

CONFORMATION OF 1-AZA-2-CYCLOALKANONES WITH LARGE RINGS: INFRARED SPECTROSCOPIC STUDY*

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Spectra of unsubstituted lactams with twelve- to fifteen-membered ring and lactams with twelve-membered ring substituted with two pairs of geminal methyl groups have been measured in tetrachloromethane and in nujol suspension. The population of partial conformations on the $\text{NH}-\text{C}_\omega$ bond was determined from the parameters of the stretching vibration bands of free $\text{N}-\text{H}$ groups and possible conformations of the studied lactams are discussed. The unsubstituted twelve-membered ring lactam exists in the equilibrium mixture in conformations typical for medium rings, as well as in conformations common in the acyclic and large-ring compounds.

In the preceding paper we tried to derive possible conformations of a series of lactams with nine- to eleven-membered rings¹. We made use of the previous finding that in secondary amides with *trans*-arrangement of the amide group the wavenumbers of the stretching vibrations of the nonassociated $\text{N}-\text{H}$ bonds can be correlated with torsion angle (partial conformation) about the bond between the amide nitrogen and the neighbouring sp^3 carbon atom². This vibration may be exploited for the determination of local conformation in molecules containing a secondary *trans*-amide group, e.g. in lactams, for the determination of conformation of the ring segment $\text{C}_\alpha-\text{CONH}-\text{C}_\omega-\text{C}_{\omega-1}$. We have now applied this approach to the conformational study of twelve-membered and larger ring lactams. Similarly to the medium-ring lactams, the existing knowledge of the conformation of these compounds in solutions is based mainly on theoretical considerations (see¹). The infrared spectroscopy^{3,4}, as well as the proton magnetic resonance⁵ (N-methyl lactams), has as yet focused the attention first of all to the detection of *trans*-amide form which in lactams with twelve-membered and higher rings is supposed to be the sole arrangement. Therefore, further experimental data can be useful. It was found that in solutions of these lactams two conformers are present which differ in the environment of the $\text{N}-\text{H}$ bond^{3,4}.

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In this communication we studied the infrared spectra of the lactams *I–IV*, particularly in the region of stretching vibrations of the nonassociated N—H bonds. The studied compounds were synthesized in this Institute by Sicher and coworkers in connection with conformational studies of medium rings^{6,7}. In the series of twelve-membered ring lactams, compounds were also available substituted with pairs of geminal methyl groups (*IVb–IVd*) which are known to have a conformation-holding effect^{8–10}. The study of these compounds made the stereochemical interpretation decisively easier.

EXPERIMENTAL

Spectra (solutions) were measured on a Perkin-Elmer 621 instrument with a precision of 0.5 cm^{-1} . Calibration was carried out with gaseous ammonia ($\nu(\text{N—H})$ region) and water vapour (in the $\nu(\text{C=O})$ region). Concentration dependence was determined for each compound^{11,12} in tetrachloromethane, and concentration at which already no association exists was determined. Standard measurements were then carried out at this concentration ($4\text{--}6 \cdot 10^{-4} \text{ M}$) in 10 cm cells, with the spectral slit width 1.5 cm^{-1} . The bands in the region $3200\text{--}3500 \text{ cm}^{-1}$ were separated on an Elliott 503 computer under assumption of Lorentzian (Cauchy) shape of bands. All data concerning bands of free N—H stretching vibrations mentioned in the text were obtained under these conditions. The percentage of individual partial conformations in solution was calculated from the integrated intensities (Table I).

The wavenumbers of the C—H stretching vibrations were taken directly from the spectra, without separation. The $\nu(\text{C=O})$ bands were measured on nonassociated compounds in concentrations $4\text{--}8 \cdot 10^{-4} \text{ M}$ (tetrachloromethane, 1 cm cells) and the wavenumbers were taken directly from the spectra. The spectra of compounds in the crystalline state were measured in nujol suspension (thickness 0.03 mm, KRS-5 cells) in the $230\text{--}4000 \text{ cm}^{-1}$ region; accuracy $\pm 2 \text{ cm}^{-1}$. The wavenumbers of selected bands are listed in Table II.

