Estimation of the Energy of Hydrogen Bonds Formed in Crystals. III. Amides

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A study of the NH···O bonding bears a particular significance in relation to the basic structure and behavior of proteins, and a fairly large amount of data of the bond have been accumulated up to now. Nevertheless, it cannot be said that the strength of the NH···O bonding has been fully examined so as to allow us to decide definitely whether this type of hydrogen bond is weaker than the OH···O bonding or not, especially in the crystalline state. Thus we find a considerable divergence in the data of the energy of NH···O bondings already published by several investigators. For instance, Coulson cites, in his well-known publication(1), 2~3 kcal./mol. for the energy of the NH···O bond, while the following data are available in the literature: 3.0 kcal./mol. (acetamide, *N*-methylacetamide)(2), (diacetylhydrazine)(3), 3.5 kcal./mol. (urea)(4), 4.2 kcal./mol. (oxamide)(5), 4.7 kcal./mol. (sulfamide)(3), 5.3 kcal./mol. (diketopiperazine)(6), ~6.0 kcal./mol.

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1) C. A. Coulson, "Valence", Clarendon Press, Oxford (1952), p. 301.

2) A. Aihara, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 73, 855 (1952).

3) S. Takagi, R. Shintani, H. Chihara and S. Seki, This Bulletin, 32, 137 (1959).

4) K. Suzuki, S. Onishi, T. Koide and S. Seki, ibid., 29, 127 (1956).

5) R. S. Bradley and A. D. Care, *J. Chem. Soc.*, 1953, 1681.

6) S. Seki, K. Suzuki and T. Koide, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 77, 346 (1956).

(δ-valerolactam and ε-caprolactam)⁷⁾, 6.1 kcal./mol. (diformylhydrazine)⁴⁾.

In this connection, the author has tried to get more knowledge on the strength of the NH···O bond, and has estimated the energy of the bond with thirteen amides in the crystalline state, following the procedure proposed in previous papers⁸⁾. The obtained values of the energy range from 3.5 to 7.0 kcal./mol., showing that the NH···O bond is not always weaker than the OH···O bond as has hitherto been presumed.

Experimental

The measurement of the sublimation pressures was done with the same apparatus as that used before³⁾. Of the materials dealt with in this investigation, formanilide and *N*-methylbenzamide were prepared in this laboratory following the usual procedure (the former from aniline and formaldehyde, the latter from methylamine and benzoylchloride). δ-Valerolactam and ε-caprolactam were kindly sent by Dr. Tsuboi, the University of Tokyo The result of the measurement of their sublimation pressures was reported before by the author⁷⁾, but, for the sake of comparison, it will be included here. 1-Phenyl-3pyrazolidone (phenydone) was sent by Dr. Kurosaki, Fuji Photo Film Co., Ltd., to whom author's thanks are due. Others were all commercial products and were purified by repeated fractional sublimation under high vacuum pressure before use.

Results and Discussion

Sublimation Pressures.—The results of measurements of sublimation pressure of thirteen amides are shown in the following tables (from Table I to Table XIII) together with their

TABLE I. SUBLIMATION PRESSURE OF FORMANILIDE

T°K	P(mmHg)$\times 10^4$	T°K	P(mmHg)$\times 10^4$
297.7	6.86	311.9	28.7
301.6	10.3	313.6	34.2
308.4	20.3	314.6	37.2
309.3	22.0	316.8	45.9
310.7	25.9	317.8	49.4

$\log P(\text{mmHg})=10.511-4071.0/T$: m. p. 48.7°C.

TABLE II. SUBLIMATION PRESSURE OF ACETANILIDE

T°K	P(mmHg)$\times 10^4$	T°K	P(mmHg)$\times 10^4$
317.7	8.03	327.7	21.2
320.0	10.2	330.1	26.8
322.7	12.9	333.2	36.2
325.4	16.4	335.8	48.1

$\log P(\text{mmHg})=11.166-4533.6/T$: m. p. 115.0°C.

TABLE III. SUBLIMATION PRESSURE OF *o*-ACETOLUIDINE

T°K	P(mmHg)$\times 10^4$	T°K	P(mmHg)$\times 10^4$
315.2	4.20	330.8	23.6
318.5	6.31	334.2	35.3
321.2	8.80	337.5	48.6
324.2	11.8	340.0	65.6
327.3	16.5		

$\log P(\text{mmHg})=12.717-5070.8/T$: m. p. 111.5°C.

