CONFORMATION OF MEDIUM RING LACTAMS: INFRARED SPECTROSCOPIC STUDY*

J.SMOLÍKOVÁ, M.HAVEL, S.VAŠÍČKOVÁ, A.VÍTEK, M.SVOBODA and K.BLÁHA

*Institute of Organic Chemistry and Biochemistry,
Czechoslovak Academy of Sciences, 166 10 Prague 6*

Spectra of ten lactams containing nine-, ten- and eleven-membered ring, nonsubstituted or substituted with one or two pairs of geminal methyl groups, have been measured in tetrachloromethane or in nujol suspension. The population of various partial conformations on the $NH-C_\omega$ bond in *trans*-amide groups, as well as the population of *cis*-amide groups was calculated from the parameters of the stretching vibration bands of the nonassociated N—H bonds. Probable conformations of individual lactams in solutions were derived from these data on the basis of the existing knowledge of the spatial arrangement of medium-ring compounds. Characteristic features of medium-ring lactams were pointed out, *inter alia* the significant population of *cis*-amide groups and partial conformations with a *syn*-periplanar arrangement of protons on the N and C_ω atoms.

The spatial arrangement of medium rings is interesting from the theoretical point of view since structural relations, not realizable in rings of other size,[1,2] are often found in these structures. Of particular interest is the question how the conformation of these rings is affected by introduction of an endocyclic double bond; this problem was studied experimentally[2-6] as well as using theoretical calculations[7,8]. Much less work has been done on medium-ring compounds containing a partial double bond in the ring, *e.g.* an amide bond. The investigations made thus far were limited to the differentiation between a *cis*- and *trans*-arrangement of the amide group in lactams and the dependence of the *cis-trans* ratio on the ring size[9-12]; in some cases conformations were also suggested for lactams with a *cis*-amide group[13]. A significant contribution to the determination of lactam conformation in crystalline state were X-ray diffraction studies, carried out in detail on eight- and nine-membered lactams[14].

Infrared spectra of *trans*-lactams exhibit several bands corresponding to stretching vibrations of the free N—H bonds; these have been ascribed to the occurrence of several conformations without any nearer assignment[11,15]. The aim of our recent work is a more detailed characterisation of possible conformations in lactams in which formation of a *trans*-amide group is already possible, *i.e.* lactams with nine-membered and larger rings[10-13,15-17]. In our studies we made use of compounds, synthesized by Sicher and collaborators in connection with other aspects of medium-

ring stereochemistry[18]. This series comprises not only the nonsubstituted lactams, described already in the literature, but also lactams substituted with one or two pairs of geminal methyl groups. This substitution, exploited for the study of medium-ring compounds by Sicher and others[5,19,20], has a conformation-holding effect and allows a rational analysis. Also in the present study compounds of this type afforded decisive results. We have studied the infrared spectra of these compounds in the region of stretching vibrations of the free N—H bonds. The interpretation was based on the results of our previous study on the conformation of open-chain N-alkylamides where a connection between the wavenumber of the band $v(\mathrm{N-H})_{free}$ and the

TABLE I

Wavenumbers (cm^{-1}) of Vibrational Bands in the Spectra of Lactams $I-III$ and Population of Partial Conformations $A-D$ (Scheme 1) on the $\mathrm{N-C_\omega}$ Bond in Nonassociated State in Tetrachloromethane

Compound	$v(\mathrm{C=O})$	$v(\mathrm{C-H})^a$	$v(\mathrm{N-H})$ (percentage)		
			trans-A	trans-D	cis
Ia	1 682·6	—	3 472·0 (32)	3 458·3 (68)	—
IIa	1 680·7	3 013	3 472·4 (46) 3 479·8 (11)^b	3 457·2 (40)	3 397 (3)
IIb	1 680·3	—	3 473·8 (74)	3 451·2 (25)	3 403 (1)
IIc	1 683·6	3 023	3 470·9 (69)	3 461·2 (23)	3 394·3 (8)
IId	1 681·6 1 668·8	3 011	3 471·6 (4)	3 455·8 (74)	3 397·5 (22)
IIe	1 680·6 1 660·6	3 025	3 471·6 (61)	3 458·3 (27)	3 393 (12)
IIf	1 679·4 1 668·4 1 651·1	3 012	—	3 453·9 (19) 3 461·7 (11)	3 404·6 (70)
IIIa	1 689·7 1 670·2	2 999	3 463·1 (8)^c	3 443·1 (21)^c	3 397·5 (47) 3 416·8 (24)
IIIb	1 689·0 1 660·5	—	3 465·9 (5)^c	3 442·2 (40)^c	3 402·9 (55)
IIIc	1 665·0 1 686·5 1 651·6	—	—	—	3 410·1 (100)

