

## Shape Similarity between Solute and Solvent Molecules: Its Role in Specific Molecular Recognition in Hydrocarbon-containing Solvents

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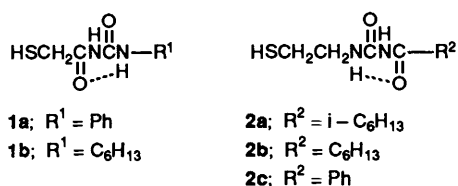
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Oxidation of a pair of associating thiols (**1** and **2**), each having a binding site [ $-\text{C}(=\text{O})\text{NHC}(=\text{O})\text{NH}-$ ] and a recognition site ( $\text{R}^1$  or  $\text{R}^2$ ), is examined mainly in hydrocarbon-containing (aqueous) alcohols. The selectivity ( $r$ ), a measure of the degree of recognition of **1** by **2** (or of **2** by **1**), in the oxidation is defined as the logarithmic ratio of the yield of an unsymmetrical disulfide to twice that of a symmetrical one. It is found that (i) higher selectivity is achieved when a hydrocarbon similar in shape to  $\text{R}^2$  is present in (aqueous) ethanol and (ii) the selectivity for  $\text{R}^2 = \text{Ph}$  ( $= \text{R}^1$ ) is higher in pure benzene than in aqueous ethanol. Correlation of the observed selectivity with physicochemical properties (relative permittivity and viscosity) of the pure solvents, reactivity difference between thiols, and other factors is discussed, together with a possible explanation of the specific recognition in terms of a 'shape similarity effect'.

Molecules, whether solute or solvent, interact with one another as well as with themselves. We have studied molecular recognition by using mainly nonpolar groups such as alkyl groups in molecular aggregates.<sup>1,2</sup> As a result a *similarity recognition hypothesis*<sup>2</sup> has been proposed, *i.e.* that three-dimensional shape similarity between interacting groups in reacting molecules is responsible for more specific and precise molecular recognition than would otherwise be achieved.

Recently we have demonstrated that higher selectivity is achieved when the nonpolar group of a propanol in a mixed solvent resembles a given nonpolar group of one of the reacting molecules in its three-dimensional shape.<sup>3</sup> This suggests that specific interactions operate between the nonpolar group of an alcohol acting as an organic cosolvent (*i.e.*, a propyl group) and a nonpolar group of the solute (*i.e.*, a propyl or pentyl group) and that the above hypothesis<sup>2</sup> could also be applied to shape similarity between solute and solvent molecules. This paper describes experimental evidence for the role of shape similarity between solute and solvent molecules in specific molecular recognition by using hydrocarbon-containing solvents and a pair of solutes, each with a hydrocarbon substituent.

Our model compound comprises a pair of acylurea derivatives (**1** and **2**), open-chain analogues of pyrimidine bases.

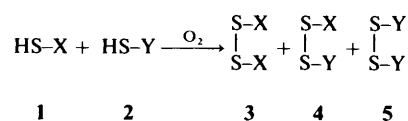


Thiols **1** and **2** each have three important sites: (i) the reaction site (SH group) where a model reaction occurs; (ii) the binding site [ $-\text{C}(=\text{O})\text{NHC}(=\text{O})\text{NH}-$ , acylurea bond] whose inner  $-\text{NHC}(=\text{O})-$  unit participates in two  $\text{NH} \cdots \text{O}$  intermolecular hydrogen bonds,<sup>2b,4</sup> and which extends in opposite directions to each other; and (iii) the recognition site ( $\text{R}^1$  or  $\text{R}^2$ ) that participates in the discrimination. In this study, we used three reaction systems (A, B and C) each containing a 1:1 mixture of **1** and **2**.

Reaction system A: **1a** + **2a**

Reaction system B: **1b** + **2b**

Reaction system C: **1a** + **2c**



Scheme 1

As a model reaction, oxidation with oxygen was chosen in relation to the correct pairing of half-cystine residues in proteins,<sup>†</sup> namely, specific S-S bond formation.

