CHEMISTRY LETTERS, pp. 1959-1962, 1990.

A Novel Type of Dimerization of a U-Shaped Unsymmetrical Disulfide Having a Pair of Acylurea Linkages in Solution

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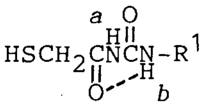
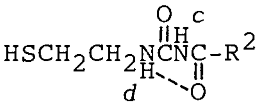
From NMR studies on an unsymmetrical disulfide having a pair of acylurea linkages, the disulfide (monomer) was suggested (i) to adopt a U-shaped conformation, based on the nonequivalence of the methylene protons and on NOE experimental data and (ii) to form dimers in solution.

Acylurea derivatives, open chain analogs of pyrimidine bases, participate in a variety of interesting chemical events. For example, crystalline 1:1 complex formation between them depends upon the shape of their substituents;[1)] the selectivity in oxidation of a pair of thiols (**1** and **2**), each having an acylurea linkage [-C(=O)NHC(=O)NH-], alters radically with the geometrical shape of nonpolar groups in R^1 and R^2.[2)] These observations are due to the ability of acylurea derivatives to strongly associate in solution.[2a,3)] With the above in mind, we examined the solution behavior of unsymmetrical disulfides (**3**) derived from **1** and



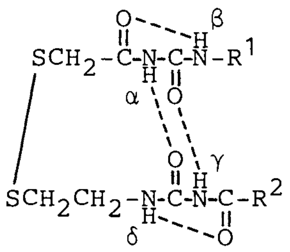
$\mathrm{HSCH_2C(=O)NHC(=O)NH\text{-}R^1}$

1



$\mathrm{HSCH_2CH_2NHC(=O)NHC(=O)\text{-}R^2}$

2



3

2, and report here the NMR evidence for the dimerization of a U-shaped unsymmetrical disulfide **3**.

Figure 1 shows a typical example of the concentration—chemical shift profiles for the NH protons of acylurea linkages both in a 1:1 mixture of thiols **1** and **2** and in the corresponding unsymmetrical disulfide **3**.[4,5] The data in Fig. 1 reveal that the chemical shifts for the H^{α} and H^{γ} protons at 0.001 mol/l in **3** are nearly equal to those at 0.020 (H^{a}) and 0.010 (H^{c}) mol/l, respectively, in the 1:1 mixture,[6] thus indicating that the H^{α} and H^{γ} protons each participate in the NH•••O *intramolecular* hydrogen bonds. This suggests that unsymmetrical disulfide **3** has a "U-shaped" structure.

The following observations support the above view. First, the CH_2 protons attached to both a sulfur atom and a carbonyl group in **3d** (R^1 = Ph and R^2 = i-C_6H_{13}) have proved not to be identical to each other, as exemplified by an "apparent" quartet (δ = 3.69 and 3.82 ppm, J = 14 Hz) in DMSO-d_6 at 35 °C.[7] Second, an NOE experiment on **3d** has revealed that irradiation of the meta protons of the phenyl group in **3d** caused an increase in the strength of the CH_3 protons (in the i-C_6H_{13} group) by 2% in DMSO-d_6 at 27 °C.

The concentration dependence of the H^{α} and H^{γ} resonances (Fig. 1) has turned out to be far larger than that for the H^{b} and H^{d} protons participating in intramolecular hydrogen bonds.[6] This finding cannot be explained by the presence of monomer **3** alone in solution, suggesting the presence of a fast equilibrium between two species—— monomer **3** and its multimer [*e.g.*, dimer (**4**)].

