[Chem. Pharm. Bull. 20(5) 922—926 (1972)]

UDC 547.298.1'26.03.04

Studies on the Stability of Amides. II.[1] Intramolecular Hydrogen Bond in 4-Hydroxyvaleramide[2]

Tsukinaka Yamana, Akira Tsuji and Yūzō Mizukami

Faculty of Pharmaceutical Sciences, Kanazawa University[3]

(Received August 7, 1971)

Study of the intramolecular hydrogen bonding in 4-hydroxyvaleramide was undertaken to ascertain its correlation with the intramolecular catalyzed hydrolysis of amides. The presence of a strong intramolecular hydrogen bond in the amide was confirmed by infrared spectral analysis in chloroform solution. These results were supported by the stabilization energy obtained from the molecular orbital calculation of the configuration models of 4-hydroxyvaleramide.

It has previously been reported that glucuronamide was hydrolyzed to two different products, glucuronolactone and glucuronic acid, by a simultaneous intramolecular reaction process[4] and that, in the hydrolysis of some hydroxyamides as well as glucuronamide, neighboring participation effect facilitated the reaction rates.[5] Numerous intramolecular catalyzed hydrolyses can generally be explained by the intramolecular hydrogen-bonding mechanism[6] or by kinetically identical general acid-base and nucleophil-catalyzed mechanism.[7] In some cases, attempts[6,8] have been made to discuss these reactions in terms of the mode of intramolecular hydrogen bonding determined in a dilute solution of hydroxyesters in carbon tetrachloride by infrared spectroscopy. Since amides are known to be strongly complexed with alcohols,[9] hydroxyamides seem to make an intramolecular hydrogen bond between internal hydroxyl group and amide group, if stereochemical condition were satisfied. Thus, the present study on the intramolecular hydrogen bonding of aliphatic hydroxyamides using infrared spectrophotometric method was undertaken in order to make a choice between these alternative explanations.

Experimental

Butyramide and butanol used were of reagent grade and solvents used were of analytical grade. 4-Hydroxyvaleramide was prepared by the known method,[10] mp 56.0° (from ether) (lit.[10] mp 56°). *Anal.*

1) Part I: T. Yamana, Y. Mizukami, A. Tsuji, Y. Yasuda and K. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 881 (1972).
2) This work was presented at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April 1971.
3) Location: *Takara-machi, Kanazawa.*
4) T. Yamana, Y. Mizukami and H. Ichimura, *Yakugaku Zasshi*, **89**, 173 (1969).
5) *a*) M.F. Wolfrom, R.B. Bennett and J.D. Crum, *J. Am. Chem. Soc.*, **80**, 944 (1958); *b*) H. Zahn and L. Zürn, *Ann.*, **613**, 76 (1958); *c*) L. Zürn, *ibid.*, **631**, 56 (1960); *d*) T.C. Bruice and F-Hans Marquardt, *J. Am. Chem. Soc.*, **84**, 365 (1962); *e*) R.B. Martin, R. Hedrick and A. Parcell, *J. Org. Chem.*, **29**, 158 (1964); *f*) T. Yamana, A. Tsuji and Y. Mizukami, *Chem. Pharm. Bull.* (Tokyo), accepted.
6) For a summary of pertinent references see B. Capon and M.I. Page, *J. Chem. Soc.* (*B*), **1971**, 741.
7) T.C. Bruice and S. Benkovic, "Bio-organic Mechanisms," Vol. 1, W.A. Benjamin, Inc., New York, 1966, p. 156.
8) T.C. Bruice and T.H. Fife, *J. Am. Chem. Soc.*, **84**, 1973 (1962); R. West, J.J. Korst and W.S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960).
9) *a*) E.D. Becker, *Spectrochim. Acta*, **17**, 436 (1961); *b*) K. Ventata Ramiah and C.A. Indira Chary, *Current Sci.*, **5**, 130 (1968); *c*) C.R. Kanekar, C.L. Khetrapal, K. Venkata Ramiah and C.A. Indira Chary, *Proc. Ind. Acad. Sci.*, **66**, 184 (1967); *d*) F.M. Arshid, C.H. Giles, S.K. Jain and A.S.A. Hassan, *J. Chem. Soc.*, **1956**, 72; *e*) F. Takahashi and N.C. Li, *J. Phys. Chem.*, **68**, 2136 (1964); *f*) L.J. Bellamy and R.J. Pace, *Spectrochim. Acta*, **27**, 705 (1971).
10) P.A. Levene and H.L. Haller, *J. Biol. Chem.*, **69**, 165 (1926).