RESULTS AND DISCUSSION

From the data in Table I it is seen that the main features of spectra of the thirteen-membered ring lactam *IIIa* and of its higher homologues, *IIa* and *Ia*, are almost identical. This is in accord with the behaviour of other homologous series of cyclic compounds, where further enlargement of the ring size beyond the thirteen-membered ring has no appreciable effect on the properties of compounds which approach asymptotically the properties of open-chain derivatives (see^{13,14}). Accordingly, the spectra of the lactams *Ia–IIIa* are similar to the spectrum of acyclic N-octadecyloctadecanamide². On the other hand, lower homologues of the lactam series with an eleven-membered to nine-membered rings exhibit diametrically different spectra¹. The twelve-membered ring homologue *IVa* represents a "transition" between these two groups.

As shown in our previous work¹, stretching vibrations of the free N—H bonds can represent a direct indication of individual conformers in solution. Analysis of the spectra has shown in all cases the presence of several bands ascribable to the men-

TABLE I

Wavenumbers (cm^{-1}) of Vibrations of Important Groups in the Spectra of Nonassociated Lactams, and Population of Partial Conformations *A–D* at the Bond N–C_ω (Scheme 1) in Tetra-chloromethane

Compound	$\nu(\text{C=O})$	$\nu(\text{C–H})^a$	$\nu(\text{N–H})$ (population, %)			
			<i>trans-A</i>	<i>trans-C</i>	<i>trans-D</i>	<i>cis</i>
N-Octadecyl-octanamide ^b	1 683.0	—	—	3 465.3(38)	3 455.3(62)	—
<i>Ia</i>	1 682.0	—	—	3 468.0(38)	3 453.2(62)	—
<i>IIa</i>	1 681.0	—	—	3 468.0(38) ^c	3 455.2(62) ^c	—
<i>IIIa</i>	1 681.2	—	—	3 469.3(38)	3 453.8(62)	—
<i>IVa</i>	1 680.6	3 013	3 474.4(14)	3 465.9(43)	3 454.7(43)	—
<i>IVb</i>	1 680.9	3 025	3 472.8(78)	—	3 454.3(20)	3 396(2)
<i>IVc</i>	1 678.5	3 025	—	—	3 450.5(40)	3 402.7(10)
					3 456.1(50)	—
<i>IVd</i>	1 682.6	3 013	—	—	3 453.1(100)	—

^a "Half-cage" vibrations; ^b ref.²; ^c ref.²⁵ gives wavenumber 3455 and 3469 cm^{-1} .

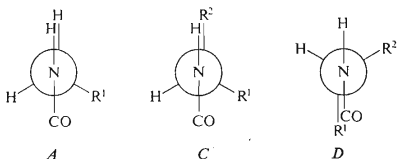
TABLE II

Wavenumbers (cm^{-1}) of Selected Bands in the Spectra of Lactams *I–IV* in Nujol Suspension

Compound	$\nu(\text{N–H})$ region ^a	Amide-I band region ^a	<i>trans</i> -Amide band region ^b	
			II	III
<i>Ia</i>	3 280s, 3 085w	1 637s	1 552	1 285
<i>IIa</i>	3 320s, 3 070w	1 635s, 1 608vw	1 540	1 252
<i>IIIa</i>	3 300s, 3 080w	1 640s	1 550	1 263
<i>IVa</i>	3 310s, 3 075w	1 632s	1 540	1 278
<i>IVb</i>	3 280s, 3 200vw, 3 080w	1 655vw, 1 643vw, 1 632s, 1 605vw	1 555	1 258
<i>IVc</i>	3 300s, 3 200vw, 3 080w	1 633s, 1 608vw	1 550	1 225
<i>IVd</i>	3 290s, 3 085w	1 635s, 1 608vw	1 550	1 282

^a s strong, w weak, vw very weak; ^b wavenumber of the strongest band.

tioned N–H vibration in a *trans*-amide arrangement, and a temperature dependence study, carried out on compound *IVb*, has confirmed that the multiplicity of bands is caused by the plurality of conformations. It is possible to ascribe the individual bands² to the partial conformations on the NH–C_ω bonds (Scheme 1; for description see ref.²) and to calculate their population; the pertinent data are given in Table I.