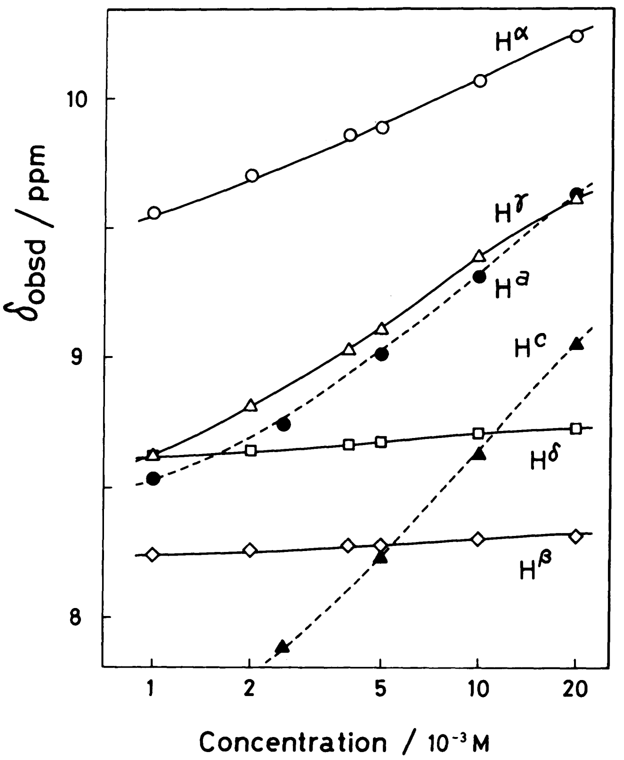


Fig. 1. Plots of δ_{obsd} for NH protons both in a 1:1 mixture of **1** (R^1 = n-C_5H_{11}) and **2** (R^2 = i-C_5H_{11}) and in **3e** (R^1 = n-C_5H_{11}, R^2 =i-C_5H_{11}) against the concentration (mol/l) in $CDCl_3$ at 35 °C. For the 1:1 mixture, the concentration is that for each thiol. ○, H^{α} in **3e**; ◇, H^{β} in **3e**; △, H^{γ} in **3e**; □, H^{δ} in **3e**; ●, H^{a} in the 1:1 mixture; ▲, H^{c} in the 1:1 mixture.

When a monomer (M) is equilibrated with a dimer (D) [2M $\rightleftharpoons$ D], the relationship $K = x_D / (x_M)^2$

holds, where K is the equilibrium constant for dimerization and x_D and x_M represent the concentrations of D and M, respectively. Since the observed chemical shift (δ_{obsd}) corresponds to the population weighted average for the two states (*i.e.*, M and D), δ_{obsd} is expressed as $\delta_{obsd} = (x_M/c)\delta_M + 2(x_D/c)\delta_D$, where δ_M and δ_D are the chemical shifts for pure M and D, respectively, and c (= $x_M + 2x_D$) is the concentration of **3** measured. These equations yield Eq. 1.

Table 1. K values for dimerization of disulfides **3** in $CDCl_3$ at 35 °C[a)]

3	R^1	R^2	K (l/mol)[b)]
3a	Ph	$n\text{-}C_5H_{11}$	58 ± 3
3b	Ph	$i\text{-}C_5H_{11}$	60 ± 2
3c	Ph	$n\text{-}C_6H_{13}$	46 ± 1
3d	Ph	$i\text{-}C_6H_{13}$	49 ± 2
3e	$n\text{-}C_5H_{11}$	$i\text{-}C_5H_{11}$	85 ± 4
3f	CH_3	$n\text{-}C_5H_{11}$	122 ± 7

a) Chemical shift measurements for each disulfide were made in total 10 to 14 times in the 0.001—0.020 mol/l range except for **3f** (6 times). b) Errors given are the standard deviations.

The K is obtained as follows: (i) estimation of δ_M from a δ_{obsd}—$1/c$ profile; (ii) determination of the tentative δ_D by use of the obtained δ_M in such a way that the deviations of K values for all of the observed c become least; (iii) determination of the tentative δ_M by use of the

$$K = \frac{\delta_M - \delta_D}{2c(\delta_{obsd} - \delta_D)}\left(\frac{\delta_M - \delta_D}{\delta_{obsd} - \delta_D} - 1\right) \qquad (1)$$

obtained δ_D in the same way as in procedure (ii); and (iv) optimization of a K value by repetition of procedures (ii) and (iii). Table 1 lists the data for K values, which range from *ca.* 50 to 120 l/mol with small

