

NEW SOLID 1:1 COMPLEXES OF ACYLUREA DERIVATIVES

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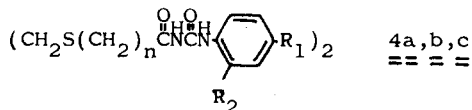
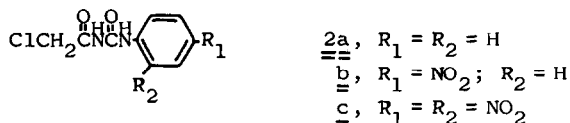
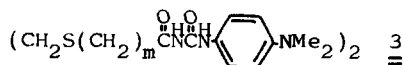
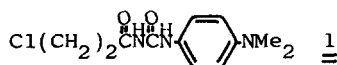
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In the course of the study on synthetic control<sup>1</sup> in which intermolecular hydrogen bonding and the other molecular interactions are so used as to control the course of organic reactions and to increase the reaction rate<sup>2</sup> through regulation of the orientation of a pair of model compounds, several attempts have been made to investigate the relationship between complex formation and selectivity of substitution reaction of a pair of chlorides having various acylurea linkages.

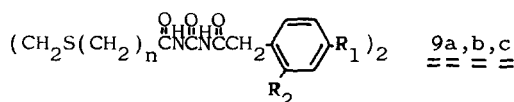
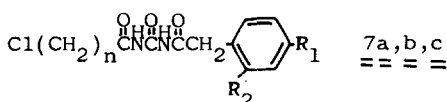
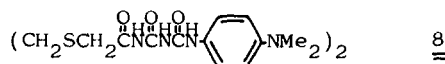
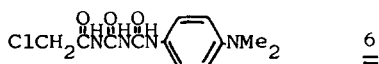
This paper describes a study on the formation of novel 1:1 complexes in relation to bioorganic chemistry. A pair of model compounds, a donor and an acceptor, are made up of both an "acylurea" moiety ( $\overset{\text{O}}{\parallel}\text{NH}-$ ,  $\overset{\text{O}}{\parallel}\text{NH}-\overset{\text{O}}{\parallel}\text{NH}-$ , or  $\overset{\text{O}}{\parallel}\text{NH}-\overset{\text{O}}{\parallel}\text{NH}-\overset{\text{O}}{\parallel}\text{NH}-$ ) being intended to participate in the intermolecular hydrogen bonding and a substituted aromatic ring to participate in charge-transfer interaction.<sup>3</sup> Chloroacylurea derivatives,<sup>4</sup> model compounds for this study, were easily prepared by treatment of acyl isocyanates with amines in ether at 0°, with amides in boiling acetonitrile, or with urea derivatives in acetonitrile at room temperature. Other model compounds, bissulfides<sup>4</sup> (white or pale yellow powder), were also readily synthesized by treatment of the corresponding chlorides with ethanedithiol and triethylamine in acetonitrile at room temperature.

Equimolar amounts of a pair of chlorides, 1 and 2c,<sup>5</sup> were dissolved in boiling acetonitrile, and then the solution was allowed to stand at room temperature. The solution became reddish orange, however, no solid complex could be



isolated. In contrast to the former case, treatment of bissulfide 3 ( $m=2$ , mp 216.5-217.0°(dec)) with bissulfide 4c ( $n=1$ , mp 218-219°(dec)) in DMF-acetonitrile afforded the reddish brown 1:1 complex (5), mp 189-190°(dec).<sup>6</sup> Anal. Calcd for  $\text{C}_{46}\text{H}_{54}\text{N}_{14}\text{O}_{16}\text{S}_4$ : C, 46.54; H, 4.59; N, 16.52; S, 10.78. Found: C, 46.45; H, 4.50; N, 16.40; S, 10.68.

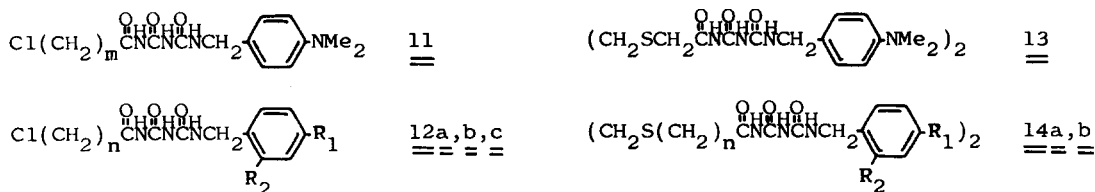
This interesting phenomenon was also observed in the next combinations of two chlorides and of two bissulfides. Although no solid complex between a pair of chlorides (6 and 7b ( $n=1$ )) could be isolated, bissulfide 8 (mp 204-205°(dec))



and bissulfide 9b ( $n=1$ , mp 175-178°) formed the yellow 1:1 complex (10), mp 201-202°(dec), in more than 53% yield. Similarly, the yellow complex (mp 192-193°(dec)) was isolated in more than 43% yield by use of 9b ( $n=2$ ) in place of 9b ( $n=1$ ) in the above experiment. The infrared spectrum of 10 showed a new carbonyl band at the lower frequency (1660  $\text{cm}^{-1}$ ) in comparison with that of a mixture of 8 and 9b ( $n=1$ ).<sup>7</sup>

These two observations indicate primarily that a 1:1 complex between a pair of bissulfides D-D and A-A having duplicated acylurea linkages was produced in some cases in contrast to the result that no complex formation was observed between a pair of chlorides D and A. This finding is of special interest in connection with allosteric proteins which are made up of two or more identical subunits.

