^{1}H Nuclear Magnetic Resonance Study of High-pressure Effects on *cis–trans* Interconversion of *N*-Methyl-lactams

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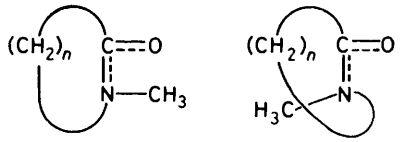
An increase in pressure has been found to provide a shift in the conformational equilibrium toward a higher *s-cis* population for 15-, 17-, and 20-membered-ring lactams, while a slight decrease in the *s-cis* population upon increase in pressure has been observed for an 11-membered-ring lactam. The results are interpreted in terms of the difference in the molecular shape and polarity of *s-cis*- and *s-trans*-isomers.

The structure and thermodynamic properties of *N*-methyl-lactams have been extensively studied at atmospheric pressure,[1-3] with the solvent and the temperature as the variables. As is well known, hindered rotation about the carbonyl carbon–nitrogen bond is shown by a doubling of the *N*-methyl resonance in the n.m.r.[1] The assignment of the absorptions corresponding to the *s-cis*- and *s-trans*-conformations (I) and (II), respectively, has been made on the basis of aromatic solvent-induced chemical shifts.[3] To our knowledge, however, no n.m.r. studies of *N*-methyl-lactams at high pressure have so far been reported. As expected, there are sharp contrasts in the shape and polarity of the molecule between the two conformers (I) and (II). This may give rise to a difference in the partial molar volume, possibly causing a displacement of the equilibrium with the application of hydrostatic pressure. In general, an increase in pressure displaces an equilibrium in the direction reducing the partial molar volume.

The present study focuses on the effect of increased pressure on the equilibrium (I) ⇌ (II) in an attempt to provide a better understanding of the volume profile of these conformers. In variable-pressure experiments, using a simplified version [4] of high-pressure, high-resolution n.m.r. techniques,[5,6] samples of each *N*-methyl-lactam were examined in purified chloroform in 10 mol % concentration. This represents the effective limit of sensitivity of the spectrometer in gaining a sufficient signal to noise ratio for the measurement of the equilibrium constants in our high-pressure cell. The following criteria governed our choice of solvent. (1) It should remain a liquid at high pressure and room temperature and give sufficient solubility to the lactams. (2) As will be shown later, the pressure effect on the equilibrium is very small so that the precise measurement of signal intensity was of primary importance. Chloroform meets these requirements. It gives, besides the resonances of the lactam, only one sharp resonance line, which can be used as a lock signal. This enabled us to conduct the experiment with an efficient field stabilization effected by the internal lock technique. Furthermore, it provided a sufficiently large chemical shift separation between the two peaks of the *N*-methyl resonance and thus facilitated the precise measurement of the signal intensity.



(I) *s-cis* (II) *s-trans*

Experimental

N-Methyl-lactams were prepared by *N*-methylation [7] of the corresponding lactams. The lactams were prepared from the corresponding ketones by the Schmidt reaction [8] (for n = 13, 15, and 18) or by Beckmann rearrangement [9] of their oximes (for n = 7 and 9). Chloroform was washed with sulphuric acid, dilute sodium carbonate solution, and water, dried ($CaCl_2$), distilled in a 30 cm Widmer column, and stored in a refrigerator. Just before use, it was passed through a column of neutral alumina. The sample solution was dried over anhydrous magnesium sulphate and then introduced into a high-pressure cell as shown in Figure 1(i). The cell with i.d. ≒ 1.5 mm, o.d. ≒ 6.0 mm, and length (shoulder to shoulder) 90—110 mm was made by heat-drawing a thoroughly cleaned Pyrex tube and was wound with fishing line. The high-pressure technique was the same as that described previously [4] except for some minor improvements. For example, instead of a mercury layer separator which was used to partition the inside of the cell, a modified free piston composed of a glass rod, PTFE rings, and mercury was employed [Figure 1(ii)]. This composite free piston proved to function well as an efficient separator. The high-pressure cell was put in a safety jacket [4a] fitted with a commercial spinner rotor. The assembly was settled in a standard high-resolution n.m.r. probe, equipped with a variable-temperature controller. High pressure was generated by thermal expansion of the pressure indicator (phenylacetylene), which was introduced into the cell at low temperature and was sealed in it. The estimation of the inner pressure was achieved by measurement of the ethynyl proton chemical shift of phenylacetylene whose pressure dependence was thoroughly investigated. The precision of the estimated pressure is ±30—50 bar. Prior to a measurement at a fixed pressure, the temperature was directly read in a thermometer held in the safety jacket, which was settled and spun in the n.m.r. probe. Thus the temperature of the sample under the n.m.r. conditions was estimated to be maintained at 35.0 ± 0.2 °C throughout the experiment. A high-pressure ^{1}H n.m.r. experiment with sample spinning was conducted on a JEOL PS-100 high-resolution spectrometer operating at 100 MHz. Continuous-wave operation was used, while the field control was effected by means of the one sample system (internal) n.m.r. lock. A linear sweep rate of 27 Hz/50 s in the upfield direction and a low amplitude of the radio frequency field were used to record the absorption spectra. At least 15 measurements were made at a fixed pressure. With the internal lock field stabilization, the reproducibility of the equilibrium constant was in general ±0.007.