Calcd. for $C_5H_{11}O_2N$: C, 51.25; H, 9.48; N, 11.96. Found: C, 51.56; H, 9.62; N, 11.61. Ethyl 4-hydroxybutyrate was prepared by the method of Brown, *et al.*[11] and purified by distillation, bp 49—51° (0.2 mmHg) [lit.[11] bp 43—44° (0.15 mmHg)].

Spectral measurements were carried out with a Jasco-DS-402 G spectrophotometer, using a 1 mm or 5 mm cell.

Result and Discussion

Infrared Spectra

For the investigation of an intramolecular hydrogen bond, measurements of infrared spectral absorption is generally carried out at as low concentration as possible in a non-polar solvent such as carbon tetrachloride.[12] Unfortunately, however, hydroxyamides synthesized in this work were not well soluble in carbon tetrachloride and only 4-hydroxyvaleramide[13] was found to be slightly soluble in chloroform which was used for the present investigation.

The spectra of 4-hydroxyvaleramide were measured between 3100 and 3700 cm^{-1} at various concentrations in chloroform solution and its absorption curves are given in Fig. 1. The amide in a low concentration (0.02M) shows three bands at about 3540, 3480 and 3400 cm^{-1}. As the concentration of the amide increases, two new peaks appear at about 3340 and 3200 cm^{-1}. In the concentration range examined there was no free O-H absorption band at 3600—3650 cm^{-1}. Because of the overlapping of the bonded and nonbonded N-H and bonded O-H absorption bands in the region between 3200 and 3600 cm^{-1}, it is difficult to assign the absorption peaks in Fig. 1. In connection with the possible interpretation of these bands, spectral measurements described below were carried out in chloroform solutions.

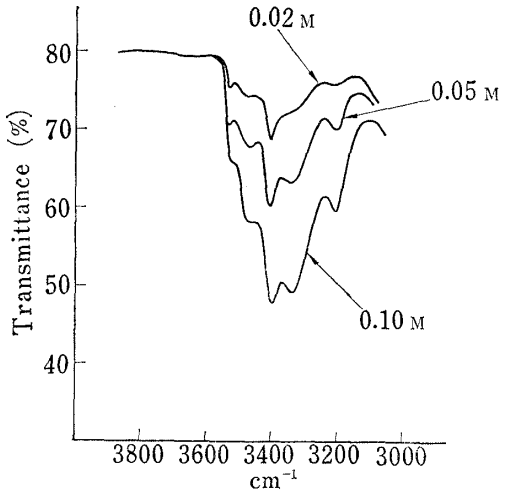

Fig. 1. Infrared Spectra of 4-Hydroxyvaleramide

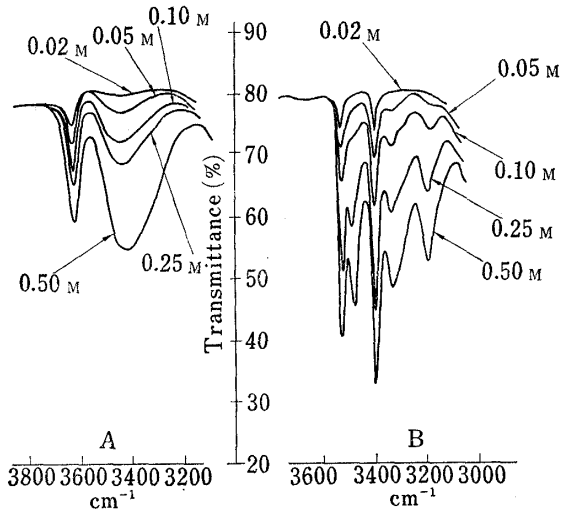

Fig. 2. Infrared Spectra of Butyl Alcohol (A) and Butyramide (B)