^{a} "Half-cage" vibrations; ^{b} higher value of $v(\mathrm{N-H})$ due to a steric interaction with non-adjacent C—H bonds; ^{c} non-planar amide group.

partial conformation on the bond between nitrogen and the neighbouring carbon atom of the alkyl group was derived[21]. The whole problem seemed attractive to us since it could contribute to our knowledge of conformation of cyclic peptides.

EXPERIMENTAL

Compounds I— III were prepared from the corresponding ketones by Beckmann rearrangement of their oximes. The structure of the obtained compounds was proved in connection with previous studies[22].

Spectra were measured on a Perkin-Elmer 621 instrument. The accuracy of the measurements was $\pm$ 0·5 cm^{-1}, the frequency was checked with gaseous NH_3 (in the $v(N—H)$ region) and with water vapour (in the $v(C{=}O)$ region). In the measurements of stretching vibrations of N—H bonds the concentration dependence was measured[23,24] (in tetrachloromethane) in order to distinguish between the *cis-* and *trans-*amide groups and further to determine the concentration at which already no association exists. This concentration, $4-6 . 10^{-4}$M, was then used in all standard measurements (10 cm cells, spectral slit width 1·5 cm^{-1}) and all data in the text concerning the stretching vibration bands of free N—H groups relate to these conditions. The stretching vibration bands of free N—H groups were separated on an Elliott 503 computer under assumption of Lorentzian (Cauchy) shape of the bands. From the integrated intensities of the separated bands the percentage of individual partial conformations of the N—H bonds in solution was computed (Table I).

1-*Aza*-2-*cyclodecanone* (IIa) was deuterated by lyophylisation of its aqueous solutions. The deuterated compound exhibited the same number of bands $v(N—D)_{free}$ as was the number of bands $v(N—H)_{free}$ in the non-deuterated compound. The shift of the bands caused by deuteration was in accord with the calculated one.

The wavenumbers of the stretching vibrations of the C—H bonds were taken directly from the spectra without separation. The $v(C{=}O)$ bands were measured on nonassociated compounds (concentration $4-8 . 10^{-4}$M) in tetrachloromethane in 1 cm cells. The wavenumbers were taken directly from the spectra (Table I).

Spectra of compounds in the crystalline state were measured in nujol mull (0·03 mm in KRS-5 cells) in the region $230-4000$ cm^{-1}, accuracy $\pm$ 2 cm^{-1}. The selected data are summarised in Table II.

RESULTS AND DISCUSSION

The obtained spectroscopic data, suitable for conformational consideration, are summarised in Table I. In contrast to large rings (see[25]), the medium-ring compounds exhibit absorption bands which may serve as indicators of sterically strained structures: first of all the bands of *cis*-amide groups and the bands of stretching vibrations of C—H bonds exhibiting extraordinary high wavenumbers, which are found in the spectra of saturated polycyclic systems where the two C—H bonds are pressed against each other (in "half-cage" structures[26,27]). Another such indication should be the existence of N—H bonds in unfavourable partial conformations.

The stretching vibration of free N—H bonds can directly indicate the conformers present. The spectral analysis showed practically in all cases the presence of several bands. The results of deuteration of compound IIa and of the temperature dependence for compounds Ia, IIa and IIe indicate that the multiplicity of the bands is caused

