Marked Effect of the Shape of Solvent Molecules on Molecular Recognition in the Oxidation of Associating Thiols

Tadashi Endo,* Hiromichi Takei, Takashi Isago, Kazuo Guro, Yutaka Nakajima, Jun-ichi Kato,† and Masato M. Ito‡
Department of Chemistry, College of Science and Engineering, Aoyama Gakuin University, Chitosedai, Setagaya-ku, Tokyo 157, Japan

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Oxidation of a pair of associating thiols (**1** and **2**), each having a binding site [–C(O)NHC(O)NH–] and a recognition site (R^1 or R^2), is examined in binary solvent mixtures of a propanol with water and organic co-solvents. The selectivity (*r*)—a measure of the degree of recognition of (**1**) by (**2**) [or of (**2**) by (**1**)]—in the oxidation is represented by the logarithmic ratio of the yield of an unsymmetrical disulphide to twice that of a symmetrical one. It is found that (*i*) higher selectivity is achieved when the non-polar group of a propanol in a mixed solvent resembles a given non-polar group of one of the reacting molecules in three-dimensional shape and (*ii*) the above solvent shape effect' on the selectivity is produced more markedly in aqueous propanols than in the corresponding non-aqueous ones. Correlation of the observed selectivity with physico-chemical properties of (aqueous) propanols, reactivity difference between thiols, and so on is discussed together with a possible explanation of the solvent shape effect on the degree of recognition of non-polar groups.

Many attempts have been made to elucidate factors controlling chemical selectivity. These include electronic effects,[1] steric effects,[2] and proximity effects through chelation,[2] micelle formation,[3] inclusion,[4] and hydrogen bonding.[5] Solvent effects on chemical selectivity have also been investigated.[6–10] These effects were, however, mainly examined from the point of view of *polarity* of solvents.

Another interesting property of a solvent is its *three-dimensional shape.* If reactions are performed in molecular aggregates, the shape of solvent molecules might be expected to affect chemical selectivity as well as reactivity due to its influence on, for example, the stability of the aggregates.

We report here the full details on the effect of the shape of solvent molecules on the selectivity in oxidation of a pair of associating thiols by using binary solvent mixtures of a propanol with water and organic co-solvents.[11]

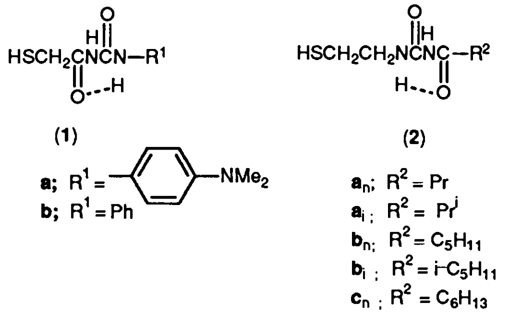
Our model compound comprises a pair of acylurea derivatives (**1**) and (**2**), open-chain analogues of pyrimidine bases (*e.g.*, uracil and thymine). Thiols (**1**) and (**2**) each have the three sites—(*i*) the reaction site (SH group) where a model reaction occurs, (*ii*) the binding site [–C(O)NHC(O)NH–, acylurea bond] the inner –NHC(O)– unit of which participates in two NH ··· O intermolecular hydrogen bonds[12] and extends in the opposite direction, and (*iii*) the recognition site (R^1 or R^2) that participates in the discrimination. Thiol (**1**) has the same group as a cysteine side chain ($HSCH_2$), (**2**) being a derivative of cysteamine (the decarboxylated compound of cysteine).

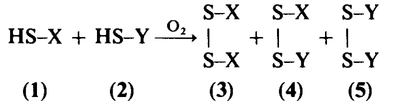
In this study, we used two sets of reaction systems: (*i*) systems A_{n3}, A_{i3}, A_{n5}, and A_{i5} and (*ii*) systems B_{n5}, B_{i5}, and B_{n6}. System

System A_{n3}: (**1a**) + (**2a**$_n$) System A_{i3}: (**1a**) + (**2a**$_i$)
System A_{n5}: (**1a**) + (**2b**$_n$) System A_{i5}: (**1a**) + (**2b**$_i$)
System B_{n5}: (**1b**) + (**2b**$_n$) System B_{i5}: (**1b**) + (**2b**$_i$)
System B_{n6}: (**1b**) + (**2c**$_n$)

A_{n3} consists of a 1:1 mixture of (**1a**) and (**2a**$_n$) [R^2 = Pr], A_{i3} of (**1a**) and (**2a**$_i$) [R^2 = Pr^i], and so on.

