

3167

A nuclear magnetic resonance study of hydrogen bonding of δ -valerolactam

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The association of amide groups of δ -valerolactam through hydrogen bonding has been investigated by means of high resolution nuclear magnetic resonance spectroscopy in CCl_4 and CDCl_3 solutions. Chemical shifts of the NH proton signal were measured over a wide range of temperatures and concentrations. Thermodynamic properties associated with the $\text{N}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bond formation were evaluated from a least squares analysis by a direct search procedure with a digital computer. The obtained enthalpy values for hydrogen bond formation are in general agreement with results obtained by other methods.

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Introduction

The application of nuclear magnetic resonance (n.m.r.) spectroscopy to the study of hydrogen bonding equilibria has been extensive and relatively successful (1-4). Our own interest in interamide interactions (5, 6) has prompted us to investigate the utility of n.m.r. for systems involving $\text{N}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bonding. Many systems involving amide-to-amide hydrogen bonding have been previously investigated by infrared (i.r.) spectroscopy (5-10). The purpose of the present study was to examine a model system which has been thoroughly studied by another technique and thus to obtain some information regarding the applicability of n.m.r. spectroscopy to problems involving amide-to-amide hydrogen bonding.

Accordingly, we have investigated the dimerization of δ -valerolactam through hydrogen bonding in CCl_4 and CDCl_3 at various temperatures. *cis* Amides, such as lactams, are conformationally not as closely related to polypeptide chains as *trans* amides, such as *N*-methylacetamide. However, the *cis* amides do offer some distinct advantages. It has been shown that polymers higher than dimers are not formed in appreciable amounts (5, 8, 9). This simplifies considerably the interpretation of spectroscopic data and facilitates thermodynamic computations. Furthermore, there are indications that thermodynamic parameters, particularly bond-enthalpies, are quite similar for hydrogen bonds between *cis* amides and between *trans* amides, as evidenced by a comparison of work on *N*-methylacetamide (9) and the latest results on lactams (6).

Experimental

δ -Valerolactam, obtained from the Aldrich Chemical Company,¹ was purified by vacuum distillation. It was stored under nitrogen in the dark at less than 10°. Sample preparation was performed in a nitrogen atmosphere. Carbon tetrachloride, Baker-Analyzed, obtained from the J. T. Baker Company, was dried over Linde type 4A molecular sieve. No differences were observed between the NH chemical shifts of lactam in specially dried CCl_4 and in CCl_4 used without further purification. Chloroform-*d*, obtained from NMR Specialties Company, was also dried over Linde type 4A molecular sieve. It was stored in a nitrogen atmosphere in the dark over molecular sieve. Prior to the preparation of each sample the purity and dryness of the chloroform-*d* were determined by careful observation of the near infrared region where OH groups absorb. Samples were prepared gravimetrically.

The n.m.r. spectra of solutions of δ -valerolactam in CCl_4 and CDCl_3 were obtained with a Varian DP-60 and a DA-60 IL spectrometer, respectively. Tetramethylsilane, obtained from NMR Specialties Company, was used as an internal reference. The Varian V-4340 variable temperature apparatus was used with the DP-60. Temperature measurements were made by means of a copper-constantan thermocouple situated just inside the Dewar probe insert in the incoming gas stream. Calibration was performed using a similar thermocouple placed directly in a sample tube at the receiver coil. The Varian V-4343 variable temperature apparatus was used with the DA-60 IL. The Varian charts for the temperature variation of the OH proton resonance of ethylene glycol and of methanol were used to calibrate the apparatus. Accuracy of the temperature measurements was $\pm 1^\circ$.

Each solution of δ -valerolactam in CCl_4 and in CDCl_3 displayed only one proton resonance which could be assigned to the NH proton. The midpoint of the broad NH line was considered as the chemical shift, δ , of the NH resonance. Line positions, observed with

¹Mention of commercial items is for your convenience and does not constitute an endorsement by the U. S. Department of Agriculture over others of a similar nature.

