On the Molecular Association in Amides as Revealed by Their Near-Infrared Absorption Spectra.

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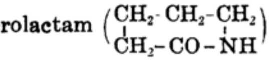
As a part of his investigations on the hydrogen bondings in compounds with the peptide linkage, the present writer made some observations of near-infrared absorption spectra of *N*-methylacetamide and δ-valerolactam, two representatives of compounds with the said linkage, one being of the single chain type and the other of the cyclic type. Some of the results obtained are of interest in relation to the general problems of association in amides. It is the purpose of this paper to give the results of the writer's observations of the above-mentioned two substances, and to present a view as to their molecular configurations, and then to discuss some problems of association in amides.

Experimental.

The infrared absorption in the 2.6~3.6 μ region were measured of *N*-methylacetamide ($CH_3CONHCH_3$) and δ-valerolactam  $\left(\begin{array}{c}CH_2\text{-}CH_2\text{-}CH_2\\ | \qquad\quad |\\ CH_2\text{-}CO\text{-}NH\end{array}\right)$ in liquid state and in carbon tetrachloride solutions.

The optical system of the spectrometer used in the investigation consists of concave mirrors and 60° quartz prism. This was used in conjunction with the thermocouple and galvanometer system. As the source of radiation a tungsten filament lamp in a quartz bulb, running at 80 volts and 1.6 amperes, was used. To determine the wave-lengths of the absorption bands the following standards were used: 2.769 μ band of phenol, 3.233 μ and 3.295 μ bands of benzene, and 3.416 μ and 3.508 μ bands of cyclohexane, in dilute carbon tetrachloride solutions.

The samples of *N*-methylacetamide and δ-valerolactam for this investigation were prepared respectively by K. Mayumi and I. Okano and by K. Hoshino and S. Yumoto, to whom the writer's thanks are due. These were subjected several times to vacuum distillation. The melting points determined with the distilled samples were: 28°C for *N*-methylacetamide and 40°C for δ-valerolactam. Carbon tetrachloride used as the solvent, which was washed with water, dried over phosphorus pentoxide, and distilled, was confirmed to give no absorption band due to impurities in the said region of the spectra.

Results and Their Interpretations.

In Tables 1 and 2 certain results obtained by the present measurements are shown. (Cf. Figs. 1 and 2.)

Table 1. Infrared absorptions in 3 μ region of *N*-methylacetamide.

	States	Temperatures (°C)	Wave-lengths (in μ) of absorption maxima, with molar absorption coefficients in parentheses		
			Free *N-H* band	*N-H* association bands	
	In CCl$_4$ solution				
Concentrations	0.0014 mol/l.	15	2.88 (17)		
	0.0032	15	2.88 (14)	2.97 (9)	
	0.031	13	2.88 (12)	3.00 (33)	3.22 (18)
	,,	40	2.88 (14)	2.97 (15)	
	0.079	16	2.88 (9)	3.03 (35)	3 22 (27)
	,,	39	3.88 (9)	2.99 (25)	3.22 (12)
	Liquid state	30		3.03 (73)	3.22 (54)

Table 2. Infrared absorptions in 3 μ region of δ-valerolactam.

	States	Temperatures (°C)	Wave-lengths (in μ) of absorption maxima, with molar absorption coefficients in parentheses		
			Free *N-H* band	*N-H* association bands	
	In CCl$_4$ solution				
Concentrations	0.0015 mol/l.	15	2.92 (11)	3.11 (41)	3.24 (26)
	,,	50	2.92 (16)	3.11 (18)	3.24 (10)
	0.016	13	2.92 (6)	3.11 (46)	3.24 (38)
	,,	50	2.92 (12)	3.11 (18)	3.24 (12)
	0.023	13	2.92 (4)	3.11 (49)	3.24 (40)
	,,	40	2.92 (7)	3.11 (28)	3.24 (23)
	Liquid state	40		3.09 (55)	3.23 (30)

As is seen from the tables, the absorption intensity for the band at 2.88 μ of *N*-methylacetamide in carbon tetrachloride solution increases with lowering of the concentration of the solution and with rise of its temperatures; while the reverse was observed as to the absorption intensities for the bands at 2.97 ~ 3.03 μ and 3.22 μ. This fact may be explained, as usual, by assigning the band at 2.88 μ to the N-H vibration of the free molecules and the bands at 2.97 ~ 3.03 μ and 3.22 μ to the N-H vibrations of the associated molecules. In the same way, the absorption at 2.92 μ of δ-valerolactam may be assigned to the N-H vibration in the free molecules of δ-valerolactam, and the bands at 3.11 μ and 3.24 μ to the N-H vibrations in its associated molecules. It is thus shown