Ia, n = 9
IIa, n = 8
$IIIa$, n = 7

$IIIb$

$IIIc$

IIb

IIc, R = H
IIe, R = CH₃

IId, R = H
IIf, R = CH₃
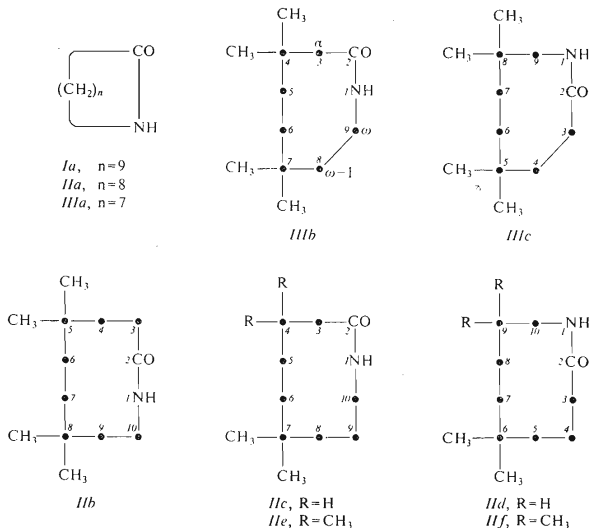
by a plurality of conformations. We observed a similar situation also in open-chain N-alkylacetamides substituted with primary, secondary or tertiary alkyls[21]. We were able to ascribe distinct wavenumber ranges of $v(N—H)_{free}$ (Scheme 1) to individual

3472—3476 cm⁻¹   3463—3469 cm⁻¹   3455—3460 cm⁻¹
 A C D
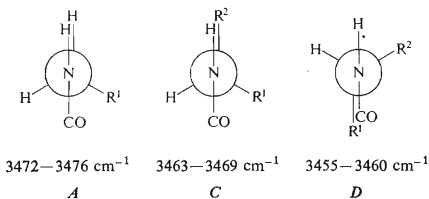
Scheme 1

partial conformations $A - D$ of the N—C alkyl bond, and on the basis of this concept we were able to interpret spectra of a series of amides. Making use of these relations we can detect individual partial conformations of N—H bonds also in the lactams studied at present and to determine their population. On the basis of data thus obtained it is possible to consider the probable conformers of a given lactam. Each partial conformation on the NH—C_ω bond must correspond to at least one conformer. The number of stretching vibration bands of the free N—H group determines then a minimum number of conformers present in the equilibrium.

Conformational analysis of medium-ring lactams can be based on the present ideas about the conformation of carbocyclic medium-ring compounds. Dale[28] concludes that substitution of a CH_2 group for oxygen, NH, CO or similar groups will not substantially alter the geometry of the parent ring system. It is therefore very probable that also in lactam molecules we shall find three types of carbon atoms: W, Y and Z (in Scheme 2 the middle carbon atoms of the chain) which are defined by the conformation of a five-membered fragment of the ring. It is necessary to consider the partially double bond character of the amide bond and therefore a more profound effect on the geometry can be expected than should arise in the case of the mere sum of CO and NH groups. As a result of the partially double bond character of the amide bond, not only the atoms of CO and NH group but also the carbon atoms of the neighbouring groups α-CH_2 and ω-CH_2 in the *trans*- as well as in the *cis*-arrangement of the amide group are held in one plane. However, these deformations due to the presence of amide group will be smaller than the deformations due to a double bond C=C (in cycloalkenes[2–8]) because the amide group has a substantially lower rotational barrier and therefore its deviation from planarity can be energetically less demanding.

According to these considerations, the hydrocarbon part of the ring in the nonsubstituted lactam has in principle the same conformation as in the corresponding cycloalkane and the amide unit, C_α—CO—NH—C_ω—$C_{\omega-1}$, has such a conformation which allows the linkage of the terminal atoms of the hydrocarbon part (this conformation is detected as the partial conformation on the NH—C_ω bond). In each nonsubstituted compound, the mentioned amide unit can substitute the hydrocarbon fragment in more than one position of the carbocyclic ring and the population of the corresponding conformers in the equilibrium mixture is determined by their relative

W Y Z
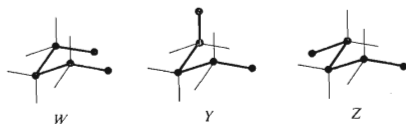
SCHEME 2

thermodynamic stability. Geminal methyl groups tend of course strongly to occupy energetically advantageous positions[5,19,29,30] which in the medium rings are only on carbon atoms of the conformational type Y (Scheme 2). Therefore, introduction of these groups can stabilize certain conformers under simultaneous restriction or even exclusion of other conformations. In some cases this substitution may lead to conformers other than that found in nonsubstituted compounds, however, the resulting geometry is again similar to carbocyclic systems substituted in the same manner.