Oxidation of a 1:1 mixture of **1** and **2** with oxygen in the presence of a catalytic amount of triethylamine gives one unsymmetrical (**4**) and two symmetrical disulfides (**3** and **5**) (Scheme 1). The selectivity ( $r$ ), a measure of the degree of the recognition of **1** by **2** (or of **2** by **1**), is defined as the logarithmic ratio of the yield of unsymmetrical disulfide **4** to twice that of the symmetrical disulfide **3** [eqn. (1)].

$$r = \ln\{[4]/(2[3])\} \quad (1)$$

### Results and Discussion

In our previous work,<sup>3</sup> substituent  $\text{R}^1$  was mainly a  $p\text{-Me}_2\text{NC}_6\text{H}_4$  group, and the solvents were aqueous propanols. In order to verify the role of shape similarity between solute and solvent molecules,  $\text{C}_6\text{H}_{13}$  and Ph groups were used as  $\text{R}^1$ , and propanols (organic cosolvents) were replaced by hydrocarbons and lower alcohols. In the present study, we used the following three kinds of solvent systems: a hydrocarbon (RH) or an alcohol ( $\text{R}'\text{OH}$ ) itself (system I), binary mixtures of an  $\text{R}'\text{OH}$  with an RH or water (system II), and ternary mixtures containing an RH, an  $\text{R}'\text{OH}$ , and water (system III); the structure of an RH molecule is closely related to that of substituent  $\text{R}^2$ .

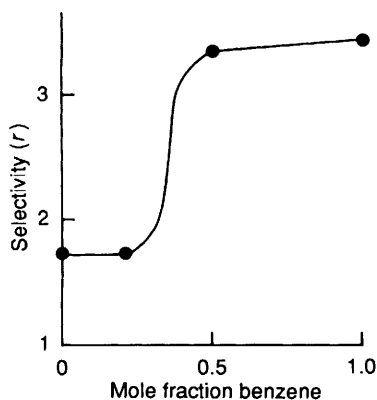
*Effect of Shape of a Hydrocarbon as a Cosolvent.*—First, the selectivity was examined in hydrocarbon-containing (aqueous) alcohols. In the case of reaction system B ( $\text{R}^2 = \text{C}_6\text{H}_{13} = \text{R}^1$ ), the effect of shape similarity between solute and solvent molecules was not observed: the selectivity at 35 °C remained practically unchanged with two solvent systems III [ $\text{C}_6\text{H}_{14}$ -

<sup>†</sup> The correct pairing of half-cystine residues has been suggested to depend upon specific noncovalent bonds.<sup>5</sup>

**Table 1** Selectivity ( $r$ ) in various solvent systems at 35 °C

R <sup>1</sup>	R <sup>2</sup>	Solvent			
		System <sup>a</sup>	RH	R'OH <sup>b</sup>	$r$
C <sub>6</sub> H <sub>13</sub>	C <sub>6</sub> H <sub>13</sub>	III	C <sub>6</sub> H <sub>14</sub> (0.30) <sup>c</sup>	PrOH(0.50) <sup>c</sup>	2.75(0.30) <sup>d</sup>
C <sub>6</sub> H <sub>13</sub>	C <sub>6</sub> H <sub>13</sub>	III	C <sub>8</sub> H <sub>18</sub> (0.30)	PrOH(0.50)	2.70(0.15)
Ph	i-C <sub>6</sub> H <sub>13</sub>	II	—	EtOH(0.90)	3.27(0.03)
Ph	i-C <sub>6</sub> H <sub>13</sub>	III	C <sub>6</sub> H <sub>14</sub> (0.30)	EtOH(0.60)	2.90(0.17)
Ph	i-C <sub>6</sub> H <sub>13</sub>	III	i-C <sub>6</sub> H <sub>14</sub> (0.30)	EtOH(0.60)	5.48(0.20)
Ph	i-C <sub>6</sub> H <sub>13</sub>	I	—	EtOH(1.00)	3.58(0.05)
Ph	i-C <sub>6</sub> H <sub>13</sub>	II	i-C <sub>6</sub> H <sub>14</sub> (0.30)	EtOH(0.70)	4.90(0.06)
Ph	Ph	II	—	EtOH(0.90)	1.72(0.05)
Ph	Ph	III	C <sub>6</sub> H <sub>6</sub> (0.50)	EtOH(0.40)	3.33(0.17)
Ph	Ph	III	C <sub>6</sub> H <sub>6</sub> (0.20)	EtOH(0.70)	1.72(0.26)
Ph	Ph	I	—	EtOH(1.00)	1.98(0.08)
Ph	Ph	II	C <sub>6</sub> H <sub>6</sub> (0.50)	EtOH(0.50)	5.36(0.25)
Ph	Ph	I	C <sub>6</sub> H <sub>6</sub> (1.00)	—	3.43(0.18)