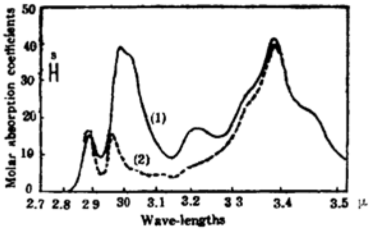


Fig. 1. Absorption curves of *N*-methylacetamide in CCl_4 solution (0.031 mol/l), (1) at 13°C, (2) at 40°C. (s: Slit width)

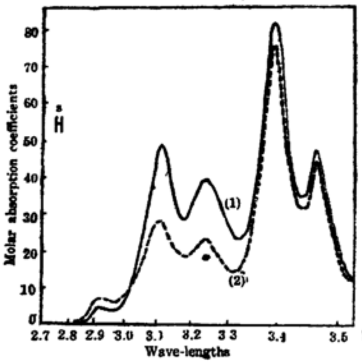


Fig. 2. Absorption curves of δ-valerolactam in CCl_4 solution (0.023 mol/l), (1) at 13°C, (2) at 40°C (s: Slit width)

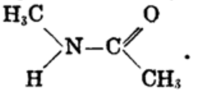
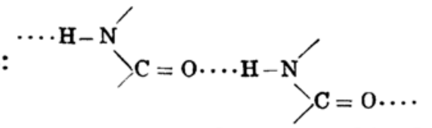
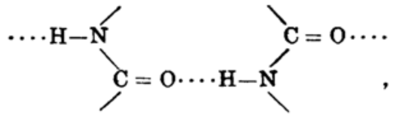
that the molecules of *N*-methylacetamide as well as those of δ-valerolactam associate through their intermolecular N-H····O bondings. There are, however, remarkable differences, as enumerated below, between these two kinds of molecules in the absorption intensities and the positions of the bands in their 3μ region absorption spectra, indicating the difference in their modes of molecular association.

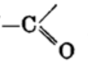
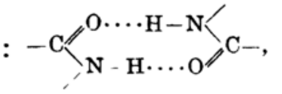
(i) The N-H band (at 2.92μ) of the free molecule of δ-valerolactam is located at a longer wave-length than that (at 2.88μ) of the free molecule of *N*-methylacetamide. This shows that the N-H bonding in the δ-valerolactam molecule is perturbed a little to weaken the bonding, in comparison with that in the *N*-methylacetamide molecule, even in the monomer state—i. e. intramolecular perturbation.

(ii) The tendency of molecular association in carbon tetrachloride solutions is stronger for δ-valerolactam than for *N*-methylacetamide. Thus, even at such a low concentration as 0.0015 mol/l., δ-valerolactam molecules are for a major part in associated state, while at about the same concentration (0.0014 mol/l.), *N*-methylacetamide molecules are in isolated state. In other words, the change in free energy (ΔF) accompanying the dissociation of dimer is much greater for δ-valerolactam than for *N*-methylacetamide.

(iii) With lowering of concentration of the solution or with rise of its temperature, there takes place the shift of the absorption maxima of the N-H association band of *N*-methylacetamide, from 3.03μ to 2.97μ, but no such shift of the absorption maxima of the bands of δ-valerolactam. This fact indicates that there can be only one kind of associated molecules of δ-valerolactam, while there are more than one kind of associated molecules of *N*-methylacetamide, in the respective solutions.

The molecular configurations of *N*-methylacetamide and δ-valerolactam that are consistent with what have been stated above are as follows:

N-Methylacetamide. In the molecule of *N*-methylacetamide, the hydrogen on the nitrogen is *trans*(1) to the oxygen:  $(H_3C)(H)N-C(=O)CH_3$. The associated molecules, which cause the $2.97 \sim 3.03\,\mu$ bands, are chain type polymers:  or , the adjacent molecules being combined through the single $N-H\cdots O$ bonding. On this configuration, polymers of various lengths are possible, in consistence with the indication that there are more than one kind of associated molecules of *N*-methylacetamide.

δ-Valerolactam. In the molecule of δ-valerolactam, the hydrogen on the nitrogen is *cis* to the oxygen:  $(H)N-C(=O)$. The intramolecular perturbation, mentioned in (i), may be attributed to the attraction between these hydrogen and oxygen atoms, viz. the intramolecular hydrogen bonding: $N\text{-}H\cdots O$. The associated molecules, which cause the $3.11\,\mu$ band, are ring dimers: , the two molecules being combined through the double $N-H\cdots O$ bondings. This configuration is consistent with the indication that there is only one kind of associated molecules of δ-valerolactam. Further, intermolecular double bondings in δ-valerolactam, in contrast to the single bonding in *N*-methylacetamide, account for the greater dissociation energy in the latter.

