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INTERMOLECULAR ASSOCIATION THROUGH HYDROGEN BONDING. SYNTHESES AND INFRARED STUDIES OF ACYLUREA DERIVATIVES

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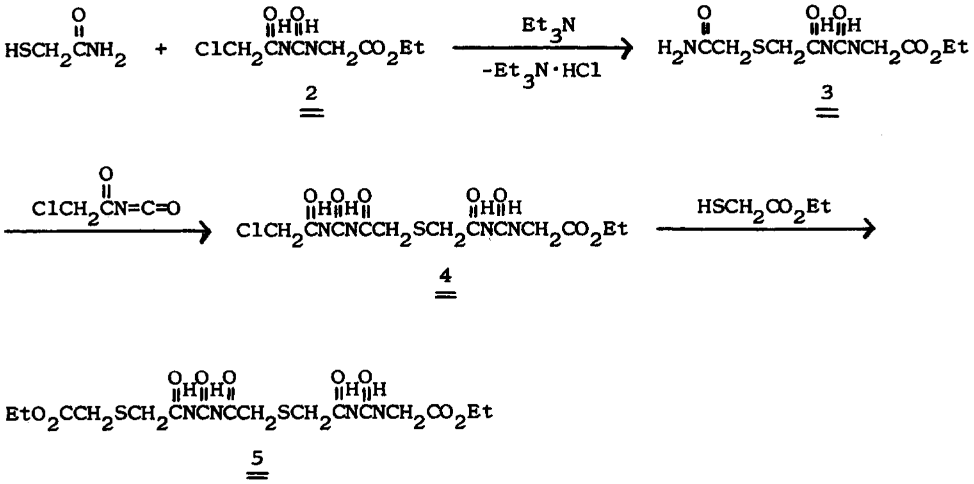
The hydrogen bonding, one of the typical molecular interactions, has widely and systematically been studied from a "static" point of view, i.e., from stabilization of the double-stranded structure of the nucleic acid and from that of specific conformations of proteins or from theoretical treatment.

This paper describes preliminary investigations on syntheses and infrared studies of acylurea derivatives as a model system for highly specific organic reactions. As one possible model compound, acylurea derivatives were chosen, by assuming that they could form strong N-H···O hydrogen bonds. Since acyl isocyanates are known to convert amines or amides under mild conditions to acylurea derivatives$^{1)}$, the use of acyl isocyanates$^{2)}$ is therefore thought to provide a good method for their preparations.

In view of high nucleophilicity of thiols toward the carbon atom, the successive use of thiols with the N-H bonds and of chloroacetyl isocyanate (**1**) would lead to the formation of the desired acylurea derivatives. Treatment of 2-mercaptoacetamide with 5-chloroacetylhydantoic acid ethyl ester (**2**) and triethylamine in ethanol at room temperature for 1 hr gave the corresponding sulfide (**3**), mp 187-188° (EtOH), in 92% yield. The acylurea derivative (**4**), mp 151-152° (EtOH-H_2O), was obtained as white needles in 98% yield by the reaction of **3** with **1** in refluxing dioxane for 5 hr. In addition, **4** reacted easily with ethyl 2-mercaptoacetate and triethylamine in DMF at room temperature for 2 hr to afford the sulfide$^{3)}$ (**5**), mp 117-118° (EtOH), in 79% yield as white powder. Anal.



$$\mathrm{HSCH_2\overset{O}{C}NH_2} + \underset{\textstyle 2}{\mathrm{ClCH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}CH_2CO_2Et}} \xrightarrow[-\mathrm{Et_3N\cdot HCl}]{\mathrm{Et_3N}} \underset{\textstyle 3}{\mathrm{H_2N\overset{O}{C}CH_2SCH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}CH_2CO_2Et}}$$

$$\xrightarrow{\mathrm{ClCH_2\overset{O}{C}N{=}C{=}O}} \underset{\textstyle 4}{\mathrm{ClCH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}\overset{O}{C}CH_2SCH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}CH_2CO_2Et}} \xrightarrow{\mathrm{HSCH_2CO_2Et}}$$

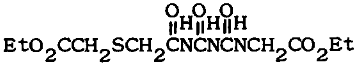
$$\underset{\textstyle 5}{\mathrm{EtO_2CCH_2SCH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}\overset{O}{C}CH_2SCH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}CH_2CO_2Et}}$$

Calcd for $C_{16}H_{24}N_4O_9S_2$: C, 40.00; H, 5.03; N, 11.66; S, 13.32. Found: C, 40.17; H, 4.74; N, 11.95; S, 13.02.