<sup>a</sup> For solvent systems, see the text. <sup>b</sup> Methanol was not used as R'OH, because ternary mixtures (RH, MeOH and H<sub>2</sub>O) are generally immiscible with one another. <sup>c</sup> Values given in parentheses represent mole fractions of the components of the solvent systems. <sup>d</sup> Errors given in parentheses are three times the standard deviations.



**Fig. 1** Dependence of the selectivity ( $r$ ) for reaction system C at 35 °C in solvent system III (benzene–ethanol–water) upon mole fraction of benzene. Mole fraction of water was 0.1 except when mole fraction of benzene was 1.0. Errors (three times the standard deviations) for  $r$  values range from  $\pm 0.05$  to  $\pm 0.26$ .

PrOH–H<sub>2</sub>O ( $r = 2.75$ ) and C<sub>8</sub>H<sub>18</sub>–PrOH–H<sub>2</sub>O ( $r = 2.70$ ),\* mole fractions of the hydrocarbon and PrOH being 0.30 and 0.50, respectively (Table 1).

Interesting aspects of the data ( $R^2 = i\text{-C}_6\text{H}_{13}$ ) in Table 1 are that (i) the presence of isohexane (RH) in aqueous EtOH greatly increases the selectivity ( $r$ ) from 3.27 (solvent system II) to 5.48 (solvent system III), (ii) the use of hexane instead of isohexane markedly decreases the  $r$  value from 5.48 to 2.90, and (iii) the presence of isohexane in EtOH increases the selectivity from 3.58 (solvent system I) to 4.90 (solvent system II). A similar effect was observed for RH = C<sub>6</sub>H<sub>6</sub> ( $R^2 = \text{Ph}$ ) (Table 1):  $r$  values markedly increase (i) from 1.72 (EtOH–H<sub>2</sub>O) to 3.33 (C<sub>6</sub>H<sub>6</sub>–EtOH–H<sub>2</sub>O) and (ii) from 1.98 (EtOH) to 5.36 (C<sub>6</sub>H<sub>6</sub>–EtOH). These observations suggest that the presence of a hydrocarbon molecule similar in shape to a solute molecule in (aqueous) EtOH markedly increases the selectivity.

**Effect of Shape of a Hydrocarbon as a Pure Solvent.**—As the second approach to investigate the shape similarity effect mentioned above, pure benzene was chosen as a solvent (Table 1). The selectivity ( $R^2 = \text{Ph}$ ) in this solvent ( $r = 3.43$ ) turned out to be higher than in, for example, H<sub>2</sub>O–EtOH (mole fraction of EtOH = 0.90) ( $r = 1.72$ ). In this connection, the data in Fig. 1 show that the selectivity increases with mole

fraction of benzene ( $x_B$ ) in solvent system III in such a way that the  $r$  vs.  $x_B$  curve is sigmoid-like.

**Mechanism of the Oxidation.**—It has been demonstrated that the product ratio in this type of oxidation is kinetically controlled on the basis of the observations that (i) the product ratios do not change as the oxidation proceeds and (ii) a thiol–disulfide exchange reaction occurs only slowly under conditions similar to those for the oxidation.<sup>1</sup> Considering that the amount of the thiols participating in the thiol–disulfide exchange is reduced as the oxidation proceeds, the exchange reaction does not have so great an influence on the selectivity.