Ten-Membered Ring Lactams

The nonsubstituted ten-membered ring lactam IIa exists predominantly in two approximately equally populated conformers with partial conformations A and D. The conformer with the N—H bond in the partial conformation A results from the most advantageous situation of the amide group in the preferred cyclodecane conformation (see[31,32], "boat-chair-boat" conformation according to Hendrickson[33]). In this form, the CO and NH groups substitute the two neighbouring CH_2 groups of the conformational type Z; the dihedral angle between these groups approaches most closely (about 150°, see[34]) the transoid arrangement of the amide group. The conformation of 6-oxononanolide[35] determined by X-ray diffraction is also in accord with this concept: in this compound the trans-lactone group is incorporated into the "boat-
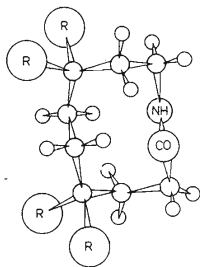

Fig. 1

"Boat-chair-boat" Conformation of Compound IIa (R = H) and IIb (R = CH$_3$)

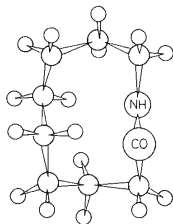Partial conformation A of the N—H bond. The N—H bond sticks out below and the C=O bond above the projection plane.

Fig. 2

Compound IIa in the "Boat-chair-chair" Conformation of the Cyclodecane Skeleton

Partial conformation D of the N—H bond. The N—H bond sticks out below and the C=O bond above the projection plane.

chair-boat" conformation of cyclododecane instead of carbon atoms of the conformational type Z. In the said conformer of the lactam IIa all the characteristics of the preferred "boat-chair-boat" geometry of cyclodecane are retained, including the four carbon atoms of the conformational type Y in position 3, 5, 8, 10 $(cf.$ Fig. 1).

The partial conformation A of the N—H bond may, however, fit also another preferred[33,36] conformation of cyclodecane denoted by Hendrickson as "boat-chair-chair"[33]. The flipping of the $C_{(4)}$ atom does not affect the geometry in the vicinity of the N—H bond and therefore the difference between both conformers cannot be indicated by the wavenumber of the band $v(N\text{---}H)_{free}$. In the conformer "boat-chair-chair", which arose by flipping of $C_{(4)}$, the conformational type Y is preserved only on $C_{(8)}$ and $C_{(10)}$. If the flipping takes place at $C_{(9)}$, giving rise to a chair (and the $C_{(4)}$ atom remains in the original position), another conformation of the type "chair-chair-boat" arises. In this case, however, the N—H bond, in the immediate vicinity of which the change took place, is now in the partial conformation D (see Fig. 2). In this conformer the conformational type Y is retained at $C_{(3)}$ and $C_{(5)}$.

Of the two minor conformations, one contains a cis-amide grouping whereas the other one, characterized by an unusually high wavenumber $v(N\text{---}H)_{free}$, has a $trans$-amide arrangement. A similar shift to higher wavenumbers was observed in acetanilides with bulky $ortho$-substituents[37,38] and in sterically hindered alcohols[39]. We assume that this phenomenon indicates such a conformation of the ten-membered
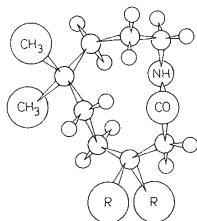

FIG. 3

The Assumed Most Favourable Conformation of IIc (R=H) and of IIe (R=CH₃)

Partial conformation A of the N—H bond. The N—H bond sticks out below, the C=O bond above the projection plane.
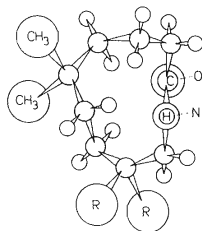

FIG. 4

The Assumed Most Favourable Conformation of IId (R=H) and One of the Conformations with $trans$-Amide Group of IIf (R=CH₃), $v(N\text{---}H)$ 3461·7 cm⁻¹

Partial conformation D of the N—H bond. The N—H bond sticks out above, the C=O bond below the projection plane.

ring in which one of the non-vicinal hydrogen atoms is close to the N—H bond, causing thus its steric compression.

