). Heating the solution to 50°C leads to the coalescence [through an acceleration of rotation relative to the $C(O)-N_{(2)}$ bond] of the intense N-methyl signals from the trans form, which are close to one another, and at 86°C the fusion of all the N-methyl signals takes place [through rotation around the $C(O)-N_{(1)}$ bond]. As can be seen from Fig. 7, in $CCl_4$ solution it is possible to trace the coalescence of the signals from all four N-methyl groups. So far as concerns the two multiplet signals of equal intensity from the $C^{\delta}H_2$ protons, they do not change their shape appreciably in the same range of temperatures (see Fig. 6). This excludes the possibility of the assignment to the cis and trans configurations of the amide groups of (X) and confirms the fact that they are due to the two nonequivalent protons on the $C^{\delta}$ atom.

According to Go and Scheraga [38], it follows from a conformational analysis of Pro–Pro fragments that the realization of the $\delta$ ($\Phi = 120°$, $\Psi \sim 280° - 360-30°$) and R ($\Phi = 120°$, $\Psi \sim 120°$) conformations is possible. The first has a considerably lower energy (see also [24]). A considerable displacement of the equilibrium in the direction of the R conformation, which has a high dipole moment [15], can be expected only in polar solvents. In view of the fact that the energy barrier of the transition from the $\delta$ to the R form is fairly high and is comparable with the barriers of cis $\rightleftarrows$ trans transitions [38, 39], we have attempted to observe these conformations from the spectra of the diamide (X) taken at a low temperature in solutions containing $CD_3OD$ ($CD_3OD-C_6D_5CD_3$, 1 : 1 and $CD_3OD-CF_2Cl_2$, 1 : 2). However, lowering the temperature to $-110$ to $-132$°C led only to a uniform broadening of the signals in the spectrum without signs of coalescence. It follows from this that the diamide (X) exists in a conformation of the $\delta$ type both in nonpolar and in polar solvents. The question of the influence of the solvent on the conformation of (X) will be considered in more detail in a paper in which the results of a study of the ultraviolet spectra and circular dichroism curves of compounds (I-X) are described [17].

An important parameter of the NMR spectra of peptides is the spin–spin coupling constant of the protons of the $NH-C^{\alpha}H$ fragment, the stereochemical dependence of which has been established previously [1, 2]. As can be seen from Table 3, compounds (I), (II), (V), and (VI) are characterized by high values of the constants ${}^3J_{NH-C^{\alpha}H}$ (8.2-9.4 Hz) which shows a very low proportion of the gauche rotamers with respect to the $N-C^{\alpha}$ bond (with an angle $\Theta$ between the $H-N-C^{\alpha}$ and $N-C^{\alpha}-H$ planes of 50-130° [1] and the angular coordinates $\Phi \sim 0-10°, 110-190°$, and 290-360° [40]) (Fig. 8). Higher values of the constants for the valine derivatives (V) and (VI) (9.0-9.4 Hz) show the preferential trans orientation of the NH and $C^{\alpha}H$ protons

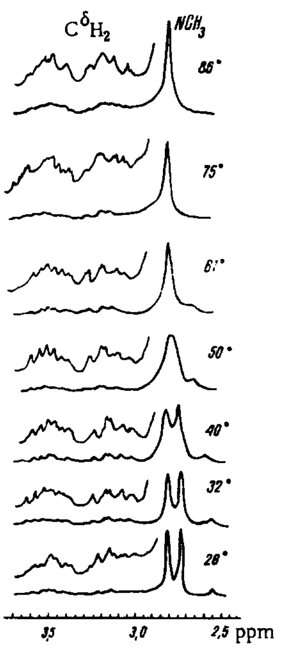

Fig. 6

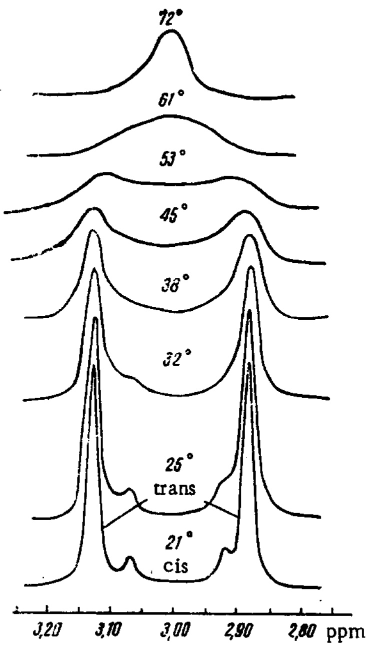

Fig. 7

Fig. 6. Region of signals from the N$-$CH$_3$ and C$^δ$H$_2$ groups of compound (X) in CCl$_4$$-$C$_6$H$_6$ (1 : 1) at various temperatures.