TABLE I
Observed NH chemical shifts for δ -valerolactam in CCl_4 at 33°

Concentration of lactam, (mf)	δ (Hz from TMS)
0.008	475.5
0.009	479.1
0.011	485.1
0.015	487.1
0.018	488.7
0.020	488.9
0.025	491.3
0.030	493.4
0.035	494.5
0.040	495.8
0.045	497.0
0.050	497.7
0.055	497.9
0.060	498.9
0.070	498.7
0.080	499.0
0.090*	498.5
0.100	497.8
0.193	495.0
0.352	491.3
0.478	490.8
0.597	489.5
0.700	489.2
0.798	488.9

*Points at this and higher concentrations were not used in the thermodynamic calculations.

TABLE II
Observed NH chemical shifts for δ -valerolactam in CCl_4

Concentration of lactam, (mf)	δ (Hz from TMS)		
	Temperature 5°	Temperature -10°	Temperature -20°
0.002	485.4	506.5	518.7
0.004	499.1	515.3	523.5
0.006	503.5	517.8	527.5
0.008	509.5	523.0	528.9
0.010	511.4	523.4	530.2
0.020	515.0	525.5	531.0
0.030	515.8	525.5	531.6
0.040	517.3	526.0*	531.1*
0.050	517.9	525.6	530.6
0.070	518.1*	525.3	530.0
0.085	516.5	525.3	529.3
0.100	515.8	523.1	527.0
0.150	514.0	521.4	526.3
0.200	512.0	519.0	522.9

*Points at this and higher concentrations were not used in the thermodynamic calculations.

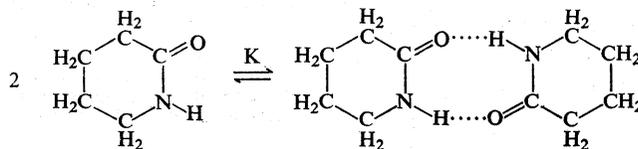
the DP-60, were determined by interpolation between calibration side bands. Line positions, observed with the DA-60 IL, were determined by interpolation between two values of the frequency difference of the fixed and swept oscillators. All chemical shifts in Hz downfield from tetramethylsilane are the averages of at least four measurements made with the DA-60 IL with alternate up and downfield sweeps. At least fourteen measurements were made with the DP-60 due to its lesser stability. The least accurate values are precise to within 3 Hz on the basis of 2σ (twice the standard deviation) values. Such error is largely the consequence of the uncertainty of locating the midpoint of the broad NH line, especially for the more dilute solutions. The observed NH chemical shifts are given in Tables I, II, and III.

TABLE III
Observed NH chemical shifts for δ -valerolactam in CDCl_3

Concentration of lactam, (mf)	δ (Hz from TMS)			
	Temperature 33°	Temperature 5°	Temperature -10°	Temperature -20°
0.010	382.0		412.7	
0.020	408.8	439.1	454.0	464.5
0.030	420.7	446.6	464.6	474.7
0.041	426.2	453.0	466.9	477.9
0.052	442.7	467.4	484.4	494.6
0.061	451.0	476.3	492.5	501.1
0.073	444.8	474.6	488.7	497.3
0.083	453.3	480.5	493.2	502.0
0.091	459.5	483.0	495.9	503.3
0.097	458.4		488.3	
0.150	469.6	492.4	504.9	513.1
0.203	476.9	499.5	511.0	517.2
0.255	484.6	505.0	514.9	521.8
0.300	484.7	507.0	517.7	523.3
0.359	488.3	506.0	516.0	522.0
0.408	491.7	509.0	518.8	525.4
0.449	491.9	509.8	518.9	525.1
0.490	494.3	511.5	519.9	525.5

Treatment of Data

Previous careful studies strongly indicate that δ -valerolactam forms only cyclic dimers with two $\text{N}-\text{H}\cdots\text{O}=\text{C}$ hydrogen bonds per dimer (6, 8, 9). If we assume that in dilute solution only hydrogen bonding occurs among lactam molecules to form cyclic dimers and that the solvent does not compete with the solute in the formation of hydrogen bonds, then dimerization can be represented by the simple equilibrium:



The dimerization equilibrium constant in reciprocal mole fraction (mf^{-1}) units is

$$[1] \quad K = \frac{[D]}{[M]_i^2} = \frac{XS}{\left[\frac{(1-X)S}{S(C-2X)}\right]^2} = \frac{X(1-X)}{(C-2X)^2}$$

where C = initial mole fraction of δ -valerolactam in terms of monomer, S = total number of moles in the system in terms of lactam monomer and of solvent, and X = equilibrium number of moles of the dimer divided by S . At equilibrium the total number of moles equals the sum of the moles of lactam monomer, lactam dimer, and solvent.

$$[2] \quad (C - 2X)S + SX + (1 - C)S = S(1 - X)$$

The observed chemical shift, δ , for the NH resonance is expressed as the weighted average of the contributions of the two NH-containing species

$$[3] \quad \delta = \left(\frac{C - 2X}{C}\right)\delta_M + \left(\frac{2X}{C}\right)\delta_D$$

where δ_M = chemical shift of the NH resonance of the lactam monomer and δ_D = chemical shift of the NH resonance of the lactam dimer. The factor 2 results from the presence of two hydrogen bonds in the cyclic dimer. Solving eq. [1] for X , the physically meaningful root is

$$[4] \quad X = \frac{1}{2} \left\{ \frac{(4KC + 1) - (-4KC^2 + 8KC + 1)^{\frac{1}{2}}}{4K + 1} \right\}$$

As shown in Fig. 1, the variation of the NH chemical shift with concentration of lactam in CCl_4 does not increase monotonically but passes through a maximum at approximately 0.04–0.08 mf. Apparently the dimerization equilibrium given above is insufficient to explain all the data. Perhaps at higher concentrations in CCl_4 a different kind of interaction also occurs which influences the NH chemical shift.² It is conceivable

²Yonezawa and Morishima compared the *cis* N -methyl proton chemical shifts of neat N,N' -dimethylformamide, N -methyl- γ -butyrolactam, and N,N' -dimethylacetamide with those of 0.1 mf CCl_4 solutions. In each case they observed an upfield shift for the neat liquid relative to the 0.1 mf CCl_4 solution. This observation has been explained in terms of an intermolecular dipolar interaction (association) between the nitrogen and the oxygen ($\text{N}\cdots\text{O}$) of different molecules (11).

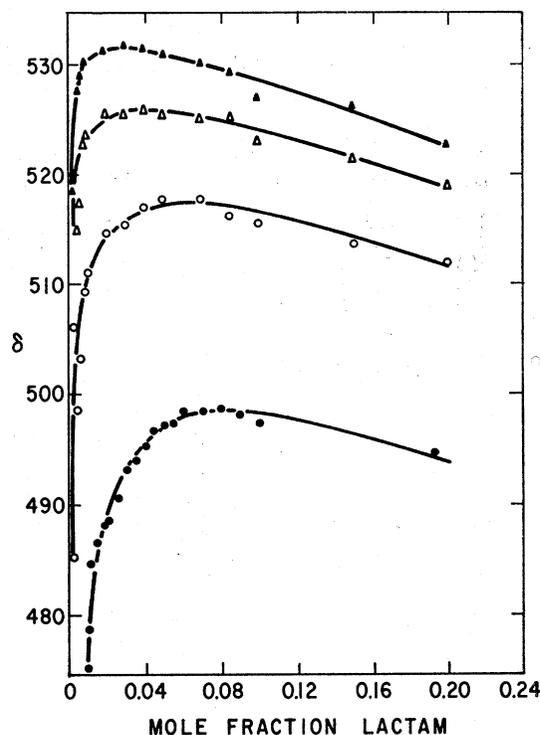


FIG. 1. Variation of δ with concentration in CCl_4 at various temperatures: \blacktriangle , -20° ; \triangle , -10° ; \circ , 5° ; \bullet , 33° .