The preferred conformation of cyclodecane ring ("boat-chair-boat") is fixed by introduction of two pairs of geminal methyl groups on the carbon atoms 5 and 8 (conformational type Y). As a result, the population of the conformer with N—H partial conformation A in 5,5,8,8-tetramethyl-1-aza-2-cyclodecanone (*IIb*) is in-creased (to 74%); in this case it represents only the "boat-chair-boat" conformer (see Fig. 1). The amount of the conformer with partial conformation D of the N—H bond is decreased (to 20%). Under assumption of a fixed geometry in the vicinity of geminally substituted atoms $C_{(5)}$ and $C_{(8)}$, the conformer with the partial conforma-tion D can be derived only by rotation of the amide group 180° around the bonds C_α—CO and NH—C_ω. The third conformer with transannular interactions with C—H, characterized by the high wavenumber v(N—H) in the spectrum of *IIa*, is evidently absent in *IIb*, since in its spectrum even "half-cage" bands are not detect-able, in contrast to all other compounds with 1-aza-2-cyclodecanone ring. On the whole, we may suppose that the "boat-chair-boat" conformation of the ten-membered lactam ring is not very advantageous. Even the optimum conformation holding substitution

TABLE II
Wavenumbers (cm^{-1}) of Some Vibrational Bands in the Spectra of Lactams in Nujol

Compound	Region of v(N—H)[a]		Region of amide-I band[a]		Region of *trans*-amide bands[b]	
					II	III
Ia	3 300 s	3 080 w	1 628 s		1 546	1 288
IIa	3 305 s	3 095 w	1 632 s,	1 605 vw	1 550	1 288
IIb	3 270 s	3 085 w	1 632 s,	1 605 vw	1 553	1 298
IIc	3 280 s	3 090 w	1 635 s,	1 609 vw	1 568	1 240
IId	3 280 s	3 090 w	1 635 s,	1 608 vw	1 555	1 219
IIe	3 302 s, 3 200 vw,	3 092 w	1 635 s,	1 609 vw	1 552	1 259, 1 269
IIf	3 319 s, 3 200 w,	3 080 w	1 650 vw, 1 635 s 1 605 vw		1 552	1 280
IIIa	3 300 s	3 080 w	1 638 s		1 578	1 280
IIIb	3 280 s	3 080 w	1 642 s		1 542	1 225
IIIc	3 280 sh, 3 200 s,	3 070 w	1 655 s		—	—

[a] s strong, w weak, vw very weak, sh shoulder; [b] wavenumber of the strongest band in the *trans*-amide-III region.

in the compound *IIb* did not completely eliminate minor conformations of other types and therefore a significant population of "boat-chair-boat" conformations in the nonsubstituted lactam *IIa* is even less probable.

In 1-aza-2-cyclodecanones *IIc—IIf*, in which the pairs of geminal methyl groups are placed at other ring atoms, the same type of conformations as in *IIa* and *IIb* cannot be retained because at least one of the methyl groups would occupy an intraannular position. The probable conformations can again be derived under the assumption of a fixed geometry at the substitution sites. The conformations derived in this manner have the C=O and N—H groups interchanged under retention of the geometry of the hydrocarbon part of the molecule (see Fig. 3 and 4). Each of them can then give rise to another conformer (less stable) by turning the amide group 180° around the bonds C_α—CO and NH—C_ω; this conformer differs from the original one by partial conformation of the N—H bond (*A* and *D*, respectively; see Fig. 5 and 6). If the N—H group and the geminal methyl groups are in relative positions 1 and 7, the partial conformation *A* is preferred (the case of the 7,7-dimethyl derivative *IIc*, see Fig. 3). If the positions of the C=O and N—H groups are interchanged, the partial conformation *D* is preferred (the case of the 6,6-dimethyl derivative *IId*, see Fig. 4). In this compound the conformer with the partial conformation *A* is highly strained and in the conformational equilibrium it is replaced by the conformer with a *cis*-amide group (the population of which rises to 22%). The cause of the instability of the conformer with the partial conformation *A* in *IId* (Fig. 5) must be seen in the interaction of the hydrogens at $C_{(7)}$ with the carbonyl oxygen. The same interaction takes place also in the case of the compound *IIc* (Fig. 6) in conformer with
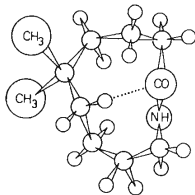

FIG. 5

The Assumed Less Favourable Conformer of *IId* with *trans*-Amide Group and Partial Conformation *A* of the N—H Bond

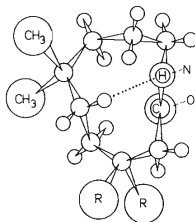The N—H bond sticks out below, the C=O bond above the projection plane.