Fig. 7. Region of the signals from the N$-$CH$_3$ groups of compound (X) in CCl$_4$ at various temperatures.

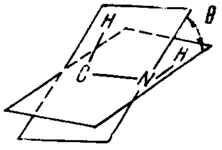

Fig. 8

($\Phi \sim 60 \pm 20°$). These conclusions are in complete agreement with the results of conformational analysis performed by the semiempirical method [41, 42]. On the other hand, the results of quantum-chemical calculation agree considerably less well with ours, since they predict a predominance of rotamers with respect to the N$-$C$^α$ bond differing significantly from the cis and trans forms ($\Phi \sim 30°$, 90-180, and 280°) [43, 44].

According to the spin$-$spin coupling constants of the protons of the C$^α$H$-$C$^β$H fragments in the valine derivatives (V) and (VI), both gauche and trans rotamers with respect to the C$^α$$-$C$^β$ bonds are present ($^3J = 7.3$ and 6.6 Hz in CDCl$_3$), and of the sterically more hindered N-methylvaline derivatives (VII) and (VIII) it is mainly the trans rotamers that are realized ($^3J =$ 11.2 and 10.8 Hz in CDCl$_3$) (see Table 2).

The $^1$H NMR spectra do not give more detailed information on the relative amounts of the various conformers of compounds (I-X) within their trans and cis forms. This question will be discussed in following papers [13-17].

## EXPERIMENTAL

The $^1$H NMR spectra were measured in polar (CD$_3$)$_2$SO and nonpolar (CCl$_4$ and CDCl$_3$) solvents at 25°C with concentrations of $2 \cdot 10^{-1}$ M on a JNM-4H-100 instrument with a working frequency of 100 MHz and with stabilization of the resonance conditions on one sample. Tetramethylsilane was used as internal standard The chemical shifts were determined with an accuracy of ± 0.005 ppm, and the spin$-$spin coupling constants with an accuracy of ± 0.1 Hz. The temperatures of the samples were found by means of a copper$-$constantan thermocouple with an accuracy of ± 2°C from special calibration graphs.

The spin$-$spin coupling constant $^3J_{NH-C^αH}$ of compound (I) in dilute CDCl$_3$ solution ($3.5 \cdot 10^{-3}$ M) was measured on a Varian HA-100D instrument with a C-1024 accumulation device. The value given in Table 3 (8.3 Hz) was determined at 32°C with respect to the signal from C$^α$H accumulated with the simultaneous irradiation of the region of the C$-$CH$_3$ signals with a strong radiofrequency field. The same values of

TABLE 3. Spin–Spin Coupling Constants of the NH–C$^{\alpha}$H and C$^{\alpha}$H–C$^{\beta}$H Protons, Hz

| Compound | Solvent | $^{3}J^{*}_{NH-C^{\alpha}H}$ | $^{3}J_{C^{\alpha}H-C^{\beta}H}$ |
|---|---|---|---|
| I | $CDCl_3$ | 8,7 (8,3†) | — |
|  | $(CD_3)_2SO$ | 8,4 | — |
| II | $CCl_4$ | 8,4 | — |
|  | $(CD_3)_2SO$ | 8,2 | — |
| V | $CDCl_3$ | 9,4 | 7,3 |
|  | $(CD_3)_2SO$ | 9,0 | 7,3 |
| VI | $CCl_4$ | 8,5 | 7,8 |
|  | $CDCl_3$ | 9,2 | 6,6 |
|  | $(CD_3)_2SO$ | 9,4 | 4,7 |
| VII | $CCl_4$ | — | 11,0 |
|  | $CDCl_3$ | — | 11,2 |
|  | $(CD_3)_2SO$ | — | 10,9 |
| VIII | $CCl_4$ | — | 10,5 |
|  | $CDCl_3$ | — | 10,8 |
|  | $(CD_3)_2SO$ | — | 10,6 |

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* The values of the constants are given with a correction for the electronegativity of the substituents in the peptide fragment CONHC$^{\alpha}$H [1].

† Measured at concentrations of $3.5 \cdot 10^{-3}$ M.

$^{3}J_{NH-C^{\alpha}H}$ were observed at −40°C for the $N_{(1)}H$ and for the C$^{\alpha}$H signals.

## SUMMARY

1. The proportions of the cis forms of methylamides and dimethylamides of acetylmethylalanine, acetylmethylvaline, and acetylproline in media of different polarities have been determined from the ratios of the areas of the corresponding signals in the NMR spectra.

2. The rotational states of the fragments NH–C$^{\alpha}$H and C$^{\alpha}$H–C$^{\beta}$H in the methylamides and dimethylamides of the acetylamino acids have been investigated by analyzing the vicinal spin–spin coupling constants of the protons in these fragments.

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