able that models including other equilibria (e.g., stacking of the lactam rings or hydrogen bonding among higher polymers of lactam) could be devised that would fit the experimental data over a wider range of concentration. However, in view of the increase in the number of adjustable parameters, the results of such treatments admit a variety of interpretations. The important aspect regarding dimerization through hydrogen bonding interaction is the variation of the NH chemical shift with concentration in dilute solution. (The dimerization in CCl_4 is virtually complete at the maxima of the experimental curves, e.g., approximately at 0.07 mf at 33° (6, 7).)

The experimental curves obtained for CDCl_3 solution are given in Fig. 2. Slight solvent-solvent hydrogen bonding is possible, but there is reason to believe that hydrogen bonded solvent aggregates are present in very low concentration (12–14). However, in chloroform solution, solvent to solute hydrogen bonding involving the lactam carbonyl group is appreciable. It has been shown (6, 7, 10) that such a system can be treated on the

TABLE IV
Calculated dimerization equilibrium constants of δ -valerolactam in CCl_4

δ_M^* (Hz)	Temperature 33°		Temperature 5°		Temperature -10°		Temperature -20°	
	δ_D^\dagger (Hz)	K (mf ⁻¹)	δ_D (Hz)	K (mf ⁻¹)	δ_D (Hz)	K (mf ⁻¹)	δ_D (Hz)	K (mf ⁻¹)
400	513.0	447	529.0	1704	535.2	4769	537.6	11983
300	511.6	2032	528.1	6493	534.7	16288	537.5	38498
250	511.3	3252	527.9	10046	534.6	24619	537.4	57389
200	511.2	4757	527.8	14370	534.6	34662	537.4	80051
150	511.1	6547	527.7	19466	534.5	46419	537.4	106461
100	511.0	8622	527.6	25334	534.5	59898	537.3	136649

*Preset values of the monomer shift.

†All δ_D values are calculated values of the dimer shift.

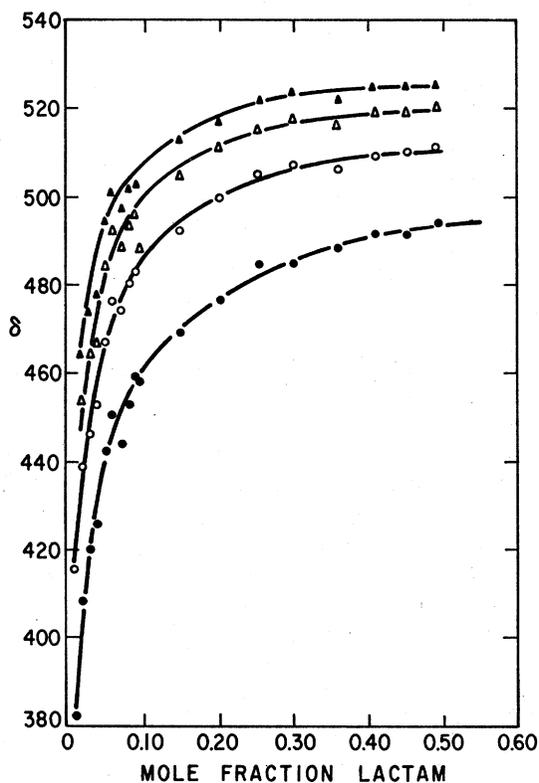


Fig. 2. Variation of δ with concentration in CDCl_3 at various temperatures, \blacktriangle , -20°; \triangle , -10°; \circ , 5°; \bullet , 33°.

assumption that essentially all lactam monomers are specifically solvated. The equilibrium constant and the ΔH value then pertain to the formation of dimers from solvated monomers. The interaction of CDCl_3 with lactam monomer will, in fact, be reflected in the differences in the calculated equilibrium constants and enthalpy values for

the two systems, as described by Klemperer *et al.* (10) and others (6, 7).