TABLE IV. SUBLIMATION PRESSURE OF *p*-ACETOTOLUIDINE

T°K	P(mmHg)$\times 10^4$	T°K	P(mmHg)$\times 10^4$
330.7	6.20	337.9	13.0
332.1	7.23	340.6	17.5
333.1	7.93	343.4	23.2
334.0	8.98	346.5	31.6
335.2	10.1	350.1	46.6

$\log P(\text{mmHg})=12.437-5172.9/T$: m. p. 149°C.

TABLE V. SUBLIMATION PRESSURE OF *p*-ACETAMINOBENZALDEHYDE

T°K	P(mmHg)$\times 10^4$	T°K	P(mmHg)$\times 10^4$
328.3	5.59	337.4	14.9
330.1	6.73	339.9	19.4
332.6	8.82	342.4	25.2
335.1	11.5	345.4	32.8

$\log P(\text{mmHg})=12.516-5177.7/T$: m. p. 155.5°C.

TABLE VI. SUBLIMATION PRESSURE OF BENZANILIDE

T°K	P(mmHg)$\times 10^4$	T°K	P(mmHg)$\times 10^4$
353.0	3.93	363.7	10.6
355.4	4.73	366.7	13.7
357.0	5.64	368.9	16.4
360.2	7.53		

$\log P(\text{mmHg})=11.264-5181.2/T$: m. p. 163.5°C.

TABLE VII. SUBLIMATION PRESSURE OF BENZAMIDE

T°K	P(mmHg)$\times 10^3$	T°K	P(mmHg)$\times 10^3$
325.3	1.04	334.3	2.67
327.4	1.31	335.4	3.00
328.4	1.39	337.0	3.49
330.0	1.70	338.9	4.37
332.9	2.33	341.9	5.86

$\log P(\text{mmHg})=12.579-5063.6/T$: m. p. 130.5°C.

TABLE VIII. SUBLIMATION PRESSURE OF *N*-METHYLBENZAMIDE

T°K	P(mmHg)$\times 10^4$	T°K	P(mmHg)$\times 10^4$
308.0	7.06	320.9	27.3
310.6	9.16	323.7	35.3
313.0	11.9	326.8	47.8
315.7	15.7	329.3	60.9
318.5	21.0		

$\log P(\text{mmHg})=11.358-4469.8/T$: m. p. 79.8°C.

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7) A. Aihara, ibid., 74, 631, 634 (1953).

8) A. Aihara, This Bulletin, 32, 1242 (1959); 33, 194 (1960).

TABLE IX. SUBLIMATION PRESSURE OF α-PHENYLACETAMIDE

T°K	$P(\mathrm{mmHg})\times10^4$	T°K	$P(\mathrm{mmHg})\times10^4$
330.0	5.18	340.9	16.4
332.9	7.12	344.0	21.9
335.2	9.09	348.0	31.7
338.2	12.4	351.8	46.5

$\log P(\mathrm{mmHg})=12.242-5123.7/T$: m. p. 158.5°C.

TABLE X. SUBLIMATION PRESSURE OF N-ACETYL-α-NAPHTHYLAMINE

T°K	$P(\mathrm{mmHg})\times10^4$	T°K	$P(\mathrm{mmHg})\times10^4$
337.9	2.66	348.0	6.93
341.0	3.56	350.6	8.80
342.3	4.18	354.5	12.2
345.5	5.47	359.7	20.8

$\log P(\mathrm{mmHg})=10.959-4912.2/T$: m. p. 159°C.

TABLE XI. SUBLIMATION PRESSURE OF 1-PHENYL-3-PYRAZOLIDONE

T°K	$P(\mathrm{mmHg})\times10^4$	T°K	$P(\mathrm{mmHg})\times10^4$
327.8	4.18	340.4	13.2
331.0	5.46	343.9	17.5
333.9	6.85	348.2	24.6
336.8	9.09		

$\log P(\mathrm{mmHg})=10.025-4397.5/T$: m. p. 120.8°C.