Results and Discussion

The equilibrium constant K = [*s-trans*]/[*s-cis*] was obtained from the area under the *N*-methyl signals of the *s-trans*- and *s-cis*-conformers. Results at atmospheric pressure in

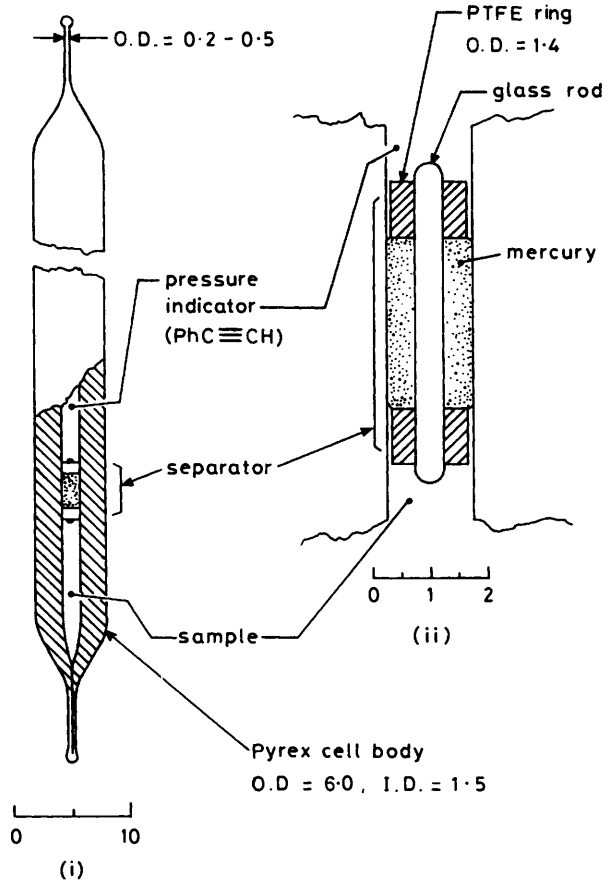


Figure 1. Rotatable high-pressure partition cell (i) with a composite-type separator (ii). Lengths are in mm

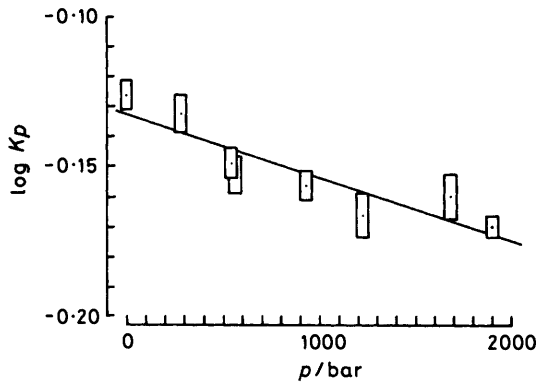
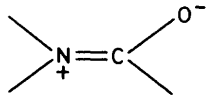


Figure 2. Pressure effect on the *cis–trans* equilibrium of *N*-methyl-14-tetradecanelactam, 10 mol % in chloroform, at 35 °C



(III)

carbon tetrachloride and chloroform solution are presented in the Table. For $n = 7$, 9, and 13, an increase in K with increasing ring size was observed, which is in qualitative agreement with reported results.[1-3] In going from $n = 13$ to 18, however, K decreases. This is contrary to the prediction in the literature.[3] Present observations therefore throw doubt, so far as the lactams with $n \geq 13$ are concerned, on the validity of the assumption that as the ring size is increased, liberation of the strain present in the ring takes place and the *s-trans* conformation becomes more stable.[3] An investigation to settle this matter is required.

We now turn to the behaviour of the lactams under pressure. As an example of the high-pressure study of the equilibrium in chloroform, Figure 2 shows the pressure dependence of K for *N*-methyl-14-tetradecanelactam ($n = 13$). In this case, K is evidently depressed by the application of hydrostatic pressure. The data can be fitted to the well known equation (1) where ΔV represents the volume change $\Delta V \equiv$

$$\Delta V = -\frac{RT}{P - P_0} \ln(K_p/K_{p_0}) \qquad (1)$$

$V(s\text{-}trans) - V(s\text{-}cis)$. The linear approximation as shown in Figure 2 gives ΔV +1.2 cm^3 mol^{-1}, which demonstrates that the partial molar volume of the *s-trans* isomer is indeed larger than that of the *s-cis*-form. The results are in the Table. In summary, an increase in the partial molar volume in the *s-cis* to *s-trans* conversion (in other words, a shift in the equilibrium towards the *s-cis*-isomer upon increase in pressure) is noted for $n = 13$, 15, and 18 while a slight reduction in the partial molar volume is observed for $n = 9$.