Methods of Calculation

The relationship between the NH chemical shift and lactam concentration is a function of three parameters: the chemical shifts of lactam monomer, δ_M , and lactam dimer, δ_D , and the dimerization equilibrium constant, K . If the monomer and dimer shifts are known, then either the observed NH chemical shift at any given concentration or the slope of the NH chemical shift - concentration curve at any given point is sufficient to determine K . The dimer shift can be estimated from the maximum of the curve. If the limiting slope at low concentration is known, δ_M can be determined by extrapolation. As shown in Figs. 1 and 2, the slope of the experimental curves continuously increases as the concentration approaches zero. Consequently, no graphical extrapolation can be attempted with a reasonable degree of accuracy.

In order to carry out a more thorough analysis of the experimental data, a numerical method was used. Arbitrary values of δ_M were chosen, and values of K and δ_D were determined from a least squares analysis by a direct search procedure (15).³ The search procedure involves the independent variation of arbitrary initial values of δ_D and K until the root mean square (r.m.s.) error between the calculated and observed curves reaches a minimum for a given value of δ_M . For the CDCl_3 system all the experimental data points (Table III) were used in the calculation. For the CCl_4 system only those data points

³The computations were carried out on an IBM-1130 computer.

TABLE V
Calculated dimerization equilibrium constants of δ -valerolactam in CDCl_3

δ_M^* (Hz)	Temperature 33°		Temperature 5°		Temperature -10°		Temperature -20°	
	δ_D^\dagger (Hz)	K (mf^{-1})	δ_D (Hz)	K (mf^{-1})	δ_D (Hz)	K (mf^{-1})	δ_D (Hz)	K (mf^{-1})
350	531.0	18	537.6	41	546.6	52	545.8	86
300	521.9	45	534.6	81	534.5	100	544.5	154
250	517.2	85	533.0	134	541.7	166	543.6	242
200	514.5	139	531.9	201	540.5	249	543.1	350
150	512.8	207	531.3	281	539.7	348	542.7	478

*Preset values of the monomer shift.

†All δ_D values are calculated values of the dimer shift.

(see Tables I and II, the Experimental section, and footnote 2) pertinent to the dimerization equilibrium were used. The results are shown in Tables IV and V.

Results and Discussion

All the calculated curves based on preset values of δ_M fit the observed data with a relatively small degree of error (r.m.s. error of 1–2 Hz for CCl_4 and 3–5 Hz for CDCl_3 which are of the same order of magnitude as experimental error). For the lactam- CCl_4 system, only the low concentration portion of the experimental curves was considered, as discussed in previous sections. The observed and some of the calculated curves for the lactam- CDCl_3 system are given in Fig. 3. The calculated dimer shift is nearly independent of the preset monomer shift used in the calculation. The calculated equilibrium constant increases as the preset monomer shift decreases. On this basis, no one value of the monomer shift and the corresponding equilibrium constant can be taken as more realistic than any other.

In general, the information that can be obtained from the chemical shift-concentration curves depends primarily on the value of the equilibrium constant. We have examined the theoretical curves obtained from the treatment given above on the basis of a unit chemical shift difference between the monomer and dimer species. Several values of the equilibrium constant over a wide range were included in the calculations. On this basis certain limitations of the n.m.r. method seem to be indicated. If K is large, the slope at low concentrations is sufficiently steep that no meaningful extrapolation to infinite dilution is possible. On the other hand, if K is very small, the curve is nearly linear; only two of the