A few words may be added here concerning the $3.22\,\mu$ association band of *N*-methylacetamide. In its pure liquid state, this band is comparable in absorption intensity with the $3.03\,\mu$ band. It is not apparent to the writer, to what this $3.22\,\mu$ band is to be assigned. But, since the Raman spectra(2) in the region of the skeletal frequencies of the *N*-methylacetamide molecule show that in its pure liquid state only one skeletal structure is possible, and moreover since the writer's observation reveals that the molecule of *N*-methylacetamide, is *trans*, this 3.22μ band must be due to something in the associated molecules consisting

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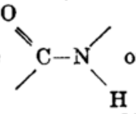
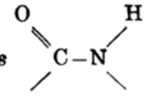
(1) In a molecule with the $-CONH-$ linkage, the $C-N$ bond has some double-bond character, due to resonance, $O=C-NH- \leftrightarrow \overset{-}{O}-C=\overset{+}{N}H-$; and this tends to cause the molecule to take the coplaner configuration, i e. *trans*  or *cis*  configuration.

(2) S. Mizushima, T. Simanouti, S. Nagakura, K. Kuratani, M. Tsuboi, H. Baba and O. Fujioka. (To be published.)

only of *trans* molecules. Buswell and others(3) assigned the 3.22 μ band of monosubstituted amides to the ring dimer structure of their associated molecules, componental monomer of which must be of *cis* form. In the light of what has been just mentioned, this view is not appropriate for the 3.22 μ band of *N*-methylacetamide. More information than we have at present is needed before we can discuss further this question. A fact, perhaps worthy of mention in the present connection, is that neither the Raman line for this band nor the infrared absorption band corresponding to its overtone has ever been observed.(2)

As to the assignment of the 3.24 μ association band of δ-valerolactam too, nothing can be said at present. This, as well as the above, is a question yet to be solved.

Discussion on Some General Problems of Molecular Association in Amides.

Some general problems of association in amides will now be discussed. In this field the studies made by A. M. Buswell and his collaborators(3) (4) are important. Some of their data, along with the present writer's, are given in Table 3. It is chiefly on these data that the following discussion is based.

Table 3.

3μ region infrared absorptions of amides in CCl_4 solution.

	Substances	Wave-lengths of free *N-H* bands (in μ)		Wave-lengths of *N-H* association bands (in μ)		Molar absorption coefficients of *N-H* association bands	Observers
Monosubstituted Amides	*N*-Methyl-acetamide	2.88		$2.97\xrightarrow{(b)}3.03$	3.22	0 at 0.0014 mol/l. 9 (2.97 μ) at 0.0032 mol/l.	M. Tsuboi
	N-Ethyl-acetamide	2.89		$\overset{(a)}{2.97}\xrightarrow{(b)}3.03$	3.22	$6^{(a)}$ (2.97 μ) at 0.002 mol/l.	A.M. Buswell and others(4)
	N-Cyclohexyl-acetamide	2.90		$2.97\xrightarrow{(b)}3.04$	3.23	7 (2.97 μ) at 0.002 mol/l.	A.M. Buswell and others(4)
Unsubstituted Amides	Acetamide	2.83	2.925	3.03	3.145	17 (3.145 μ) at 0.002 mol/l.	A.M. Buswell and others(3) (4)
	Propionamide	2.83	2.925	3.03	3.15	$8^{(a)}$(3.03 μ) $14^{(a)}$(3.15 μ) } at 0.002 mol/l.	A.M. Buswell and others(4)
	n-Valeramide	2.83	2.92	3.03	3.14	19 (3.14 μ) at 0.002 mol/l.	A.M. Buswell and others(3)(4)
	Benzamide	2.83	2.925	3.03	3.15	$11^{(a)}$(3.03 μ) $25^{(a)}$(3.15 μ) } at 0.002 mol/l.	A.M. Buswell and others(4)
	δ-Valerolactam	2.92		3.11	3.24	41 (3.11μ) at 0.0015 mol/l.	M. Tsuboi

(a) Read from Buswell's curves.

(b) The arrow indicates the shifting of the band on raising the concentration of the solution.