TABLE XII. SUBLIMATION PRESSURE OF δ-VALEROLACTAM

T°K	$P(\mathrm{mmHg})\times10^3$	T°K	$P(\mathrm{mmHg})\times10^3$
293.9	2.81	304.7	8.35
294.7	3.09	306.7	10.35
297.0	3.96	308.4	11.66
298.9	4.67	310.6	13.84
300.7	5.65	312.5	15.70
302.5	6.63		

$\log P(\mathrm{mmHg})=10.692-3891.0/T$: m. p. 39.3°C.

TABLE XIII. SUBLIMATION PRESSURE OF ε-CAPROLACTAM

T°K	$P(\mathrm{mmHg})\times10^3$	T°K	$P(\mathrm{mmHg})\times10^3$
294.0	1.18	305.2	4.21
295.2	1.38	306.9	5.03
297.1	1.72	308.7	6.02
298.3	1.93	310.6	7.43
300.4	2.44	312.2	8.70
301.9	2.92	313.9	10.03
303.7	3.56		

$\log P(\mathrm{mmHg})=11.839-4339.8/T$: m. p. 69.8°C.

TABLE XIV. SUBLIMATION PRESSURE OF p-AMINOACETOPHENONE

T°K	$P(\mathrm{mmHg})\times10^4$	T°K	$P(\mathrm{mmHg})\times10^4$
314.2	3.32	326.0	11.9
315.6	3.78	329.2	16.5
318.6	5.47	332.3	22.5
320.1	6.42	335.2	30.2
323.8	9.47	338.2	41.7

$\log P(\mathrm{mmHg})=11.900-4832.6/T$: m. p. 106.2°C.

vapor pressure equations obtained by the method of least squares. The linear relation between $\log p$ and $1/T$ is found to be quite satisfactory for all the measurements here mentioned.

In addition to the sublimation pressure of the amides listed above, that of p-aminoacetophenone, which should be classified as an amine in the usual sense, is also shown in Table XIV. Since the molecular structure of p-aminoacetophenone bears some resemblance to that of acetamide, except that the amino group is separated from the carbonyl group by a phenyl nucleus, it might be expected to form NH···O bonds with neighboring molecules in the crystal.

The values of the heat of sublimation (ΔH), the change of free energy at 298.2°K ($\Delta G^{298.2°}$) and of entropy (ΔS) on sublimation are shown in Table XV.

Energy of Hydrogen Bond.—Table XV shows the estimated energies (E) of hydrogen bonds (NH···O) in the fourth column, together with the hypothetical lattice energies ($\Delta H'$) obtained conventionally, assuming the additivity rule of the lattice energy, without taking into account the formation of hydrogen bonds in the crystalline state[8]. The values of E were obtained by subtracting $\Delta H'$ from ΔH.

Because the crystal structures of the majority of compounds listed in Table XV are not analyzed as yet except for those of acetanilide[9] and benzamide[10], the formation of the NH···O bond is implicitly assumed for the rest of the compounds. considering the similarity of their molecular structures, this assumption would not be unreasonable.

It is clear, from the values of E in the table, that the compounds dealt with in this investigation can be classified into three categories: the first showing little or no tendency to associate mutually by NH···O bondings (benzanilide, N-acetyl-α-naphthylamine and 1-phenyl-3-pyrazolidone); the second forming NH···O bondings of the order of 4 ± 1 kcal./mol. (formanilide, acetanilide, o- and p-acetotoluidine, p-acetaminobenzaldehyde, benzamide, N-methylbenzamide and α-phenylacetamide), and the third capable of making hydrogen bondings as strong as $6\sim7$ kcal./mol. (δ-valerolactam and ε-caprolactam).

Let us first examine those which belong to category I. An alternative nomenclature of

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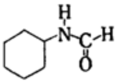
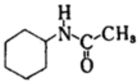
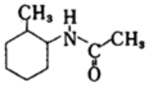
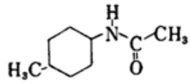
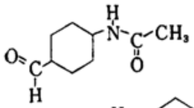
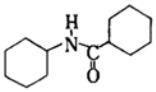
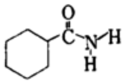
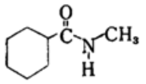
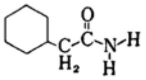
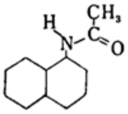
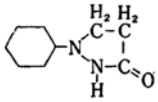
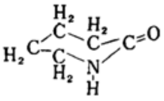
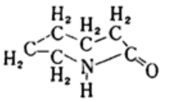
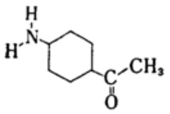
[9] C. J. Brown and D. E. Corbridge, *Nature*, **162**, 72 (1948); *Acta Cryst.*, **7**, 711 (1954).