As a model reaction, oxidation by oxygen was chosen in relation to the correct pairing of half-cystine residues in proteins,[13] 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 disulphides (**3** and **5**) (Scheme). The





$$HS\text{–}X + HS\text{–}Y \xrightarrow{O_2} \begin{matrix} S\text{–}X \\ | \\ S\text{–}X \end{matrix} + \begin{matrix} S\text{–}X \\ | \\ S\text{–}Y \end{matrix} + \begin{matrix} S\text{–}Y \\ | \\ S\text{–}Y \end{matrix}$$

(1) (2) (3) (4) (5)

Scheme.

selectivity (*r*)—a measure of the degree of the recognition of (**1**) by (**2**) [or of (**2**) by (**1**)]—is represented by the logarithmic ratio of the yield of unsymmetrical disulphide (**4**) to twice that of symmetrical disulphide (**3**) [equation (1)].

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

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† *Present address:* Department of Applied Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184, Japan.

‡ *Present address:* Department of Chemical Engineering, Faculty of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan.

Table 1. The selectivity (r) in oxidation of systems A_{n5} and A_{i5} ($R^1 = p\text{-}Me_2NC_6H_4$) in aqueous binary solvent systems each containing a propanol (PA).

	R^2			
	C_5H_{11} (A_{n5})		i-C_5H_{11} (A_{i5})[a]	
x_{PA}	r_n	r_i	r_n	r_i
0.36	−1.69(0.02)[b]	−2.25(0.03)	1.25(0.04)	1.82(0.05)
0.50	−1.75(0.06)	−2.45(0.04)	0.75(0.03)	1.64(0.03)
0.60	−1.93(0.01)	−2.19(0.04)	1.23(0.05)	1.65(0.05)
0.85	−2.00(0.04)	−2.56(0.05)	1.77(0.03)	1.92(0.04)
1.00	0.77(0.04)	0.13(0.02)	1.91(0.05)	2.29(0.07)

[a] i-C_5H_{11} = $CH_2CH_2CH(CH_3)_2$. [b] Errors given in parentheses are three times the standard deviations.

Table 2. The selectivity (r) in oxidation of systems A_{n3} and A_{i3} ($R^1 = p\text{-}Me_2NC_6H_4$) in aqueous binary solvent systems each containing a propanol (PA).

	R^2			
	Pr (A_{n3})		Pr^i (A_{i3})	
x_{PA}	r_n	r_i	r_n	r_i
0.20	−0.51(0.06)[a]	−1.03(0.05)	1.49(0.03)	1.55(0.04)
0.50	−0.26(0.03)	−0.76(0.05)	0.62(0.04)	1.03(0.02)
0.80	−0.12(0.01)	−1.16(0.05)	0.77(0.06)	1.17(0.03)
1.00	1.54(0.03)	1.29(0.02)	0.92(0.04)	1.84(0.04)

[a] Errors given in parentheses are three times the standard deviations.

Table 3. The selectivity (r) and the Δr[a] in oxidation of systems B_{n5}, B_{i5}, and B_{n6} (R^1 = Ph) in aqueous binary solvent systems each containing a propanol (PA) (x_{PA} = 0.50).

R^2	r_n	r_i	Δr
C_5H_{11}	−1.89(0.06)[b]	−2.48(0.13)	0.59
i-C_5H_{11}	1.09(0.08)	2.82(0.11)	1.73
C_6H_{13}	−2.50(0.04)	−3.03(0.15)	0.53

[a] $\Delta r = |r_i - r_n|$. [b] Errors given in parentheses are three times the standard deviations.