**Reaction Intermediates.**—<sup>1</sup>H NMR and IR spectroscopic studies of **1** and **2** revealed that **1** and **2** formed weak complexes in solution with each other as well as with themselves through two NH...O intermolecular hydrogen bonds.<sup>4a</sup> Since the two acylurea bonds in **1** and **2** extend in the opposite direction to each other, the association patterns of homodimers **6** and **8** are of head-to-tail type, that of the heterodimer **7** being of head-to-head type (Fig. 2).†

In homodimer **6** or **8**, the distance between the two HS groups is too long for the S–S bond to be formed. Therefore, homodimers **6** and **8** cannot explain the selective formation of symmetrical disulfides in some cases (i.e.,  $r < 0$ ).<sup>3,6</sup> Further, unsymmetrical disulfide **4** was suggested (i) to adopt a U-shaped conformation and (ii) to form dimers in solution.<sup>7</sup> On the basis of these findings, tetramers [two homotetramers (**9** and **13**) and three heterotetramers (**10–12**)] have been suggested to be intermediates in this oxidation (Fig. 3).<sup>2b,4a,‡</sup> There is now substantial evidence for the presence of tetramers in solution in chemical and biological systems.<sup>4a</sup>

**Factors Affecting the Selectivity.**—**Physicochemical properties of solvents.** Correlation of the  $r$  values for reaction system C ( $R^2 = \text{Ph}$ ) with the relative permittivity ( $\epsilon$ ) and viscosity ( $\eta$ ) of the pure solvent used for the oxidation was investigated. Since the order of  $\epsilon$  [2.28 (C<sub>6</sub>H<sub>6</sub>) < 24.55 (EtOH) < 37.5 (MeCN) <

\* Since octane–water mixtures were immiscible with methanol or ethanol, propyl alcohol was used in these two solvent systems III.

† See also footnote \* of ref. 3, (p. 1030).

‡ Each tetramer would afford the corresponding disulfide(s) selectively when treated with oxygen—(i) heterotetramers **10** and **11**, and probably **12**, would exclusively give the unsymmetrical disulfide **4** and (ii) homotetramers **9** and **13** would exclusively give symmetrical disulfides **3** and **5**, respectively. Relative concentrations of tetramers, which are considered to control the selectivity, depend primarily upon the reaction system employed (A, B or C).

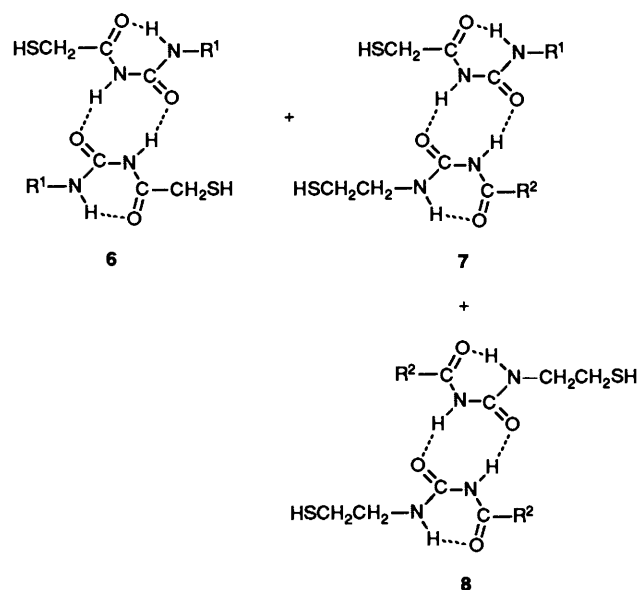


Fig. 2 Association patterns of three dimers 6–8. Dashed lines represent hydrogen bonds.