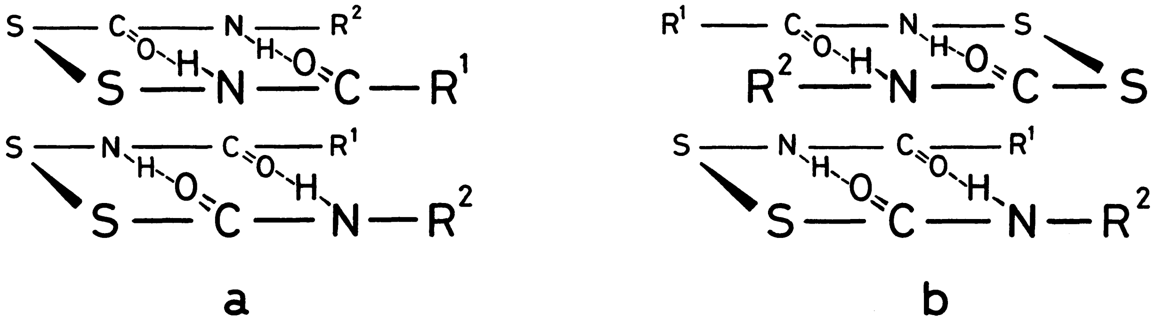


Fig. 2. Schematic drawings of possible structures of dimers **4** of **3**. --, Intramolecular hydrogen bond. Only inner -NHC(=O)- moieties in the -C(=O)NHC(=O)NH- groups are shown for simplicity.

errors < ± 7%.[8)] These results support the assumption on the monomer—single multimer (*i.e.*, dimer) equilibrium mentioned above.

Figure 2 shows possible structures of dimers (**4**) where H^{α} and H^{γ} protons form NH•••O *intramolecular* hydrogen bonds. The apparent enthalpy change[9)] for dimerization of **3c** (-6.0 ± 0.1 kcal/mol) was obtained by a usual van't Hoff plot.

In conclusion, the present study demonstrates that a U-shaped disulfide of relatively large molecular weight forms dimers in solution. The weak interactions responsible for the dimerization remain to be resolved.

We thank Mr. Takashi Isago, Mr. Shigeki Yagi, and Mr. Hideshi Gohara for their valuable assistance.

References

1) T. Endo, K. Miyazawa, M. Endo, A. Uchida, Y. Ohashi, and Y. Sasada, Chem. Lett., 1982, 1989; T. Endo, H. Tasai, K. Miyazawa, M. Endo, K. Kato, A. Uchida, Y. Ohashi, and Y. Sasada, J. Chem. Soc., Chem. Commun., 1983, 636.

2) a) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Hashimoto, and T. Ishigami, Nature, 268, 74 (1977); b) T. Endo, A. Okubo, Y. Kaneko, M. Uehara, H. Tasai, A. Sato, K. Nikki, N. Nakagawa, and S. Kamei, Bull. Chem. Soc. Jpn., 55, 2224 (1982); c) T. Endo, H. Takei, T. Isago, J. Kato, M. M. Ito, K. Guro, K. Akiyama, Y. Nakajima, and H. Kataoka, J. Am. Chem. Soc., 111, 8166 (1989).

3) T. Endo, Y. Takeda, T. Orii, Y. Kaneko, and M. Kondo, Chem. Lett., 1979, 1455.

4) Unsymmetrical disulfides **3** were prepared as described previously.[2c)] All new compounds had satisfactory spectroscopic data. The homogeneity of **3** was checked by HPLC.

5) ^1H NMR (270 MHz) spectra were measured in $CDCl_3$ on a JEOL GX-270 spectrometer with temperature regulating accessories using tetramethylsilane as an internal standard. The uncertainty in chemical shifts is < ± 0.01 ppm.

6) The H^b and H^d resonances in a 1:1 mixture of thiols **1** and **2** at 35 °C are shifted slightly from 8.15 to 8.26 and from 8.60 to 8.74, respectively, in going from 0.001 to 0.020 mol/l.

7) The apparent quartet for CH_2 protons has also been observed, for example, when (i) R^1 = Ph and R^2 = i-C_3H_7, (ii) R^1 = Ph and n-C_5H_{11}, and (iii) R^1 = p-$Me_2NC_6H_4$ and R^2 = n-C_5H_{11}.

8) The *K* can be obtained independently from both chemical shifts for the H^{α} and H^{γ} protons. The *K* values in Table 1 are the average of the values for these two protons.

9) This enthalpy change involves that for equilibrium between a conformer of U-shaped type and that of elongated one in **3**.

(Received August 2, 1990)