Table 4. The selectivity (r) and the Δr[a] in oxidation of systems A_{n5} and A_{i5} ($R^1 = p\text{-}Me_2NC_6H_4$) in binary solvent systems each containing a propanol (PA) (x_{PA} = 0.50).

R^2	Solvent	r_n	r_i	Δr
C_5H_{11}	H_2O–PrOH	−1.75(0.06)[b]	−2.45(0.04)	0.70
C_5H_{11}	MeCN–PrOH	−1.70(0.02)	−1.84(0.04)	0.14
i-C_5H_{11}	H_2O–PrOH	0.75(0.03)	1.64(0.03)	0.89
i-C_5H_{11}	MeCN–PrOH	1.27(0.04)	1.70(0.03)	0.43

[a,b] See footnotes to Table 3.

Results and Discussion

The Selectivity in Aqueous Propanols.—The selectivity was first investigated in a pair of *aqueous* mixed solvents, propyl alcohol–water and isopropyl alcohol–water. Table 1 shows the r values for a pair of systems A_{n5} and A_{i5} in these solvents. The r values for system A_{n5} ($R^2 = C_5H_{11}$) are larger in aqueous PrOH than in aqueous Pr^iOH regardless of solvent composition studied. In contrast, for system A_{i5} [R^2 = i-C_5H_{11}], r values are larger in aqueous Pr^iOH than in aqueous PrOH. In Table 2 is given the r for a pair of systems A_{n3} and A_{i3}. The r values for system A_{n3} (R^2 = Pr) are larger in aqueous PrOH, whereas those for system A_{i3} [$R^2 = Pr^i$] are larger in aqueous Pr^iOH. These results indicate that the selectivity for a system having a *branched alkyl* group becomes higher in aqueous *isopropyl* alcohol, whereas that for a system having a *straight-chain alkyl* group becomes higher in aqueous *propyl* alcohol.

In order to examine whether or not the observed 'solvent shape effect' depends upon the structures of a pair of thiols [*i.e.*, the necessity of a *p*-(dimethylamino)phenyl group], the selectivity was investigated for other reaction systems (B_{n5}, B_{i5}, and B_{n6}) (Table 3). As a result, it has been found that the solvent shape effect is also produced in these three systems.

Another measure of the solvent shape effect is to examine difference (Δr) between the selectivity in aqueous Pr^iOH (r_i) and that in aqueous PrOH (r_n) [$\Delta r = |r_i - r_n|$]. The Δr becomes largest for system B_{i5} (R^2 = i-C_5H_{11}) [Table 3, mole fraction of a propanol (x_{PA}) = 0.50]. The results mentioned above demonstrate that higher selectivity is achieved when the non-polar group of a propanol in a mixed solvent resembles a given non-polar group of one of the reacting molecules in three-dimensional shape.[11]

The Selectivity in Non-aqueous Mixed Solvents each Containing a Propanol.—Recently, we proposed that water in aqueous mixed solvents would *amplify* the degree of recognition of non-polar groups.[14] It is, thus, assumed that the solvent shape effect on the selectivity would be produced more markedly in aqueous propanols than in the corresponding non-aqueous ones. This has proved to be true for systems A_{n5} and A_{i5} (Table 4)—for example, the Δr for system A_{n5} is much larger in water–propanol (0.7) than in acetonitrile–propanol (0.1). The data in Table 4 suggest that water in mixed solvents enhances the solvent shape effect.

Reaction Intermediates.—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.[12a] Since the two acylurea bonds in (**1**) and (**2**) extend in the opposite direction to each other, association patterns of homodimers (**6** and **8**) are of the head-to-tail type, that of heterodimer (**7**) being of the head-to-head type (Figure 1).* In homodimer (**6**) or (**8**), the distance between the two HS groups is too great for the S–S bond to be formed. Therefore, homodimers (**6**) and (**8**) cannot explain the *selective* formation of *symmetrical* disulphides (*i.e.*, $r < 0$) in several cases: systems A_{n3}, A_{n5}, B_{n5}, and B_{n6} in aqueous propanols (Tables 1–3).