SCHEME 1

It appears that in large-ring lactams (thirteen- to fifteen-membered) not only the same partial conformations of N—H bonds are present as in the open-chain amide with very long unbranched hydrocarbon chain on both sides of the amide group, but also the population of these conformations is the same. This similarity indicates that large lactam rings exist in conformations identical (at least in the environment of the amide group) with conformations of acyclic compounds. The most populated conformers of the lactams *Ia–IIIa*, which manifest themselves by the partial conformation *D* of the N—H bond, have the torsion angle between the bonds CO—N and $C_\omega-C_{\omega-1}$ 120° and correspond to two parallel hydrocarbon chains connected on the one end by an ethylene unit¹⁴ and on the other one by an amide bond. Conformations of this type, with both links consisting of hydrocarbon chain, were shown

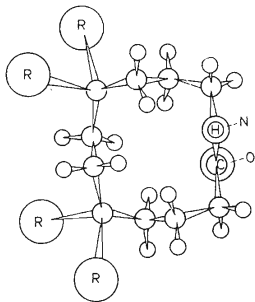


FIG. 1

Probable Conformation with Cyclododecane Skeleton in Lactam *IVa* ($R=H$) (for *IVd* $R=CH_3$)

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

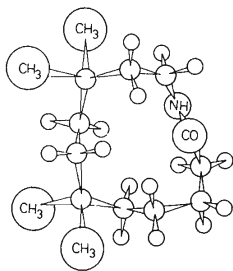


FIG. 2

Assumed Most Favourable Conformation of Lactam *IVb* with *trans*-Amide Group

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

to be present in large hydrocarbon rings by X-ray diffraction^{15,16}. A lesser fraction of the compounds in solution exists in conformers with partial conformation *C* of the N—H bond (with torsion angle between CO—N and C_ω—C_{ω-1} 180°). In conformers of this type the amide group is situated in one of two parallel carbon “zig-zag” chains, linked in the same manner as in the carbocyclic system. The same local arrangement of the amide group was found by X-ray diffraction in crystals of N,N'-hexamethylene-bis-propionamide¹⁷.

The twelve-membered unsubstituted lactam *IVa* can still exist with the partial conformation *C* which is typical for large rings. In comparison with large rings, the population of the partial conformation *D* is lowered and, at the same time, the partial conformation *A* is present which is energetically less advantageous and which is regularly found in strained medium rings¹. The conformer with partial conformation *C* has undoubtedly the same arrangement as have the corresponding conformers of higher homologues. For the analysis of the remaining conformers the existing concepts of cyclododecane conformation may be a useful lead¹⁸⁻²⁰.

Analogously to our previous work¹, conformations were suggested taking into consideration two parts of the lactam ring: the hydrocarbon segment of essentially the same conformation as the corresponding cycloalkane, and the amide part, C_α—CO—NH—C_ω—C_{ω-1}, in a conformation which allows bringing of the terminal atoms of the hydrocarbon segment together (this conformation is detected as the partial conformation on the NH—C_ω bond *A*, *C* or *D*).

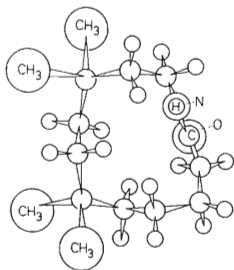


FIG. 3

Assumed Less Favourable Conformation of Lactam *IVb* with *trans*-Amide Group

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

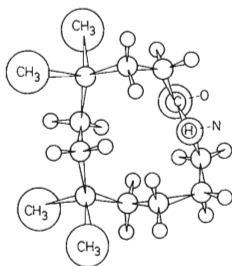


FIG. 4

Assumed Conformation of Lactam *IVc* with *trans*-Amide Group

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

The preferred conformation of cyclododecane, as known from X-ray studies¹⁹ as well as from calculations^{18,20}, consists of carbon atoms of the type Y and Z (Scheme 2, see⁷). This conformation enables incorporation of a *trans*-amide group