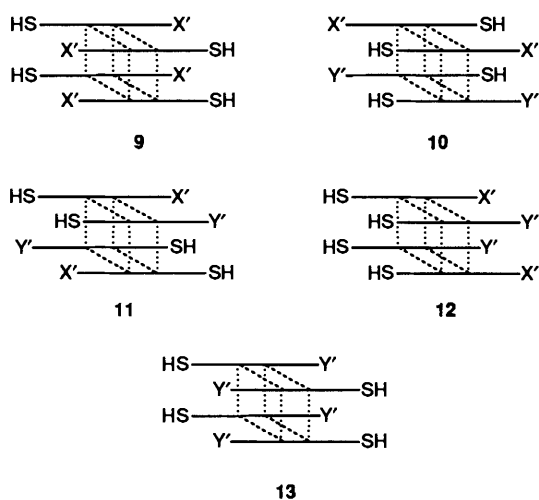


Fig. 3 Association schemes of tetramers 9–13 formed by dimerisation of dimers 6–8. -----, Hydrogen bonding responsible for the stabilisation of dimers; ·····, noncovalent weak interactions responsible for the stabilisation of tetramers.

78.39 (H<sub>2</sub>O)]<sup>8</sup> differs significantly from that of the corresponding  $r$  values in these solvents [1.31 (MeCN)<sup>9</sup> < 1.98 (EtOH) < 2.21 (H<sub>2</sub>O) < 3.43 (C<sub>6</sub>H<sub>6</sub>)],\* relative permittivities of the solvents fail to explain the selectivity.† Moreover, viscosity of the pure solvents cannot account for the selectivity, since the order of viscosity ( $\eta$ ) of pure solvents [0.33 (MeCN) < 0.60 (C<sub>6</sub>H<sub>6</sub>) < 0.89 (H<sub>2</sub>O) < 1.08 (EtOH)]<sup>8</sup> does not agree with that of the corresponding  $r$  values in these solvents.‡

**Reactivity difference between thiols.** Initial rates ( $v_0$ ), average rates until 5% consumption of thiols, for thiol **1** were *ca.* 100 times larger than those for thiol **2** in aqueous MeCN.<sup>10,11</sup> The large reactivity difference between thiols **1** and **2** is not responsible for the observed selectivity in aqueous mixed solvents. This is because  $r$  values should become negative

regardless of the reaction systems employed, if the selectivity depends upon the reactivity difference; however,  $r$  shows positive values for all reaction systems.§

Examples are known where relative rates for oxidation of a 1:1 mixture of **1** and **2** cannot explain the selectivity.<sup>10,12</sup>

**Heterogeneity of a reaction.** In solvent systems II and III, reaction mixtures are all homogeneous. However, there is a remarkable difference in the selectivity between these two solvent systems, regardless of the reaction system employed (Table 1). This clearly indicates that no relationship exists between the heterogeneity of the reaction and the selectivity.

**A Possible Explanation of the Specific Recognition in terms of 'Shape Similarity Effect'.**—The experimental results presented here indicate that the selectivity depends primarily upon the shape similarity between solute (practically, R<sup>2</sup>) and solvent (*i.e.*, RH) molecules. As mentioned previously,<sup>3</sup> there is the possibility that specific solvent structures are formed around tetramers **9–13**, though the detailed structures remain to be resolved. One possible explanation of the specific molecular recognition is that solvent molecules, including hydrocarbons, are assumed to be oriented specifically around the recognition sites (hydrocarbon substituents) of the tetramers so that the relationship between the shapes of solute and solvent molecules may affect interactions between solute molecules, thereby causing a change in the degree of molecular recognition.

The present work suggests that solute–solvent interactions would be so specific for the shapes of solute and solvent molecules as to influence the discrimination of nonpolar groups in solute molecules.