Assuming that a single multimer species in equilibrium with a monomer is a dimer, the degree of association (f), obtained by dividing the stoicheiometric mole fraction of a solute by the

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* Association patterns of homodimers and heterodimers are governed by the type of hydrogen bonds in which each hydrogen atom in an acylurea bond [$-C(O)NH^{\alpha}C(O)NH^{\beta}\text{-}R^1$ or $-NH^{\delta}C(O)NH^{\gamma}C(O)\text{-}R^2$] participates: ^1H NMR and X-ray studies of acylurea derivatives showed clearly that H^{β} and H^{δ} protons each participate in intramolecular (cyclic) hydrogen bond, while H^{α} and H^{γ} protons each participate in intermolecular hydrogen bond (Figure 1). In order for the two NH···O intermolecular hydrogen bonds to be formed between a pair of thiols (**1**) and (**2**), therefore, homodimers must be of the head-to-tail type (but not the head-to-head one), and heterodimers must be of the head-to-head type (but not head-to-tail one).

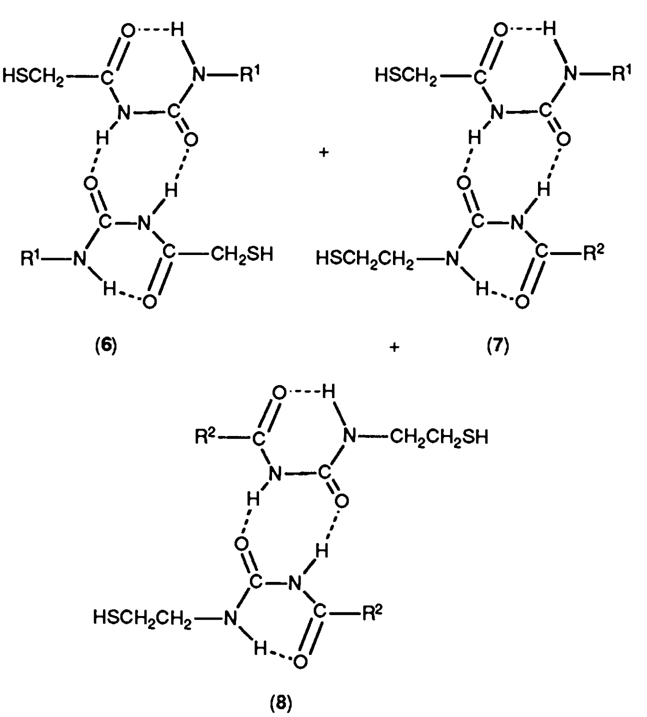

Figure 1. Association patterns of three dimers (6–8). – – – –, Hydrogen bonding.

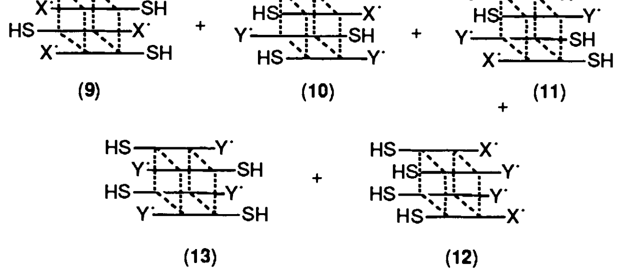

Figure 2. Association schemes of tetramers (9)–(13) formed by dimerisation of dimers (6)–(8). – – – –, Hydrogen bonding responsible for the stabilisation of dimers; · · · ·, non-covalent weak interactions responsible for the stabilisation of tetramers.

effective mole fraction of the solute,[15] ranges from 1.0 to 2.0.* The f of 1.95 for (**2b**$_i$) (at 0.06 mol dm^{-3} and 36.0 °C in CCl_4) thus suggested the presence of higher aggregates in addition to dimers.[12a]

On the basis of these findings, tetramers [two homotetramers (**9**) and (**13**) and three heterotetramers (**10**)–(**12**)] were suggested to be intermediates in this oxidation (Figure 2).[12a,†] There is now substantial evidence for the presence of tetramers in solution in chemical and biological systems.[12a,16]

Factors Affecting the Selectivity.—Physico-chemical properties of (aqueous) propanols. Propyl alcohol is only slightly more polar than isopropyl alcohol, as indicated by their relative permittivities (20.33 for PrOH and 19.92 for Pr^{i}OH at 25 °C) and $E_T(30)$ values[17] (50.7 for PrOH and 48.6 kcal mol^{-1} for Pr^{i}OH).[7] However, these two isomeric propanols have the same dipole moment[7] (5.54×10^{-30} C m).‡

The relative permittivity of aqueous propanols vary progressively with solvent composition (x_{PA}).[18] This property thus appears to have no correlation with the selectivity, since the dependence of the r on solvent composition passes through both a maximum and a minimum (Tables 1 and 2).