SCHEME 2

instead of two neighbouring carbon atoms of the conformational type Z with a torsion angle 160° about the connecting bond¹⁹. The incorporation of *trans*-amide group leaves intact the four atoms of the conformational type Y in positions 3, 6, 9 and 12, and as a result the N—H bond exists in the partial conformation A (Fig. 1). However, the resulting conformer is present in solution to the extent of at most 14% and thus it does not, under given conditions, represent the most favourable conformation. Its existence is rather a certain compromise between the tendency of the molecule to retain the largest possible hydrocarbon part in an optimum cyclododecane conformation and the thermodynamic disadvantage of partial conformation A. The conformer with partial conformation D may be derived from the same conformation by rotation of the amide group around the bonds C_α —CO and NH— C_ω by 180° . Of course, it could also indicate the presence of a conformer of the type analogous to that discussed in connection with lactams Ia—IIIa. We can neither prefer one of the two alternatives, nor exclude a simultaneous existence of both of them.

A feature of 1-aza-2-cyclododecanone (IVa), which also reminds of the medium rings, is the presence of a weak band at 3013 cm^{-1} . Since deuteration of the N—H bond does not change position of this band, we suppose it to be a C—H stretching vibration the wavenumber of which is increased as a result of a very short distance between two opposite C—H bonds. We have observed similar bands practically in all medium-ring lactams¹ and they were described already earlier in the spectra of saturated polycyclic hydrocarbons in which for steric reasons a mutual compression of C—H bonds occurs^{21,22}.

A lactam in which a substitution with two pairs of geminal methyl groups in positions 6 and 9 could fix the geometry of the preferred cyclododecane conformation according to Fig. 1 is 6,6,9,9-tetramethyl-1-aza-2-cyclododecanone (IVd). Surprisingly, in this compound we observed only a single band, corresponding to partial conformation D on the N—H bond. The disappearance of the band, corresponding to the partial conformation C, as well as the presence of the band of the increased C—H stretching vibration shows that the medium-ring character of the compound

IVd, as compared with the unsubstituted compound *IVa*, is really accentuated. As far as the partial conformation in the environment of the N—H bond is concerned¹, the situation here is reverse to the pair of analogous compounds with ten-membered ring. In the unsubstituted 1-aza-2-cyclododecanone an appreciable population of the partial conformation *A* (more than 50%) has been found¹, whereas in the lactam *IVa* the concentration of this conformation is only 14%. Substitution with pairs of geminal methyl groups in the corresponding positions (positions 5,5,8,8 in ten-membered and 6,6,9,9 in twelve-membered ring) leads in the case of 1-aza-2-cyclododecanone to a further increase of the population of the conformer *A* (apparently favourable for the given ring size) to 74% at the expenses of the partial conformation *D*, whereas in 1-aza-2-cyclododecanone this substitution results in a further decrease (absence) of the conformation *A* (in the given ring size apparently unfavourable). We may then assume that the conformer in which the compound *IVd* is exclusively present has the carbon chain in the cyclododecane arrangement similar to that in compound *IVa* but the amide group is rotated by a 180° angle (as compared with Fig. 1).

A *trans*-amide group, however, cannot be incorporated into the preferred cyclododecane conformation in the sense of Fig. 1 either in the case of 7,7,10,10-tetramethyl-1-aza-2-cyclododecanone (*IVb*) or in the 5,5,8,8-isomer *IVc* because all the methyls could not occupy an extraannular position. In spite of this we may anticipate that, in the region of substitution, even in the most advantageous conformations of

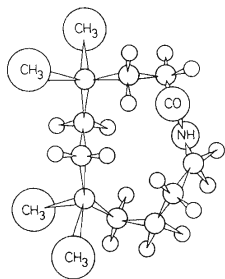


FIG. 5

The Second Possible Conformation of Lactam *IVc* with *trans*-Amide Group

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

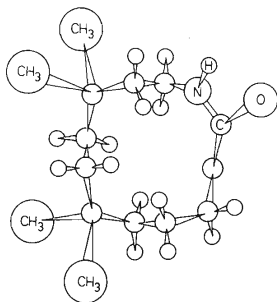


FIG. 6

The Assumed Conformation of Lactam *IVb* with *cis*-Amide Group

For lactam *IVc* the same conformation with exchanged positions of the N—H and C=O groups.