Spectra of dilute solutions of butyramide (Fig. 2-B) show sharp absorption peaks at about 3400 and 3540 cm^{-1}, respectively corresponding to the symmetrical and the antisymmetrical vibrations of the NH_2 group of the unassociated amides[14] and that of concentrated solutions of the amide exhibits three absorption peaks at about 3480, 3340, and 3200 cm^{-1}. The latter three bands may be attributed to the intermolecularly bonded N-H. The

11) H.C. Brown and K.A. Keblys, *J. Org. Chem.*, **31**, 485 (1966); *idem*, *J. Am. Chem. Soc.*, **86**, 1796 (1964).
12) G.C. Pimentel and A.C. McGlellan, "The Hydrogen Bond," W.H. Freeman and Co., California, 1960.
13) In the hydrolysis of this amide, the participation effect by the hydroxyl group was observed.[5f]
14) R.E. Richards and H.W. Thompson, *J. Chem. Soc.*, **1947**, 1248.

spectra of butanol show the free O-H absorption peak at 3640 cm^{-1} and the broad O-H absorption peak at 3400 to 3500 cm^{-1} which is due to intermolecular association and decreases with dilution and almost disappears at 0.02M (Fig. 2-A). These results indicate that the amide and the alcohol exist as a monomeric form below 0.02M concentrations and that the two peaks at 3540 and 3400 cm^{-1} in the spectrum of 4-hydroxyvaleramide (Fig. 1) can be assigned to the monomeric N-H absorption bands and the broad peaks at 3340 and 3200 cm^{-1} may be the intermolecular N-H bands. On the other hand, free O-H stretching band of 4-hydroxyvaleramide was not observed even in a dilute concentration of 0.02M, whereas butanol gave a sharp free O-H peak at 3640 cm^{-1} at this concentration. This fact suggests that all the O-H groups of the amide are forming intramolecular hydrogen bonds and this may be supported by the following results.

Equimolar mixture of butyramide and butanol gives spectra essentially identical with the spectra of 4-hydroxyvaleramide (Fig. 1) and does not show free O-H absorption band, as seen in Fig. 3-A. When the alcohol is in excess of butyramide, nonbonded O-H stretching band appears at 3640 cm^{-1} (Fig. 3-B). These results suggest that the amide forms a strong complex with butanol and are consistent with the fact that the amide and the alcohol forms a 1:1 complex.[9] On the other hand, presence of a smaller amount of butanol than 4-hydroxyvaleramide gives the free O-H absorption peak at 3640 cm^{-1} as shown in Fig. 4. These

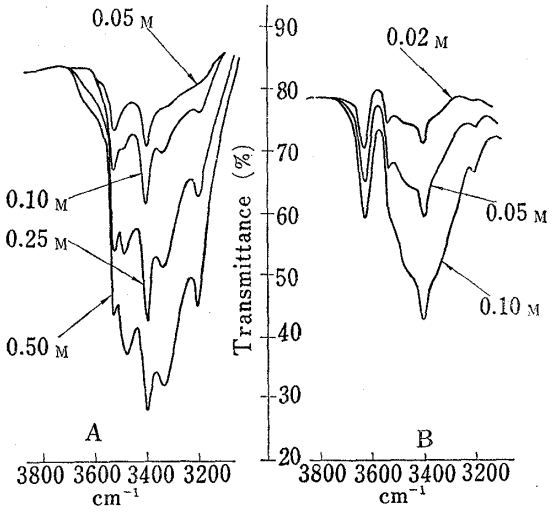

Fig. 3. Infrared Spectra of Mixture of Butyramide and Butyl Alcohol

A: Concentration ratio of amide/alcohol is 1.0.
B: Concentration ratio of amide/alcohol is 0.5.
All concentrations represented are that of the amide.