Reactivity difference between thiols. Initial rates (v_0), average rates until 5% consumption of thiols, for thiol (**1**) were about 100 times larger than those for thiol (**2**) in aqueous MeCN.[19,20] The large reactivity difference between thiols (**1**) and (**2**) is not responsible for the observed selectivity in aqueous propanols. This is because r values should become negative regardless of the reaction systems employed, if the selectivity depends upon the reactivity difference; however, the r shows large positive values for systems A_{i3}, A_{i5}, and B_{i5} (Tables 1–3).§

Examples are known where relative rates for oxidation of a 1:1 mixture of (**1**) and (**2**) cannot be used to explain the selectivity.[19,21]

Heterogeneity of reaction. In aqueous propanols, reaction mixtures are homogeneous for systems B_{n5}, B_{i5}, and B_{n6} at 35 °C. The r values, however, change remarkably from -3.03 to 2.82 (Table 3). This clearly indicates that no relationship exists between the heterogeneity of the reaction and the selectivity.

A possible explanation of the solvent shape effect. As mentioned above, the selectivity is controlled by the three-dimensional shape of solvent molecules. This suggests that specific interactions operate between a non-polar group of an organic co-solvent (*i.e.*, a Pr group) and a non-polar group of a solute (*i.e.*, R^2). In view of the above assumption, there is the possibility that specific solvent structures are formed around the tetramers.

We have shown that the degree of the recognition between molecules each having a non-polar group can be controlled by the strength of shape-specific weak interactions between the non-polar groups in the respective molecules.[21,22] One possible explanation of the *solvent shape effect* is that specific solvent structures—the formation of which may be assisted by water in aqueous mixed solvents—around the tetramers enable the recognition sites (R^1 and R^2) to orientate themselves, thereby affecting R^1–R^2 and/or R–Pr interactions.

Recently we have proposed that the three-dimensional shape similarity between interacting groups in reacting molecules is responsible for more specific and precise molecular recognition than would otherwise be achieved.[12c,23] This hypothesis has originally been intended to be applied to shape similarity between solute molecules. Our work suggests that the hypothesis would also be applied to shape similarity *between solute and solvent* molecules.

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* In monomer–dimer equilibrium, the constant for dimerisation (K) is given as $K = f(f - 1)/\{c(f - 2)^2\}$, where c represents the stoicheiometric concentration. Thus, the f of 1.95 (0.06 mol dm^{-3}) corresponds to the K of 1.24×10^4 dm^3 mol^{-1}; the f of 1.3 and 1.5 (0.01 mol dm^{-3}) corresponds to the K of 80 and 300, respectively.

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

‡ Further, it is known that (*i*) the υ (a parameter for steric effect) is 0.68 or 0.76 for Pr or Pr^i group, respectively, and (*ii*) the δ_{SA} (a measure of the extent of self-association of an amphiprotic solvent) is 1.8 or 1.5 for propyl or isopropyl alcohol. M. Charton, *Top. Curr. Chem.*, 1983, **114**, 57. M. J. Kamlet, R. Doherty, R. W. Taft, and M. H. Abraham, *J. Am. Chem. Soc.*, 1983, **105**, 6741.

§ Triethylamine-catalysed oxidation of a 1:1 mixture of (**1a**) and (**2**) (R^2 = Ph, p-MeC_6H_4, or p-EtC_6H_4) in aqueous MeCN follows the rate equation[19] $v = k_{1.7}[RSH][Et_3N]^{0.7}$.