In contrast to the results described above, it was demonstrated that the



use of 1-benzylbiuret derivatives as a donor and an acceptor leads to the formation of a 1:1 complex between a pair of chlorides. The 1:1 complex (15) of 11 ( $m=1$ , mp 166.0-166.5°(dec)) with 12b ( $n=1$ , mp 179.0-179.5°(dec)) was obtained in acetonitrile as reddish orange plates: mp 161.0-161.5°(dec); nmr (60 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.80 (s, 6, N(CH<sub>3</sub>)<sub>2</sub>), 4.24 (d, 2,  $J=1.8$  Hz,  $\text{NCH}_2\text{C}_6\text{H}_4\text{-NMe}_2$ ), 4.41 (s, 4, ClCH<sub>2</sub>CO), 4.50 (d, 2,  $J=1.8$  Hz,  $\text{NCH}_2\text{C}_6\text{H}_4\text{-NO}_2$ ), 6.84 (m, 4,  $\text{C}_6\text{H}_4\text{NMe}_2$ ), 7.76 (m, 4,  $\text{C}_6\text{H}_4\text{NO}_2$ ), 9.04 (b, 1, NH), 9.88 (b, 1, NH), 11.08 (b, 4, NH). Anal. Calcd for C<sub>24</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>8</sub>: C, 45.94; H, 4.60; N, 17.86. Found: C, 46.22; H, 4.35; N, 17.99. In case where  $m$  and  $n$  are 3 and 2, or 3 and 3, respectively, the 1:1 complexes of 11 with 12b could also be isolated as analytically pure crystals. The difference spectrum of 15 in THF showed a weak charge-transfer band at 395 nm ( $\epsilon=13$ ), while that of a 1:1 mixture of N,N-dimethylaniline and nitrobenzene showed no characteristic band under the same conditions.<sup>8</sup> This indicates that intermolecular hydrogen bonding<sup>7</sup> between the two acylurea parts in 11 and 12 "apparently" increased the interaction between the N,N-dimethylaminophenyl moiety and nitrophenyl one by keeping these two moieties in close proximity to each other. However, it was observed that 11 ( $m=1$ ) and 12c ( $n=1$ ) having 2,4-dinitrophenyl moiety did not form a solid 1:1 complex.

Bissulfide 13 (mp 188.0-188.5°(dec)) and bissulfide 14b ( $n=1$ , mp 198.0-198.5°(dec)) afforded similarly the reddish orange 1:1 complex (16), mp 201.0-201.5°(dec), in DMF-acetonitrile. There have been known many charge-transfer complexes,<sup>9</sup> hydrogen-bonded complexes between purine and pyrimidine bases,<sup>10</sup> and as special examples quinhydrone and its analogues.<sup>9,11</sup> Almost no reports have, however, been published on the complex formation in which both charge-transfer interaction and intermolecular hydrogen bonding are assumed to participate through the two distinct parts of a complex. Therefore, these solid 1:1 complexes deserve special emphasis in this respect.

The main conclusions to be drawn from the above results are as follows. First, a marked increase in possible molecular interactions leads to the formation of 1:1 complexes.<sup>7,12</sup> Second, possible complex formation depends primarily upon the number of methylene groups, m and n. Namely, the change of one methylene group in either a donor or an acceptor caused no complex formation in many cases where 1:1 complexes were obtained.<sup>6,8</sup> This phenomenon is closely related to the important problem in biology, the "recognition" of one methylene group. Some results concerning this problem will be published in the near future.

#### REFERENCES

- 1) The term "synthetic control" was kindly given to our investigation on this controlled organic reaction by Professor R. B. Woodward, Harvard University.
- 2) T. Mukaiyama, T. Endo, Y. Kojima, and T. Sato, J. Amer. Chem. Soc., 94, 7575 (1972).
- 3) This interaction may be explained as the dipole-dipole interaction.
- 4) All new compounds including solid 1:1 complexes in this paper gave satisfactory elemental analytical values. Their structures were further confirmed by their infrared and nmr spectra.
- 5) The symbols a, b, and c represent the aromatic rings being phenyl, 4-nitrophenyl, and 2,4-dinitrophenyl groups, respectively, in 2, 4, 7, 9, 12 and 14.
- 6) The 1:1 complex between 3 (m=1) and 4c (n=2) could not be isolated.
- 7) The infrared spectra of solid 1:1 complexes and of their components showed several hydrogen-bonded N-H bands in the range of ca. 3300 to 3100 cm<sup>-1</sup> and several carbonyl bands in the range of ca. 1770 to 1680 cm<sup>-1</sup>. Further, it has been demonstrated that some acylurea derivatives form strong N-H...O intermolecular hydrogen bonds in chloroform: T. Mukaiyama, T. Endo, and S. Noguchi, Tetrahedron Lett., 2291 (1971).
- 8) The 1:1 complex between 11 (m=2) and 12b (n=1) could not be isolated. The difference spectrum of a 1:1 mixture between the two chlorides in THF showed no characteristic band.
- 9) R. Foster, "Organic Charge-Transfer Complexes", Academic Press, London, 1969.
- 10) K. Hoogsteen, Acta Cryst., 12, 822 (1959); 16, 907 (1963).
- 11) These complexes, in which there is participation by the two interactions, are composed of two similar structures.
- 12) In general, the use of an acylurea derivative having at least one nitro group as an acceptor is necessary for solid 1:1 complex formation.