## Experimental

**General Procedures.**—<sup>1</sup>H NMR spectra were recorded with a JEOL GX-270 spectrometer. Chemical shifts ( $\delta$ ) are reported downfield from internal SiMe<sub>4</sub>. The mass spectral and exact mass data were taken on a JEOL JMS-DX303 mass spectrometer. M.p.s were determined on a Yamato oil-immersion apparatus and are uncorrected. HPLC separations were conducted on a Waters Model 204 system including a UV detector attached to a Waters 740 Data Module (integrator).

**Materials.**—Water was purified through a Millipore Milli-Q water purification system followed by distillation. Acetonitrile was purified by distillation from P<sub>2</sub>O<sub>5</sub> and then from CaH<sub>2</sub>. Ethanol was purified by distillation from Mg(OEt)<sub>2</sub>. Propyl alcohol and hydrocarbons were purified by distillation before use.

Thiols **1** were prepared by reaction of the corresponding thioesters [MeC(=O)SCH<sub>2</sub>C(=O)NHC(=O)NH-R<sup>1</sup>] with cysteamine as described previously.<sup>13</sup> The reaction mixtures were concentrated *in vacuo*, washed with water in order to remove acetylated cysteamine [MeC(=O)NHCH<sub>2</sub>CH<sub>2</sub>SH] because of high solubilities of the resulting thiols in MeCN, used as a solvent, dried *in vacuo*, and recrystallised from argon-saturated diethyl ether–hexane except for **1a** (benzene–hexane). Thiol **1** had the following properties [<sup>1</sup>H NMR (270 MHz) spectra of **1** were measured in CDCl<sub>3</sub> at 0.02 mol dm<sup>-3</sup>. Coupling constants are given in Hz].<sup>14</sup>

1-Hexyl-3-(mercaptoacetyl)urea **1b** (R<sup>1</sup> = C<sub>6</sub>H<sub>13</sub>): m.p. 96.0–98.0 °C (from diethyl ether–hexane) (Found: C, 49.2; H, 8.1; N, 12.8; S, 15.0. C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S requires C, 49.53; H, 8.31; N, 12.84; S, 14.66);  $\delta_{\text{H}}$  0.89 (3 H, t,  $J$  7), 1.23–1.57 (8 H, m), 2.07 (1 H,

\* Errors (three times the standard deviation) for  $r$  values range from  $\pm 0.05$  to  $\pm 0.18$ .

† The  $r$  values are at 25 °C except for MeCN (20 °C).

‡ The  $\eta$  values are at 25 °C except for MeCN (30 °C).

§ Triethylamine-catalysed oxidation of a 1:1 mixture of **1** (R<sup>1</sup> = *p*-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>) and **2** (R<sup>2</sup> = Ph, *p*-MeC<sub>6</sub>H<sub>4</sub>, or *p*-EtC<sub>6</sub>H<sub>4</sub>) in aqueous MeCN follows the rate equation<sup>10</sup>  $r = k_{1,3}[\text{RSH}][\text{Et}_3\text{N}]^{0.7}$ .

t, *J* 9, SH), 3.23–3.33 (4 H, m, SCH<sub>2</sub> and NCH<sub>2</sub>), 8.26 (1 H, s) and 9.42 (1 H, s); *m/z* 219 (M<sup>+</sup> + 1).

Thiols **2** were prepared by addition of the corresponding acyl isocyanates to freshly sublimed cysteamine in tetrahydrofuran (THF) under argon at 0 °C as described previously;<sup>1b</sup> their properties have already been reported.<sup>1b,14,15</sup>

**Preparation of Disulfides.**—Symmetrical disulfides **3** were easily obtained by treatment of **1** with O<sub>2</sub> in the presence of Et<sub>3</sub>N in MeCN at room temperature,<sup>1b</sup> and recrystallised from THF–dichloromethane. Unsymmetrical disulfides **4** were prepared by repeated recrystallisation of the oxidation mixture from THF–dichloromethane, since *r* values for all the oxidations described here were more than 1. Disulfides **3** and **4** had the following properties [<sup>1</sup>H NMR (270 MHz) spectra were measured in (CD<sub>3</sub>)<sub>2</sub>SO at 0.01 mol dm<sup>-3</sup>].<sup>6,16</sup>