[10] B. R. Penfold and J. C. B. White, ibid., **12**, 130 (1959).

TABLE XV. VALUES OF THERMODYNAMIC FUNCTIONS AND ENERGIES OF HYDROGEN BOND

Compounds	ΔH kcal./mol.	$\Delta H'$ kcal./mol.	E kcal./mol.	$\Delta G^{298.2°}$ kcal./mol.	ΔS cal./deg. mol.
	18.63±0.11	14.5	4.1	8.22±0.21	34.9±0.3
	20.75±0.37	16.5	4.3	9.44±0.70	37.9±1.1
	23.20±0.22	18.5	4.7	9.78±0.40	45.0±0.6
	23.67±0.23	18.5	5.2	10.63±0.43	43.7±0.7
	23.69±0.23	20.0	3.7	10.54±0.44	44.1±0.7
	23.71±0.29	23.5	0.2	12.27±0.53	38.4±0.8
	23.17±0.27	14.5	8.7×(1/2)	9.94±0.51	44.4±0.8
	20.45±0.08	16.5	4.0	8.85±0.15	38.9±0.2
	23.45±0.21	16.5	7.0×(1/2)	10.67±0.46	42.8±0.8
	22.48±0.30	23.0	−0.5	11.46±0.86	37.0±0.6
	20.12±0.40	20.5	−0.4	10.37±0.75	32.7±1.2
	17.81±0.12	11.5*	6.3	7.15±0.16	35.7±0.4
	19.86±0.11	13.0*	6.9	7.64±0.22	41.0±0.4
	22.11±0.13	16.5	5.6×(1/2)	9.80±0.25	41.3±0.4

* In these cases, the increment of the lattice energy due to a CH_2 group was taken as 1.5 kcal./mol., taking into consideration the volume effect due to ring formation: the value was estimated from the heat of sublimation of cyclohexane, ~8.5 kcal./mol. (the sum of the heats of vaporization and fusion).

benzanilide is *N*-phenylbenzamide and the molecule consists of two large phenyl groups attached to both sides of a peptide linkage. These phenyl groups will inevitablly prevent the molecules from approaching each other closely to make association by the NH···O bonding. The infrared absorption data[11] prove also that the NH···O bond in the crystal of benzanilide is rather weak, if it is formed to any extent: the wavelength of the N–H absorption band in the crystalline state is 2.99 μ compared with 3.08 μ in the case of acetanilide, which is known to form NH···O bonds in the crystals[9]. *N*-acetyl-α-naphthylamine is also known to show little tendency to form hydrogen bonds with dioxane and cyclohexanone as revealed from the study of ultraviolet absorption of this substance by Baba and Suzuki[12]. The small negative value of E for this compound implies that there would be no hydrogen bond formed in the crystalline state in accordance with the result of ultraviolet absorption. This may be due to the blocking effect of a phenyl nucleus located very close to the N–H group at the α-position.

As to 1-phenyl-3-pyrazolidone, Kurosaki[13] has observed the formation of associated dimers in its CCl_4 and $CHCl_3$ solutions by the infrared and dielectric technique. But, at the same time, he noticed that its tendency to associate was much decreased in $CHCl_3$ solution due to the high polarity of the solvent which interacts with the solute molecules. Therefore, if an extrapolation is allowed to be made to the extreme case where the solute is surrounded completely by the same substance as a solvent (that is, a pure liquid or solid), we may assume that the molecule should exist as a monomer in the crystalline state without making any association, because the dipole moment of 1-phenyl-3-pyrazolidone 3.5∼3.6 D[13] is much greater than that of chloroform 1.05 D[14]. The result obtained by the author shown in Table XV confirms this conclusion.