Experimental

General Procedures.—^{1}H NMR spectra were recorded with a JEOL GX-270 spectrometer. Chemical shifts (δ) are reported downfield from internal $SiMe_4$. The mass spectra were taken on a Hitachi RMU-6M spectrometer and exact mass data on a JEOL JMS-DX303 mass spectrometer. Melting points 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 CaH_2 and then from P_2O_5. Propanols were purified by distillation before use.

Thiols (**1**) were prepared by reaction of the corresponding thiolesters [$MeC(O)SCH_2C(O)NHC(O)NH$-R^1] with cysteamine as described before.[24] In the case of thiol (**1b**), the reaction mixture was concentrated *in vacuo*, washed with water in order to remove the co-existing acetylated cysteamine [$MeC(O)NHCH_2CH_2SH$] because of high solubility of the resulting thiol in MeCN used as a solvent, dried *in vacuo*, and recrystallised from argon-saturated benzene–hexane.[25,26]

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[26] and had the following properties [^{1}H NMR (270 MHz) spectra of (**2**) were measured in $CDCl_3$ at 0.02 mol dm^{-3}].[14,27]

(2a$_i$) (R^2 = Pr^i). M.p. 115.0–117.0 °C (from ether–hexane) (Found: C, 44.2; H, 7,4; N, 14.7; S, 16.6. $C_7H_{14}N_2O_2S$ requires C, 44.2; H, 7.4; N, 14.7; S, 16.8%); δ 1.21 (6 H, d, *J* 6 Hz, $CH(CH_3)_2$], 1.43 (1 H, t, *J* 8 Hz, SH), 2.46–2.56 (1 H, m, COCH), 2.71 (2 H, q, *J* 7 Hz, SCH_2), 3.50 (2 H, m, NCH_2), 8.55 (1 H, s), and 8.80 (1 H, s); *m/z* 190 (M^+).

Preparation of Disulphides.—Symmetrical disulphides (**3**) were easily obtained by treatment of (**1**) with O_2 in the presence of Et_3N in MeCN at room temperature, and recrystallised from THF–dichloromethane.[14,26]

Unsymmetrical disulphides (**4**) were prepared either by repeated recrystallisation of the oxidation mixture in cases where the *r* for a given system was larger than *ca.* 1 or by reaction of a disulphide [$2,4$-$(NO_2)_2C_6H_3S$-$SCH_2CH_2NHC(O)NHC(O)$-R^2] with thiol (**1**) in the presence of silver acetate in *N,N*-dimethylformamide (DMF) under argon as described previously[28] followed by recrystallisation of the reaction mixture in cases where the *r* for a given system was smaller than *ca.* 1. Disulphides (**4**) had the following properties [^{1}H NMR (270 MHz) spectra were measured in [$^2H_6$]DMSO at 0.01 mol dm^{-3}].[14]

(4aa$_n$) (R^1 = *p*-$Me_2NC_6H_4$ and R^2 = Pr). M.p. 172.0–173.0 °C (from THF–CH_2Cl_2) (Found: C, 48.8; H, 6.2; N, 16.2; S, 14.8. $C_{18}H_{27}N_5O_4S_2$ requires C, 49.0; H, 6.2; N, 15.9; S, 14.5%); δ 0.85 (3 H, t, *J* 7 Hz, CH_3), 1.46–1.59 (2 H, m, CH_2Me), 2.25 (2 H, t, *J* 7 Hz, $COCH_2$), 2.86 [6 H, s, $N(CH_3)_2$], 2.89–2.94 (2 H, m, SCH_2CH_2N), 3.45–3.52 (2 H, m, SCH_2CH_2N), 3.68–3.77 (2 H, m, SCH_2CO), 6.70 (2 H, d, *J* 9 Hz), 7.32 (2 H, d, *J* 9 Hz), 8.59 (1 H, s), 10.04 (1 H, s), 10.29 (1 H, s), and 10.69 (1 H, s); *m/z* 441 (M^+).