1,1'-Bis(3-hexylureidocarbonylmethyl)disulfide **3b** (R<sup>1</sup> = C<sub>6</sub>-H<sub>13</sub>): m.p. 195.0–196.0 °C; δ<sub>H</sub> 0.86 (6 H, t, *J* 7), 1.20–1.61 (16 H, m), 3.10–3.18 (4 H, m, NCH<sub>2</sub>), 3.64 (4 H, s, SCH<sub>2</sub>), 8.16 (2 H, s) and 10.41 (2 H, s) (Found: M<sup>+</sup> + 1, 435.2079. Calc. for <sup>12</sup>C<sub>18</sub>-<sup>1</sup>H<sub>35</sub><sup>14</sup>N<sub>4</sub><sup>16</sup>O<sub>4</sub><sup>32</sup>S<sub>2</sub>: M + 1, 435.2103).

2-(3-Hexylcarbonylureido)ethyl 1-(3-hexylureidocarbonylmethyl)disulfide **4bb** (R<sup>1</sup> = R<sup>2</sup> = C<sub>6</sub>H<sub>13</sub>): m.p. 170.0–171.5 °C; δ<sub>H</sub> 0.86 (6 H, t, *J* 7), 1.14–1.58 (16 H, m), 2.21–2.31 (2 H, m, COCH<sub>2</sub>CH<sub>2</sub>), 2.82–2.91 (2 H, m, SCH<sub>2</sub>CH<sub>2</sub>N), 3.12–3.20 (2 H, m, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.30–3.61 (4 H, m, SCH<sub>2</sub>CH<sub>2</sub>NH and SCH<sub>2</sub>CO), 8.56 (1 H, s), 10.30 (2 H, s) and 10.42 (1 H, s) (Found: M<sup>+</sup> + 1, 449.2262. Calc. for <sup>12</sup>C<sub>19</sub><sup>1</sup>H<sub>37</sub><sup>14</sup>N<sub>4</sub><sup>16</sup>O<sub>4</sub><sup>32</sup>S<sub>2</sub>: M + 1, 449.2259).

2-(3-Phenylcarbonylureido)ethyl 1-(3-phenylureidocarbonylmethyl)disulfide **4ac** (R<sup>1</sup> = R<sup>2</sup> = Ph): m.p. 178.0–179.0 °C (Found: C, 52.7; H, 4.8; N, 12.7; S, 14.8. C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> requires C, 52.78; H, 4.66; N, 12.96; S, 14.80); δ<sub>H</sub> 2.95–3.01 (2 H, m, SCH<sub>2</sub>CH<sub>2</sub>N), 3.52–3.62 (2 H, m, SCH<sub>2</sub>CH<sub>2</sub>N), 3.71–3.80 (2 H, m, SCH<sub>2</sub>CO), 7.06–7.97 (10 H, m), 10.32 (1 H, s), 10.73 (2 H, s) and 10.83 (1 H, s); *m/z* 432 (M<sup>+</sup>).

**Oxidation of a Pair of Thiols.**—A mixture of **1** (0.50 mmol) and **2** (0.50 mmol) in a solvent (12.5 cm<sup>3</sup>) was stirred vigorously under oxygen for 15 min in a well-stirred water bath held at 35.0 ± 0.1 °C. To this mixture was added Et<sub>3</sub>N (0.05 mmol), and vigorous stirring was continued for the time required to complete the oxidation (the oxidation was performed at least twice under the same conditions). When the oxidation was complete, the reaction mixture was evaporated to dryness. The yields of **3** and **4** were determined from their absorption at 254 nm after separation of the three disulfides **3–5** in the mixture by HPLC using LiChrosorb CN with hexane–Pr<sup>i</sup>OH (95:5) as an eluent. The *r* values given in Fig. 1 and Table 1 represent the

mean values of two or more experiments, and were reproducible to within the errors shown. Errors in *r* values shown in the text and figure captions are three times the standard deviations.

### Acknowledgements

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