Those in category II may be regarded as forming "normal" hydrogen bonds of NH···O type, the energy of the bond being about 4 kcal./mol. The small differences between the values of these compounds might have some meaning concerning the strength of the bond formed, but, considering the approximate nature of the method of estimation, a further discussion on the difference of the strength of the bond cannot be made. It is interesting, however, to see that the methyl groups substituted to the phenyl nucleus seem to incsease the strength of the NH···O bond in the case of *o*- and *p*-acetotoluidine, while the formyl group in the para position of *p*-acetaminobenzaldehyde tends to decrease the NH···O bond-forming-power of the molecule: the weakly electron-releasing inductive and hyperconjugative effects of the methyl group might cause an increase of the negative charge on the oxygen atom of the carbonyl group, thereby reinforcing the strength of the hydrogen bond, while the strong electron-withdrawing inductive effect of the formyl group might result in the reverse way. In the case of benzamide and α-phenylacetamide, the E values in Table XV were obtained by dividing the difference of ΔH and $\Delta H'$ by two, because these molecules are connected to each other by two NH···O bonds per molecule in the crystalline state, as is revealed by Penfold and White[10].

The value of E for *p*-aminoacetophenone, 2.8 kcal./mol.(=5.6/2 kcal./mol.), is somewhat smaller than those of the compounds in the second category. This is probably due to the separation of the amino and carbonyl groups by a phenyl nucleus which might prevent the mutual approach of molecules to some extent, although the positive charge on the NH group as well as negative charge on the C=O group are presumably increased to favor the formation of a strong NH···O bond due to the existence of a phenyl nucleus. An alternative way of explaining the smaller value of the energy of hydrogen bond in this compound is that it may behave as an amine forming hydrogen bonds of NH···N type in the crystalline state. This problem must be solved either by infrared absorption measurement or by crystallographic analysis.

The energies of an NH···O bond estimated for δ-valerolactam and ε-caprolactam amount to 6∼7 kcal./mol. and can be favorably compared with those observed for carboxylic acids[15] which are known to form dimers in the crystalline state as well as in liquid and in solutions. Here, it would be reasonable to assume that the two lactams exist as dimers in the crystalline state, because their molecular structures are such as to favor the formation of dimers (N–H is located in the *cis* position to C=O), just like those of carboxylic acids, although the crystal structures of the lactams are not analyzed as yet. Thus, the appreciable increase in the strength of NH···O bonds in

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[11] H. M. Randall et al., "Infrared Determination of Organic Structures", D. Van Nostrand Co., Inc., New York (1949), pp. 82, 147.

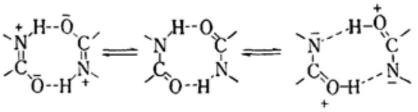
[12] H. Baba and T. Suzuki, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **81**, 366 (1960).

[13] K. Kurosaki, ibid., **79**, 1339, 1362 (1958).

[14] C. P. Smyth, "Dielectric Behavior and Structure", McGraw-Hill Book Co., Inc., New York (1955), p. 237.

[15] F. H. McDougall, *J. Am. Chem. Soc.*, **58**, 2585 (1936); E. W. Johnson and L. K. Nash, ibid., **72**, 547 (1950); R. E. Lundin, F. E. Harris and L. K. Nash, ibid., **74**, 743, 4654, (1952).

these cases, compared with a "normal" NH···O bond, can be understood as due to the conjugation of π-electrons in the ring system formed by two molecules:



A simple treatment of this problem based on the assumption of a dipole-dipole interaction between hydrogen-bond-forming molecules is mentioned in a previous paper(7). It should be mentioned that the estimated value of the energy of an NH···O bond for δ-valerolactam, 6.3 kcal./mol., is consistent with Tsuboi's value, 5.2 kcal./mol., obtained by the infrared spectroscopy on the association of the molecules in a CCl_4 solution(16).

In relation to the formation of ring dimers by the lactams mentioned above, a comment will be made on the molecular configuration of formanilide which is regarded as forming a "normal" hydrogen bond in this paper. Here it was implicitly assumed that the configurational position of the NH group was *trans* to the C=O group in this molecule, following the experimental result on the molecular structure of acetanilide(9). Recently, however, Suzuki(17) has observed the existence of a *cis* form of this molecule in a CCl_4 solution in the study of its infrared absorptions and dipole moment: *cis* and *trans* forms exist in equilibrium, the energy difference being 600 cal./mol. The problem is whether the two forms should be found even in the crystalline state or not. Considering the "normal" value of the energy of hydrogen bond for formanilide, 4.1 kcal./mol., estimated in this study, the author is inclined to conclude that the molecule exists in the crystalline state as a *trans* form, because, if there is an appreciable amount of *cis* form, forming ring dimers, the energy of the hydrogen bond should be much higher, as can be seen from the values estimated for δ-valero- and ε-caprolactam.