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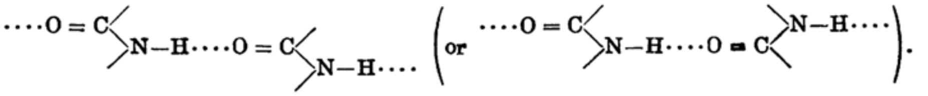
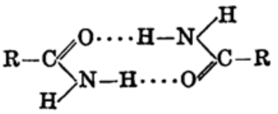
(3) A.M. Buswell, J.R. Dowing and W.H. Rodebush, *J. Am. Chem. Soc.*, **62** (1940), 2759.

(4) A. M. Buswell, W. H. Rodebush, and M.F. Roy, *J. Am. Chem., Soc.*, **60** (1938), 2444.

Structures of Associated Molecules of Amides. *Monosubstituted Amides.* The inspection of Table 3 reveals that *N*-methylacetamide, *N*-ethylacetamide, and *N*-cyclohexylacetamide are closely similar to each other in their 3 μ region absorptions in carbon tetrachloride solution. Thus, they are nearly equal with respect to the wave-lengths of N—H absorption bands of free and associated molecules, with respect to the absorption intensities of association bands, and with respect to the shifting of the 2.97 ~ 3.04 μ band with concentrations of the solutions. These show that *N*-methylacetamide, *N*-ethylacetamide, and *N*-cyclohexylacetamide are alike in the molecular configurations, both in the single and associated states. In general it may be said that: the molecules of the ordinary monosubstituted amides RCONHR′ are of the *trans* form (probably due to the steric repulsion between R and R′ in each molecule), and on association they form chain polymers:

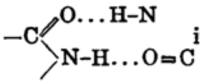


Unsubstituted Amides. Unsubstituted amides show N—H association bands at 3.03 μ and 3.14 ~ 3.15 μ. Of these two bands the former is located near the 2.97 ~ 3.03 μ band of *N*-methylacetamide and the latter near the 3.11 μ band of δ-valerolactam. Moreover, at relatively low concentration (e. g. 0.002 mol/1.) in their carbon tetrachloride solution, the absorption intensity of the 3.14 ~ 3.15 μ band of unsubstituted amides is stronger than that of the 3.03 μ band; likewise the absorption intensity of the 3.11 μ band of δ-valerolactam is stronger than that of the 2.97 μ band of *N*-methylacetamide. These facts show that the molecules $RCONH_2$ associate at first to form ring dimers:

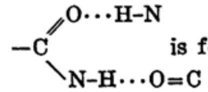


through double N—H····O bondings (the hydrogen here being that one of the two, which is *cis* to the oxygen in each molecule), and then polymers through single N—H····O bonding (the hydrogen here being the other one of the two).

N. B. The absorption band at 3.11~3.15 μ might be due to the configuration



in the ring dimer structure rather than the ring dimer structure itself, for, according to Buswell(3), the 3.14 μ band is given also by the crystal of acetamide, in which the constituent molecules, as may be seen from the X-ray analysis by F. Senti and D. Harker(5), are bonded so that the configuration



is formed but not the ring dimer structure.

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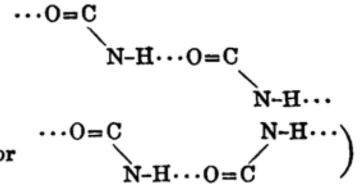
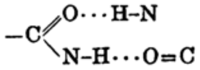
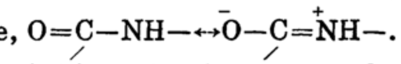
(5) F. Senti and D. Harker, *J. Am. Chem. Soc,*, **62** (1940), 2008.

N-H Stretching Vibrations in the Associated Molecules of Amides. The above conclusion concerning the relation between the frequencies of N—H stretching vibrations in amides and the configurations of their associated molecules may be summed up in Table 4. It is to be noted that the difference in frequencies of N—H stretching vibrations (in corresponding linkages) between $C-CO-NH_2$ and $C-CO-NH-C$ is comparatively small.

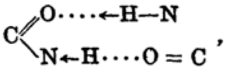
Table 4.