It can reasonably be expected that there are considerable contrasts in molecular characteristics between two isomers, in terms of which the observed difference in the partial molar volume (volume change ΔV) should be accounted for. In general, two kinds of main contribution are believed to play an important role in determining the volume change, (1) the difference in the intermolecular packing efficiency of the two isomers in a solution; and (2) the difference in the volume of polar solvation which is ascribed to intermolecular hydrogen bonding and to the electrostatic interaction of the solute dipole with a dielectric constant that represents the solvent.

Referring to the known conformation of the series of medium-ring lactams, which has been determined from *X*-ray crystallographic data,[10] and also from an examination of a molecular model, one can form some estimate of the major difference in the shape of the molecule between *s-cis*- and *s-trans*-*N*-methyl-lactams. In order to accommodate the ring strain, the amide group in the *s-trans*-isomer is considered to be twisted markedly out of planarity.[10] On these same grounds, it is also conceivable that the amide plane in the *s-trans*-isomer is virtually normal to a plane consisting of a methylene linkage.[11] This leads to a non-planar molecular shape. These geometrical features are thought to play an important role in influencing the solvation mode which must be reflected in the partial molar volume. First, the twisting of the amide group about the carbonyl carbon–nitrogen bond unquestionably reduces the contribution of a polar resonance structure (III). This weakens the polar solvation interaction (*i.e.*, the electrostriction) [12] and gives rise to a larger molar volume. Secondly, for purely geometrical reasons, a non-planar molecular shape is considered to be unfavourable to the efficient packing with the surrounding solvent molecules. This again leads to a larger molar volume. The latter concept is in accord with our recent finding on the behaviour of the biphenyl molecule under pressure,[13] where the twisted conformation was shown to have a larger molar volume than the planar one. For the *s-cis*-isomer, the situation would be reversed; consequently one derives a volume profile which is opposite to the *s-trans*-isomer. The nearly planar shape of the *s-cis*-molecule would favour tight packing with the solvent molecules, which, with

Table. *N*-Methyl proton chemical shifts δ, equilibrium constants *K*, and volume changes ΔV for *N*-methyl-lactams (I) ⇌ (II) at 35 °C

		δ,[a] 1 mol % in CCl_4		$K = [(II)]/[(I)]$		ΔV/cm³ mol⁻¹
n	B.p. (°C/mmHg)	(I)	(II)	1 mol % in CCl_4 [b]	10 mol % in $HCCl_3$ [c]	10 mol % in $HCCl_3$
7	108—110/4	2.76		0.00	0.000	
9	124—127/6	2.82	3.06	0.70	0.546	−0.6 ± 0.2
13	166—168/0.5	2.83	2.95	1.2	0.749	+1.2 ± 0.2
15	185—187/0.5	2.83	2.95	0.95	0.552	+1.6 ± 0.2
18 [d]	204—206/0.5	2.83	2.94	0.85	0.480	+1.5 ± 0.3

[a] In p.p.m. relative to internal Me_4Si. [b] With external lock field stabilization, standard deviation = ±0.05—0.1. [c] With internal lock field stabilization, standard deviation = ±0.007. [d] Sample temperature under the n.m.r. conditions (29.0 °C) was employed to attain sufficient separation between two peaks of *N*-methyl signal.

efficient solvation exerted by the polar amide group, results in a smaller molar volume.

Recently, Lüdemann and his co-workers have examined the pressure dependence of the rate constant for intramolecular rotation of a series of *NN*-dialkyl amides.[14] The observed activation volumes $\Delta V^{\ddagger} = V$(transition state) − V(ground state) = 5—10 cm³ mol⁻¹ were attributed to the steric requirement of the twisted amide group in the transition state and also, as a secondary contribution, to a reduction of the electrostriction in the transition state. These findings are mainly in support of our interpretation above. It is noted, however, that our ΔV values are considerably smaller than the $\Delta V^{\ddagger}$ values for intramolecular rotation of the dialkyl amide. A partial explanation of this may be sought in the difference in the degree of twist around the carbonyl carbon–nitrogen bond between the *trans*-conformation of the lactam and the transition state of the rotating amide molecule.

Finally, we would like to mention the small negative ΔV for the lactam with $n = 9$, for which at present an unequivocal interpretation cannot be offered. It should be pointed out that this is the smallest lactam which can exist as a mixture of *s-cis*- and *s-trans*-forms. It might be reasonable, therefore, to suppose that its *trans*-isomer has a higher ring strain which has to be liberated through some specific intramolecular distortion mechanism. For instance, it is conceivable that this type of distortion possibly accompanies occupation of a cavity in the lactam ring with an intramolecular carbonyl oxygen atom. This would produce a considerable reduction in molar volume of the *trans*-isomer, leading to the negative ΔV observed.

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