Comparison of the Energies of Hydrogen Bonds in Crystalline State between the Types NH···O and OH···O.—In order to get a general view on the strength of NH···O and OH···O bondings in the crystalline state, a comparison was made between the two types of the hydrogen bonds using the energy values of the bonds estimated by the author in series of studies(8), together with those published already by other investigators (recalculated by the author). The result is shown in Fig. 1. In this figure, numbers of the compounds which show particular values of the energy of the hydrogen bond are plotted against the energy values: for the sake of simplicity the values are rounded off to integers approximating to the original values. The following compounds and energy values are picked up mostly from the publications by Seki and his collaborators(18): CH_3OH 5.9 (6.0), C_2H_5OH 6.5 (5.8), n-C_3H_7OH 6.4 (5.6), n-C_4H_9OH 6.0 (5.1), n-$C_6H_{13}OH$ 6.5 (5.5), cyclohexanol 5.8 (3.5), pentaerythritol 5.4 (4.0), i-erythritol 5.4(19) (4.0), phenol 4.5 (5.2), hydroquinone 4.7 (4.2), ice 4.4 (4.7), hydrogen peroxide 4.5 (5.1), diformylhydrazine 6.0(4) (6.6), diacetylhydrazine 3.1(3) (4.8), diketopiperazine 5.3(6) (4.9), urea 3.5(4) (3.4), oxamide 4.2(5) (4.0), sulphamide 4.7(3) kcal./mol., respectively. The figures in parentheses are the energy values estimated by the procedure proposed by the author(2). Acetamide 3.1, N-methylacetamide 3.4(2), acetylglycine-N-methylamide 3.2(20) and acetylglycine-anilide 2.5(20) kcal./mol., respectively, are also included in Fig. 1.

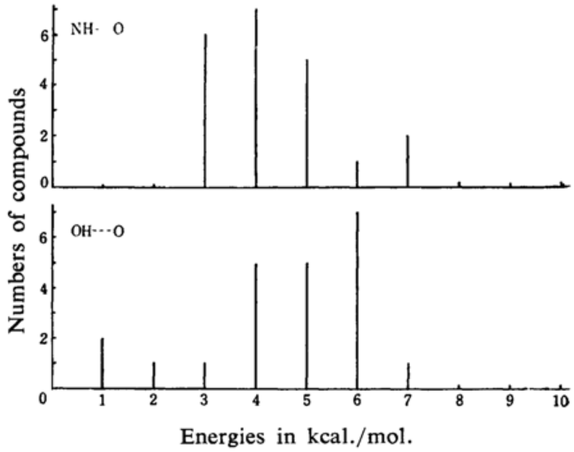


Fig. 1. Comparison of the energy of hydrogen bond between the type NH···O and OH···O.

It may be concluded from the distribution of the energy of hydrogen bonds as is seen in the figure, that the "normal" value of the energy of the NH···O bond can be 4±1 kcal./mol., while that of the OH···O bond amounts to 5±1 kcal./mol., and that a higher value both for NH···O and OH···O bonds can be ascribed to a favorable effect of conjugation in the π electron systems as is seen in the formation of ring dimers by lactams and carboxylic acids. The lower values observed in the case of

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16) M. Tsuboi, This Bulletin, **24**, 75 (1951).

17) I. Suzuki, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 353 (1959).

18) S. Seki et al., "Hydrogen Bond", Iwanami, Tokyo (1956), p. 41.

19) A. Shimada, This Bulletin, **32**, 330 (1959).

20) A. Aihara, *J. Chem. Soc. Japan, Prue Chem. Sec.* (*Nippon Kagaku Zasshi*), **76**, 495 (1955).

OH···O bonding are due to the steric hindrance by substituted groups which prevent the mutual approach of hydroxyl groups.

Summary

The energies of hydrogen bonds formed in the crystalline state of thirteen amides and one amine have been estimated following the procedure proposed in a previous paper. The values of the energy of an NH···O bond can be estimated at about 4±1 kcal./mol. for the majority of compounds treated in this paper, except two lactams which show energy values as large as 6∼7 kcal./mol. A comparison was made between the energy values of NH···O and OH···O bonding using the data obtained by the author and other investigators.

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