(4aa$_i$) (R^1 = *p*-$Me_2NC_6H_4$ and R^2 = Pr^i). M.p. 167.0–168.0 °C (from THF–CH_2Cl_2) (Found: C, 48.9; H, 6.0; N, 15.7; S, 14.6. $C_{18}H_{27}N_5O_4S_2$ requires C, 49.0; H, 6.2; N, 15.9; S, 14.5%); δ 1.03 [6 H, d, *J* 7 Hz, $CH(CH_3)_2$], 2.50–2.59 (1 H, m, COCH), 2.87 [6 H, s, $N(CH_3)_2$], 2.91–2.94 (2 H, m, SCH_2CH_2N), 3.45–3.50 (2 H, m, SCH_2CH_2N), 3.69–3.77 (2 H, m, SCH_2CO), 6.72–6.75 (2 H, m), 7.30–7.38 (2 H, m), 8.59 (1 H, s), 10.06 (1 H, s), 10.29 (1 H, s), and 10.69 (1 H, s); *m/z* 441 (M^+).

(4bb$_n$) (R^1 = Ph and R^2 = C_5H_{11}). M.p. 139.0–141.0 °C (from THF–CH_2Cl_2); δ 0.85 (3 H, t, *J* 7 Hz), 1.18–1.29 [4 H, m, $(CH_2)_2Me$], 1.46–1.55 (2 H, m, $COCH_2CH_2$), 2.23–2.29 (2 H, m, $COCH_2CH_2$), 2.82–2.94 (2 H, m, SCH_2CH_2N), 3.42–3.52 (2 H, m, SCH_2CH_2N), 3.70–3.80 (2 H, m, SCH_2CO), 7.07–7.12 (1 H, m), 7.29–7.36 (2 H, m), 7.49–7.54 (2 H, m), 8.57 (1 H, s), 10.29 (2 H, s), and 10.81 (1 H, s) (Found: M^+ + 1, 427.1437. $C_{18}H_{27}N_4O_4S_2$ requires *M* + 1, 427.1474).

(4bc$_n$) (R^1 = Ph and R^2 = C_6H_{13}). M.p. 146.5–148.0 °C (from MeCN–CH_2Cl_2); δ 0.82–0.88 (3 H, m), 1.18–1.29 (6 H, m), 1.44–1.53 (2 H, m), 2.22–2.30 (2 H, m, $COCH_2CH_2$), 2.82–2.94 (2 H, m, SCH_2CH_2N), 3.42–3.52 (2 H, m, SCH_2CH_2N), 3.69–3.82 (2 H, m, SCH_2CO), 7.06–7.14 (1 H, m), 7.28–7.37 (2 H, m), 7.49–7.55 (2 H, m), 8.57 (1 H, s), 10.28 (2 H, s), 10.82 (1 H, s) (Found: M^+ + 1, 441.1668. $C_{19}H_{29}N_4O_4S_2$ requires *M* + 1, 441.1631).

Oxidation of a Pair of Thiols.—A mixture of (**1**) (0.50 mmol) and (**2**) (0.50 mmol) in 12.5 cm^3 of a solvent was stirred vigorously under oxygen for 15 min in a well-stirred water bath which was thermostatted to ± 0.1 °C for 20–50 °C. To this mixture was added Et_3N (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 completed, the reaction mixture was evaporated to dryness. The yields of (**3**) and (**4**) were determined by use of their absorption at 280 (systems A_{n3}, A_{i3}, A_{n5}, and A_{i5}) and 254 nm (systems B_{n5}, B_{i5}, and B_{n6}) after separation of three disulphides (**3**–**5**) in the mixture by HPLC using μ-Bondapak-CN (systems A_{n3}, A_{i3}, A_{n5}, and A_{i5}) and LiChrosorb CN (systems B_{n5}, B_{i5}, and B_{n6}) with hexane–Pr^{i}OH [85:15 (systems A_{n3}, A_{i3}, A_{n5}, and A_{i5}) and 95:5 (systems B_{n5}, B_{i5}, and B_{n6})] as an eluant. The *r* values given in Tables 1–4 represent the mean values of two or more experiments and were reproducible within the errors shown therein. The errors in *r* values are far smaller for systems A_{n3}, A_{i3}, A_{n5}, and A_{i5} because of the larger molar extinction coefficients (ε)[26] of the corresponding disulphides (**3** and **4**).

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