compounds *IVb* and *IVc* the sequence of carbon atoms of certain conformational types typical for the preferred cyclododecane conformation will be preserved. Naturally, the mutual 1,4-position of the pairs of geminal methyl groups does fix not only the cyclododecane conformation but also the preferred cyclododecane conformation ("boat-chair-boat", see²³), since the part determined by the sequence of carbon atoms of the conformational types $Y-Z-Z-Y$, forced by substitution, is common for the preferred conformations of both cycloalkanes.

An information about the geometry of the lactam *IVb* may be gained by comparison of its spectra in the $\nu(\text{N-H})$ region with the spectra of 5,5,8,8-tetramethyl-1-aza-2-cyclodecanone (*V*) where we have found¹ 74% of the partial conformation *A*, 25% of the partial conformation *D* and 1% of a *cis*-conformation. The population of partial conformations of the N-H bonds in compounds *IVb* and *V* is practically identical and therefore we may assume in both compounds substantially the same geometry in the neighbourhood of the N-H group, *i.e.* in positions 1,7,8,9,10,11 and 12 in *IVb* and in positions 1,5,6,7,8,9 and 10 in *V*, for both main conformations present in the equilibrium. If we accept the assumption that in lactam *V* the conformer, characterized by the N-H bond in the partial conformation *A*, exists in the preferred cyclododecane conformation "boat-chair-boat"²³ we may ascribe the conformational types $Y-W-Y-Z-Z-Y$ to the sequence of the carbon atoms 5-12 also in the conformer of *IVb* which has the partial conformation *A* of the N-H bond. The remaining part of the molecule, represented by carbons 3,4,5 and 6, can retain the geometry of the cyclododecane conformation (Fig. 2). The spatial arrangement of the conformer corresponding to the partial conformation *D* in *IVb* arises then by a mere rotation of the amide group around the bonds $\text{C}_\alpha-\text{CO}$ and $\text{NH}-\text{C}_\omega$ by a 180° angle (Fig. 3), similarly to the lactam *V* (see¹).

In lactam *IVc*, differing from lactam *IVb* only in the interchanged position of C=O and N-H groups, the partial conformation *A* is detectable not at all; on the other hand two distinct bands were detected, ascribable to partial conformation *D*. One of them can be derived from the arrangement depicted in Fig. 2 (for *IVb*) by mutual exchange of C=O and N-H groups (resulting in the partial conformation *D* of the N-H bond). This is a conformer with a maximum possible retention of cyclododecane geometry (Fig. 4). The second conformer could have a changed position of carbons 10, 11 and 12 and the amide bond rotated by 180°, as compared with the first conformer (Fig. 5).

In solutions of both tetramethyl derivatives *IVb* and *IVc*, conformers having *cis*-amide groups are present, even though in minor quantity. Their spatial arrangement can be derived directly from the preferred cyclododecane conformation by putting the amide group instead of carbons of the conformational type *Y* and *Z* (with a torsion angle 70°, see¹⁹). The introduction of a *cis*-amide group distorts the conformation as a whole only very little. The derived spatial arrangement (Fig. 6)

is analogous to that derived by Sicher and collaborators for 5,5,8,8-tetramethylcyclododecene²⁴.*

Lactams with twelve-membered ring exhibit thus very expressively the following characteristic features of the medium ring geometry which are accentuated by a suitable substitution: the presence of *cis*-conformers, the presence of conformers with partial conformation *A* of the N—H bond, and a mutual compression of C—H bonds detectable by an increased wavenumber of stretching vibration bands. In comparison with lactams with smaller number of atoms in the ring, the twelve-membered lactam exhibits a greater mobility which allows it to adopt also conformations other than typical for medium rings.

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* In the paper²⁴ the orientation of carbons 11 and 12 in this conformer of *cis*-5,5,8,8-tetramethylcyclododecene has been erroneously reversed.