Further, a detailed study of the infrared absorption[4] of some acylurea derivatives was made by employing the dilution technique as a method of observing N-H stretch absorption due to inter- or intramolecular hydrogen bonding. The ratio of hydrogen-bonded N-H absorption (ca. 3235-3330 cm^{-1}) to free N-H absorption (ca. 3395-3410 cm^{-1}) remarkably increases as an acylurea derivative changes from 2 to 6 and from 6 to the acylbiuret derivative[5] (7) as shown in

$$\mathrm{ICH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}CH_2CO_2Et}$$

6



$$\mathrm{EtO_2CCH_2SCH_2\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}CH_2CO_2Et}$$

7

Fig.1. It is of special interest to note that 7 forms hydrogen bonds unexpectedly to a greater extent than 5 and that 7 is almost completely hydrogen-bonding at a concentration as low as 1.03×10^{-3}M. Acylbiuret derivative 7 appears to form stronger hydrogen bonds in comparison with the tetra-, penta- and hexapeptides reported by Shields[6]. It seems reasonable to conclude that the bands at 3235 and ca. 3265 cm^{-1} are primarily due to intermolecular hydrogen bonding in 6 and 7, respectively, and that the bands at ca. 3330 cm^{-1} arise from intramolecularly hydrogen-bonded NH groups. This is further supported by the observation that

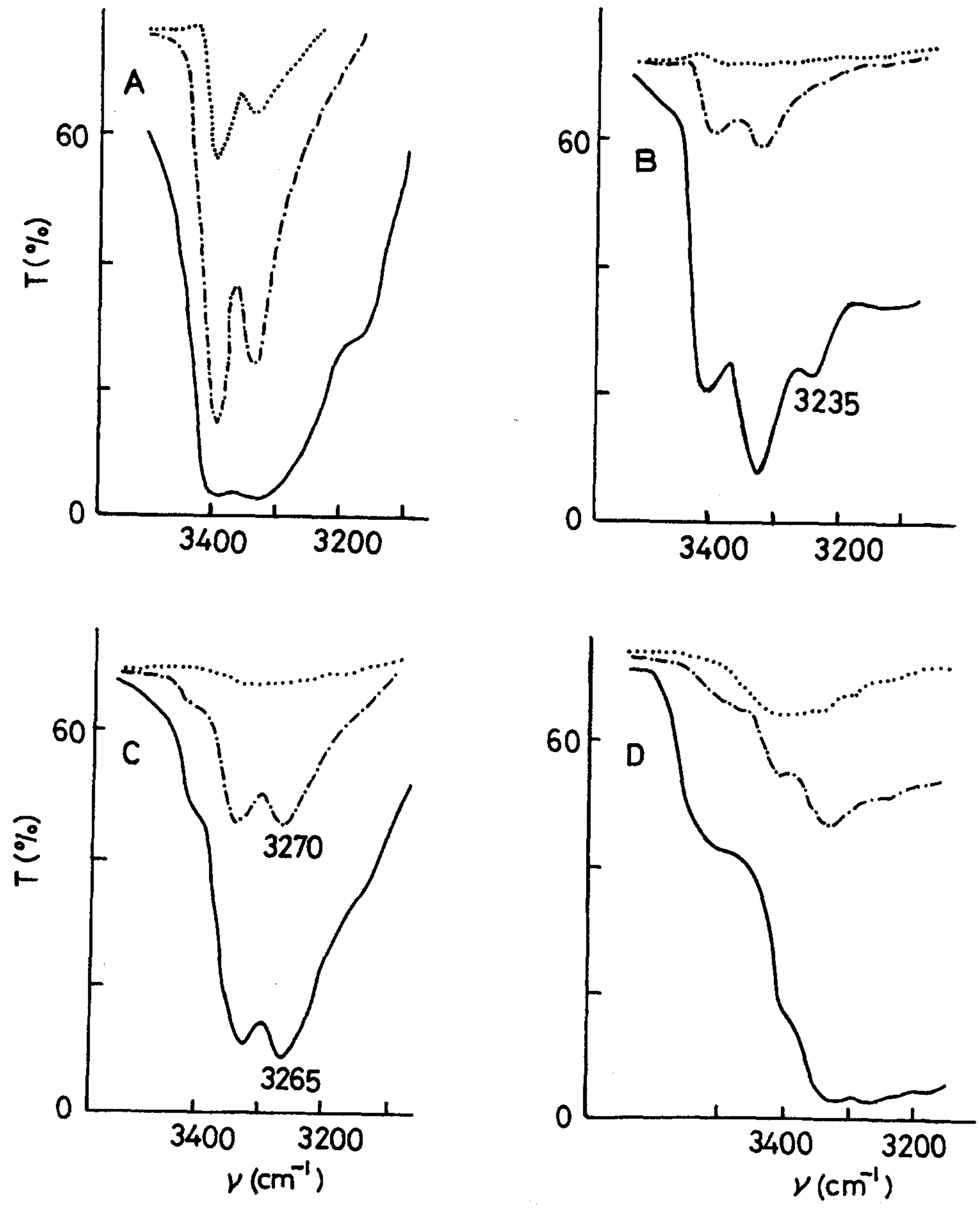
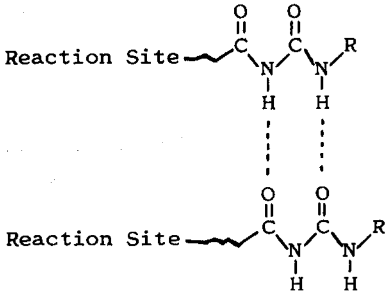