FIG. 6

The Assumed Less Advantageous Conformation of *IIc* (R=H) and of *IIe* (R=CH₃) with *trans*-Amide Group and Partial Conformation *D* of the N—H Bond

The N—H bond sticks out above, the C=O bond below the projection plane.

the partial conformation D where higher wavenumber of the band $\nu(N\!-\!H)_{free}$ indicates a steric interaction between the hydrogens at $C_{(6)}$ and the N—H group. Of course, this interaction is not so great as is the interaction $C_{(7)}\!-\!H$ with the carbonyl oxygen and therefore the population of the corresponding conformer does not decrease extremely.

The conformer population in 4,4,7,7-tetramethyl-1-aza-2-cyclodecanone (IIe) differs only insignificantly from the population in the 7,7-dimethyl derivative IIc. The introduction of further two geminal methyls did not apparently affect the conformational situation even though all the three conformers coming into consideration (for conformers with *trans*-amide group see Fig. 3 and Fig. 6 with geminal methyl groups on $C_{(4)}$) are energetically considerably demanding. In *trans*-amide conformers, one of the methyls occupies a not completely extraannular position (*cf.* a similar case of 1,1,5,5-tetramethylcyclodecane-8-carboxylic acid[20]), the *cis*-amide conformer, as seen on models, has a 1,3-interaction between the carbonyl oxygen and one of the methyl groups. In spite of this, certain tendency to increase the population of the *cis*-amide conformer can be observed. This tendency is very significant in the 6,6,9,9-tetramethyl derivative IIf, as it could have been anticipated also on the basis of the situation in the 6,6-dimethyl derivative IId. Similarly to the compound IId, the population of conformer with partial conformation A in the compound IIf is very limited (this conformation was not detected at all). The population of conformer with partial conformation D is, however, also appreciably decreased and two additional bands occurred, one of which indicates the presence of a conformer with steric interaction of the NH bond with a non-neighbouring C—H bond.

We assume that the two conformers of IIf with partial conformation D differ in the energetic demands of the geminal methyl groups in particular positions. In one of these conformations, methyls on $C_{(6)}$ occupy pure extraannular position whereas a rigorously extraannular position on $C_{(9)}$ is not available. The geometry
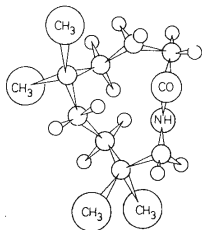

Fig. 7

The Assumed Conformation of IIf Containing *trans*-Amide Group and Partial Conformation D of the N—H Bond ($\nu(N\!-\!H)$ 3453·9 cm^{-1})

The N—H bond sticks out below, the C=O bond above the projection plane.

of this conformer is analogous to the geometry of the compound *IId* (*cf.* Fig. 4 substituted with further two geminal methyls at $C_{(9)}$) and one of the methyls at $C_{(9)}$ interacts with the N—H bond: this results in an increase of the wavenumber ν(N—H). In the other of these conformations the methyls on $C_{(9)}$ occupy a purely extraannular position and therefore they do not interact with the N—H bond. The geometry of this conformer differs considerably from the previous one and the amide group is turned by an angle of 180° (see Fig. 7).

The population of the conformer with *cis*-amide group is considerably increased; contrary to *IIe*, the 1,3-interaction between carbonyl oxygen and one of the methyl groups does not occur in this conformer which therefore becomes the principal component of the conformational population in solution. On the other hand, in the crystalline state the compound *IIf* exists predominantly in conformer (conformers) with a *trans*-amide group, even though also here the *cis*-isomer is safely detectable. A similar change of the preferred conformation of the amide group can be observed in the case of 1-aza-2-cyclononanone (*IIIa*) in which only *trans*-isomer was found in the crystalline state (Table II, X-ray determination see[14]).

From the data in Table I it is obvious that in the series of 1-aza-2-cyclodecanones the population of the energetically more demanding *cis*-form increases with increasing steric strain which is given by the specific substitution. In all cases we observed only one stretching vibration band of the N—H bond ascribable to a *cis*-amide. We may therefore assume that the *cis*-amide group in each of compounds *IIa*—*IIf* is present only in a single conformer which is apparently substantially more rigid than the conformers with a *trans*-amide group. The *cis*-amide group can be incorporated without substantial distortion of the geometry into the preferred cyclodecane conformation ("boat-chair-boat") in the positions *Y* and *Z* with the dihedral angle of about 55° (see ref.[40]). Putting a multiple bond into this position leads for lactams *II* to a conformation analogous to the conformation of *cis*-cyclodecene adduct with $AgNO_3$ found by Dunitz[2] by X-ray diffraction. As indicated by the relatively constant ν(N—H) values, this conformation exists probably in all lactams *II*, except for *IIb* where a conformation similar to that of the $AgNO_3$–5,5,8,8-tetramethyl-*cis*-decene[2] is assumed. The increase of the wavenumbers above 3400 cm^{-1} in *IIf* is explained by a steric 1,3-interaction of the N—H bond with methyl group. The presence of a greater amount of a *cis*-form was indicated also by the presence of a second stretching vibration band of C=O (about 1600 cm^{-1}).