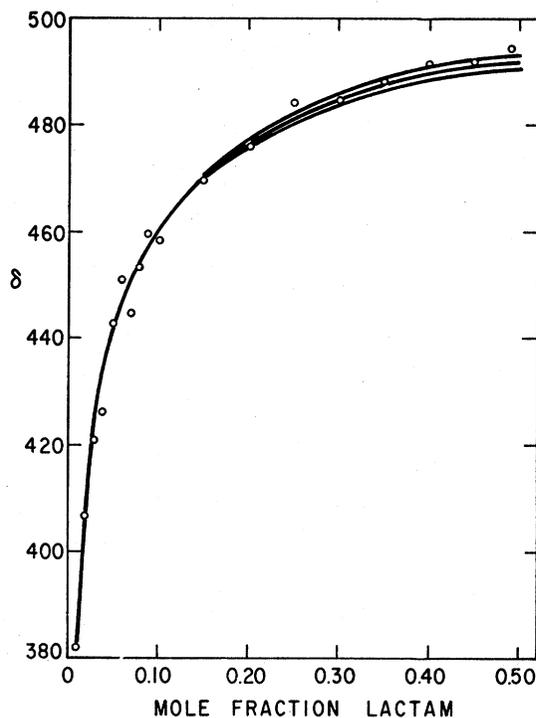


FIG. 3. Comparison of observed and calculated data for lactam in CDCl_3 at 33°. Solid lines are calculated curves for various values of δ_M . Upper curve, $\delta_M = 300$ Hz; middle curve, $\delta_M = 250$ Hz; lower curve, $\delta_M = 200$ Hz.

necessary three parameters can be determined. If K lies in an intermediate range close to unity, the system is amenable to complete analysis. In the lactam systems studied, K lies to the high side of this range.

Even though accurate extrapolation cannot be made, one can set limits to the possible choices of δ_M . The downfield limit is given by the lowest

TABLE VI
Calculated ΔH for the hydrogen bonding
dimerization of δ -valerolactam

In CCl_4		In CDCl_3	
δ_M^* (Hz)	ΔH^\dagger (kcal/mole)	δ_M^* (Hz)	ΔH^\dagger (kcal/mole)
400	-9.43	350	-4.35
300	-8.41	300	-3.43
250	-8.20	250	-2.90
200	-8.06	200	-2.56
150	-7.96	150	-2.22
100	-7.89		

*Preset values of the monomer shift.
†Calculated.

value of the observed shift. The upfield shift can be set by the chemical shift of a nonhydrogen-bonded N—H proton, e.g., that of piperidine monomer (16, 17) at approximately $\tau = 8.9$. This range, in fact, guided the choices for δ_M used in the calculations described above.

Despite the inability to fix precisely the value for K , ΔH can be more closely estimated. With the assumption that δ_M and δ_D are temperature independent, ΔH can be calculated for a given δ_M using the van't Hoff equation with the calculated values for K as given in Tables IV and V. The results are shown in Table VI. Regardless of the appreciable variation of K corresponding to possible choices of δ_M , the calculated values for ΔH fall in a relatively narrow range. Therefore, a reasonable estimate of ΔH can be obtained even though a full analysis of the experimental data cannot be made. The results obtained for ΔH are in essential agreement with those from i.r. measurements as shown in Table VII. Note that the difference in ΔH between the CCl_4 and

TABLE VII
Infrared results for δ -valerolactam*

Temperature (°C)	$K(\text{CCl}_4)$ (mf^{-1})	$K(\text{CHCl}_3)$ (mf^{-1})
25	1182	28.0
40	517	20.9
55	273	16.8
	$\Delta H = -7.1$ kcal/mole	$\Delta H = -3.1$ kcal/mole

*Reference 6.

CDCl_3 systems is ~ 5 kcal/mole. This difference reflects the specific solvation of lactam monomer and amounts to a ΔH of solvation of ~ -2.5 kcal/mole of monomer, close to the value of -2 kcal/mole estimated for CDCl_3 -amide interactions by Klemperer *et al.* (10).

Conclusion

Dimerization equilibria described by equilibrium constants on the order of unity are ideally suited to n.m.r. investigation. For such systems, the chemical shift of both monomer and dimer can be precisely obtained and a value of K readily calculated. For the hydrogen bonding of δ -valerolactam, K is large. Nevertheless, even in this system for which the monomer shift cannot be reasonably estimated, a value for ΔH may still be obtained because of its slow variation with assumed values of the monomer shift.

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