Fig.1. (A) Compound 2: ——, 5.30×10^{-2}; •—•—•, 1.06×10^{-2}; ········, 1.06×10^{-3}.
(B) Compound 6: ——, 1.02×10^{-2}; •—•—•, 1.02×10^{-3}; ·······, 1.02×10^{-4}.
(C) Compound 7: ——, 5.15×10^{-3}; •—•—•, 1.03×10^{-3}; ·······, 1.03×10^{-4}.
(D) Compound 5: ——, 1.04×10^{-2}; •—•—•, 1.04×10^{-3}; ·······, 1.04×10^{-4}.
Concentrations in moles/liter.

the new band present at the lower frequency (3235 cm^{-1}) disappeared on dilution in Fig.1B. In addition, the ratio of the intensity of the band at ca. 3265 cm^{-1} to that at ca. 3330 cm^{-1} in 7 increases substantially with increasing concentrations (Fig.1C). These observations suggest that the use of acylbiuret derivatives as model compounds would be effective for synthetic control by the intermolecular association as shown below. The result of this trial will be reported in the near future.



REFERENCES

1) All new compounds gave satisfactory elemental analytical values.
2) A. J. Speziale and L. R. Smith, J. Org. Chem., 27, 3742 (1962).
3) The structure of 5 was further established by its infrared and nmr spectra.
4) The path length of the solutions was 8 mm and KRS-5 windows were used in the cells. Chloroform was used as a solvent except that carbon tetrachloride was used in the case of 7. The use of chloroform in place of carbon tetrachloride as a solvent in the case of 7 caused no essential change in its infrared spectrum except for a shift to lower frequency by ca. 2 or 10 cm^{-1}.
5) This compound, mp 78-80°, was prepared in the same way as with 5.
6) J. E. Shields, S. T. McDowell, J. Pavlos, and G. R. Gray, J. Amer. Chem. Soc., 90, 3549 (1968).