Nine-Membered Ring Lactams

In nine-membered ring lactams, the *cis*-amide group becomes the element controlling the spatial arrangement of the molecule in solution. Spectrum of the nonsubstituted 1-aza-2-cyclononanone (*IIIa*) exhibits, besides two *trans*-amide bands, two *cis*-amide bands corresponding to a population greater than 70%. This is the result

of a greater flexibility of nine-membered ring (cf. analogous greater flexibility of cyclononane in comparison with cyclodecane[2]). The wavenumbers of bands, which we have obtained by separation, do not differ substantially from the values observed by Hallam and Jones[13]; these authors ascribe the two bands of lower wavenumber to planar cis-amide groups and the bands of higher wavenumber to non-planar trans-amide groups. Analogously to the lactams II, we ascribe the band at 3463 cm^{-1} to the N—H vibration in the partial conformation A, and the band at 3443 cm^{-1} to the partial conformation D, both conformers having a non-planar amide group. Also the higher wavenumber of the trans-amide band (v(C=O) 1689 cm^{-1}) corresponds to the non-planar arrangement of the trans-amide group. Remarkably, even the cis-amide band has a significantly higher wavenumber (v(C=O) 1670 cm^{-1}) than the corresponding band of the substituted compound IIIb (1660 cm^{-1}), the change of the valence angle of the carbonyl group being probably an important factor. The introduction of geminal methyl groups into the positions 4,4,7,7 (compound IIIb) results in certain destabilization of conformers with cis-amide group (obviously eliminates that one which is characterized by higher wavenumber) favouring trans-amide group with partial conformation D. The destabilization of the conformers with cis-amide group is the result of 1,3-interaction of one of the methyl groups with the carbonyl oxygen, analogously to the case of the compound IIe. Thus, the introduction of substituents manifests itself by a decreased number of conformers — by a greater rigidity of the molecule. This tendency is very marked in 5,5,8,8-tetrasubstituted isomer IIIc which in solution exists exclusively in one conformer with a cis-amide group. The exclusive existence of the cis-amide form is caused by the absence of an interaction between C=O and CH$_3$ groups (in this compound where the positions of C=O and N—H groups are interchanged, the CH$_3$ group interacts with the N—H bond which is indicated by an increase of the wavenumber v(N—H) in comparison with IIIb).

The infrared spectra of the compounds IIIa—IIIc in the crystalline state (Table II) indicate in all cases only one conformation: in compounds IIIa and IIIb a conformation with a trans-amide group, whereas the compound IIIc shows (also in solution) an extraordinary preference for a single cis-amide conformation.

Eleven-Membered Ring Lactam

As expected, 1-aza-2-cycloundecanone (Ia) exists in solution solely in conformations with trans-amide groups. The probable geometry can be derived, analogously to the case of IIa, from the conformation, computed by Bixon and Lifson[36] for cycloundecane, by incorporation of a transoid amide group instead of CH$_2$—CH$_2$ segment with dihedral angle of about 165°. The conformers, derived in this manner, have then the N—H bond in the partial conformation A, or, if we interchange the positions of C=O and N—H groups, in the partial conformation D. The conformation D

is sterically advantageous and the consequent higher population of this conformer is allowed by the greater flexibility of the eleven-membered ring as compared with the ten-membered ring.

Stereochemical Characteristics of the Medium-Ring Lactams

The most important features of the conformers existing in equilibrium mixtures in solutions of medium-ring (9 — 11-membered) lactams can be summarized as follows: *a*) The approximate conformations of the lactams can be derived from the preferred conformations of the corresponding cycloalkanes. *b*) In addition to the conformers with *trans*-amide group, conformers with *cis*-amide group also exist in all lactams, and their population grows by introduction of an internal strain caused by a suitable substitution. *c*) Besides the partial conformation *D* of the N—H bond, the partial conformation *A*, detected in open-chain compounds only in N-methylamides, is regularly present among the conformers with *trans*-amide group.

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Translated by M. Tichý.