Frequencies of N-H stretching vibrations	$C-CO-NH_2$	$C-CO-NH-C$
(A) in single $N-H\cdots O=C$	——	3360 cm.$^{-1}$ (2.97 μ)
(B) in 	3300 cm.$^{-1}$ (3.03 μ)	3360~3280 cm.$^{-1}$ (2.97~3.04 μ)
(C) in 	3180~3170 cm.$^{-1}$ (3.14~3.15 μ)	3210 cm.$^{-1}$ (3.11 μ)

The fact that the frequencies are lower in (B) than in (A), as shown in Table 4, may be explained as follows: In the molecule of an amide, there is an electric polarity due to resonance,  $O=\underset{/}{C}-NH-\leftrightarrow\overset{-}{O}-\underset{/}{C}=\overset{+}{N}H-$. This polarity must increase, if the oxygen of this molecule accepts the hydrogen (or proton) of another molecule, and accordingly the electronegativity of the nitrogen must increase too. Hence, the $N-H\cdots\cdot O$ bonding must be stronger in the associated molecules of the polymer (B) than in those of the non-ring type dimer (A), and the N—H bond in the former must be weaker than that in the latter. This explains why the frequencies of N—H stretching vibrations is lower in the former than in the latter.

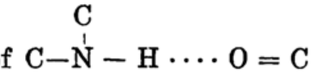
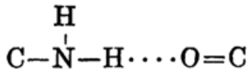
That the frequencies are lower in (C) than in (B) and (A) (Table 4) may be explained as follows: Let the potential energy V of the system (C) be

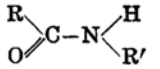
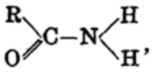
$$V=\frac{1}{2}k_1(q_1^2+q_2^2)+k_2q_1q_2,$$

where q_1 and q_2 are the displacements (at a given time) from equilibrium in the stretching vibrations of the two N—H's in the system, the signs of q_1 and q_2 being taken as positive for stretching and as negative for contraction; k_1 the force constant of each N—H; and k_2 the force constant corresponding to the interaction between the two N—H's. Then we obtain the frequency ν, for the infrared-active vibration: ,

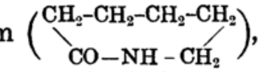
$$\nu = \frac{1}{2\pi c}\sqrt{\frac{k_1-k_2}{m}},$$

where m is the reduced mass of N—H. In (C), the Coulomb repulsion between the two hydrogens (or protons) is probably the most effective interaction between the two N—H's. If so, k_2 must be positive, because the stretching of the distance of one N—H in the system (C) tends to contract the distance of the other N—H, while k_2 must be nearly zero in (B) and (A). This explains why the frequencies are lower in (C) than in (B) and (A).

Association Tendencies of Amide Molecules. As is seen from Table 3, δ-valerolactam shows a stronger tendency towards association than unsubstituted amides, both of which are capable of forming the ring dimer. This fact may be explained as follows: In the amide or lactam molecule, the nitrogen atom, positively charged due to resonance, would attract the electrons of the hydrogen atoms and leave the protons bare to be attached to negatively charged oxygen atoms of another molecule. This process would be more effective (per one N—H) in the case where only one hydrogen is on the nitrogen than in the case where two hydrogens are on it. Hence, the dissociation energy of  $\mathrm{C{-}\overset{C}{N}{-}H\cdots O{=}C}$ bonding must be greater than that of  $\mathrm{C{-}\overset{H}{N}{-}H\cdots O{=}C}$ bonding. This explains the difference in association tendencies of the two kinds of molecules.

Buswell and his collaborators⁽⁴⁾ indicated that the monosubstituted amides in general show a smaller tendency towards association than the unsubstituted amides. This difference in associasion tendencies is, according to the present writer's view, due to the difference in molecular structures of these two kinds of amides, the one, , being incapable of forming ring dimers, the other, , capable. It is rather probable, however, that the dissociation energy per one N—H····O bonding is greater in monosubstituted amides (and lactams) than in unsubstituted amides.

Supplement.

While this paper was in press, the writer made some observations on the infrared absorptions of ε-caprolactam  $\left(\begin{array}{c}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\\ CO-NH-CH_2\end{array}\right)$, another example of the cyclic compounds with the peptide linkage, and found the following facts: (1) ε-Caprolactam shows in its carbon tetrachloride solution the free N–H absorption band at 2.90μ and the N–H association bands at 3.09μ and 3.23μ. (2) ε-Caprolactam has a stronger tendency of molecular association than monosubstituted amides, the molar absorption coefficient at 3.09μ of ε-caprolactam being as great as 22 even in such a dilute carbon tetrachloride solution as 0.0007 mol/l. (3) No shifting occurs in the positions of the absorption maxima of the N–H association bands with change of the concentration of the solution. These facts show that in the ε-caprolactam molecule, as in the δ-valerolactam molecule, H on N is *cis* to O, and that the molecules associate to form ring dimers.

In conclusion the writer wishes to express his sincere thanks to Professor San-ichiro Mizushima and Assistant Professor Takehiko Simanouti for their kind guidance throughout the present work.

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