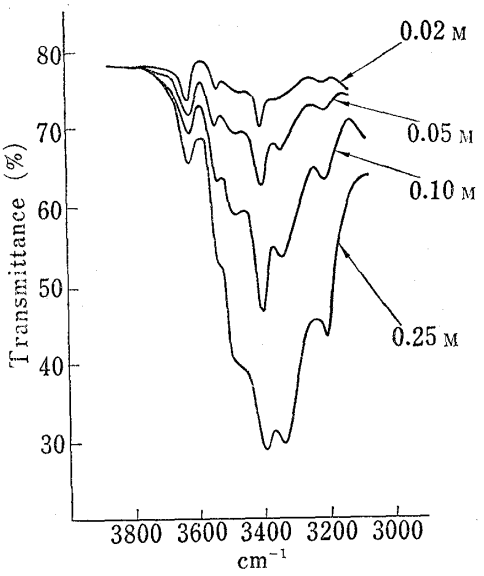

Fig. 4. Infrared Spectra of Mixture of 4-Hydroxyvaleramide and Butyl Alcohol

Concentration ratio of amide/alcohol is 2.0.
All concentrations represented are that of the amide.

results confirmed that most of 4-hydroxyvaleramide forms a strong intramolecular hydrogen bonding in chloroform solution, and that the corresponding bonded O-H stretching frequency appears at about 3480 cm^{-1} (the difference between bonded and free O-H stretching frequencies, $\Delta\nu$, was *ca.* 160 cm^{-1}) which was observed even at a dilution of 0.02M, as seen in Fig. 1. In order to clarify the position of the intramolecular bonded O-H absorption bands and to decide the bonded structure of 4-hydroxyvaleramide, the infrared spectra of ethyl 4-hydroxybutyrate were measured in carbon tetrachloride and chloroform, the absorption curves of which are shown in Fig. 5. In this curve sharp O-H absorption bands at 3640 cm^{-1} in both solvents are due to non associated O-H group of ester, and the absorption peaks at 3500 cm^{-1} ($\Delta\nu$=140 cm^{-1}, in CCl_4) and at 3480 cm^{-1} ($\Delta\nu$=160 cm^{-1}, in $CHCl_3$), whose absor-

bances change proportionally with the concentration of the ester, are probably attributed to the intramolecular hydrogen bonding of the type O-H···O=C as previously suggested.[15] It may be concluded from this result that the absorption peak at 3480 cm^{-1} in the spectra of 4-hydroxyvaleramide can be assigned to the intramolecular hydrogen bonded O-H stretching, and that the large $\Delta\nu$ value ($\Delta\nu$=160 cm^{-1}) is attributed to the hydrogen bonding O-H··· O=C between the hydroxyl group and the amide carbonyl.

Molecular Orbital Calculation

Table I lists the total energies calculated by the extended Hückel method[16] for various systems of the hydrogen bonded structure in Fig. 6. In this calculation, covalent bond length and hydrogen bonded distance were taken from the literature.[12,17] As shown in Table I, O-H···O=C hydrogen bonded model (Model 2) is more stable than the other hydrogen bonded structures. This is consistent with the result[18] that amides form strong complexes with alcohols in the type of O-H···O=C and not O-H···NH_2.

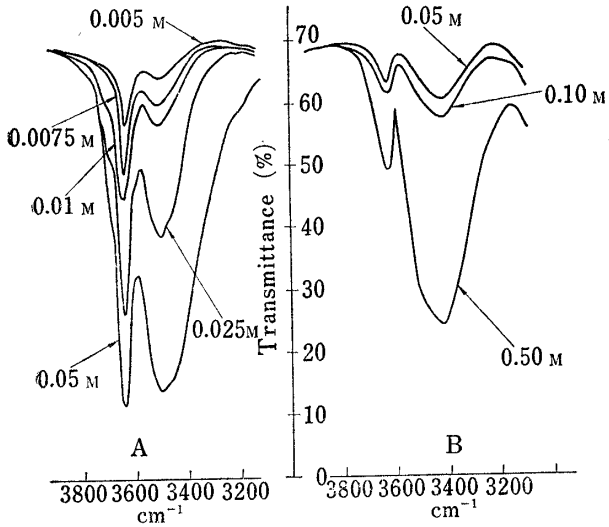

Fig. 5. Infrared Spectra of Ethyl 4-Hydroxybutyrate in Carbon Tetracloride (A) and in Chloroform (B)

A: measured at 5 mm thickness
B: measured at 1 mm thickness

Table I. Total Energy of 4-Hydroxyvaleramide

Model	Total energy (eV)
1	−800.6071
2	−801.9522
3A	−800.4948
3B	−800.3503

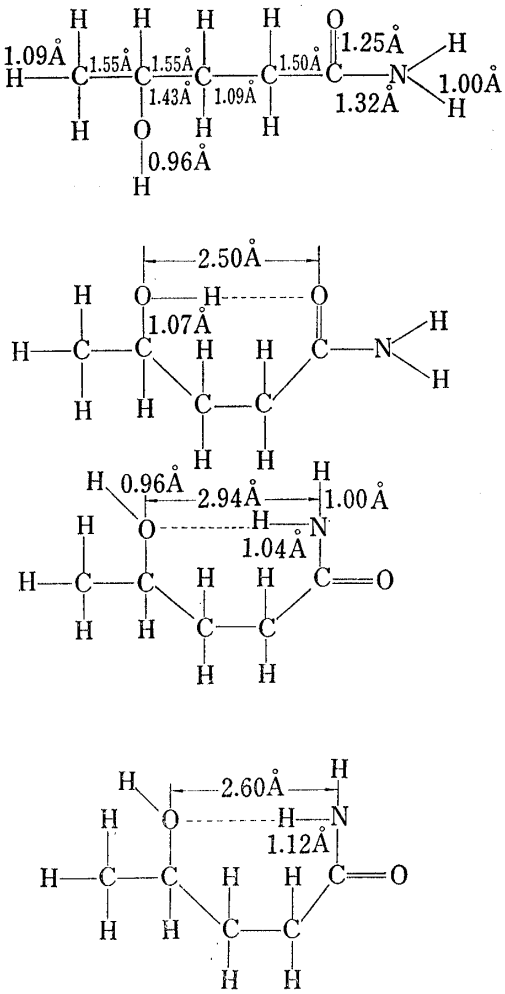

Fig. 6. Configuration Models of 4-Hydroxyvaleramide

15) N. Mori, S. Omura and N. Kobayashi, *Bull. Chem. Soc. Japan.*, **38**, 2149 (1965); N, Mori, Y. Asano and Y. Tsuzuki, *ibid.*, **41**, 1871 (1968).
16) Y. Mizukami and T. Yamana, *Yakugaku Zassshi*, **92**, 322 (1972).
17) S. Furberg and S. Helland, *Acta Chem. Scand.*, **16**, 2373 (1962); R. Norrestam, P.E. Werner and M. von Glehn, *ibid.*, **22**, 1395 (1968); K. Morokura, H. Kato, T. Yonezawa and K. Fukui, *Bull. Chem. Soc. Japan*, **38**, 1263 (1965).
18) M. Tsuboi, *Bull. Chem. Soc. Japan*, **25**, 160 (1952).

As present molecular orbital calculation shows, high polarity of the carbonyl group in amide is due to the interaction of π orbital of the carbonyl group and $2p_z$ orbital of the nitrogen atom.[9b] Because of the polarity of carbonyl group, there may be a strong interaction between alcohol-OH hydrogen and carbonyl oxygen of the amide. The total energy in the molecular orbital calculation suggests that the predominant intramolecular hydrogen bonded structure of 4-hydroxyvaleramide is presumably the same as Model 2.

The calculation of molecular orbital was carried out on the FACOM 230-35 at the Data Processing Center, Kanazawa University.

Acknowledgment The authors are indebted to Mr. Y. Itatani for elemental analysis and also to Miss Y. Tamura for her technical assistance.