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Evidence for the Similarity Recognition Hypothesis. Structure Dependence of the Selectivity in Oxidation of a Pair of Associating Thiols Each Having an Alkyl Group

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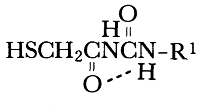
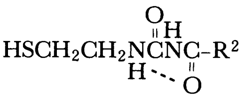
Synopsis. In base-catalyzed oxidation of a pair of associating thiols [$HSCH_2$-$CONHCONH$-R^1 and $HSCH_2CH_2$-$NHCONHCO$-R^2] (R^1=n-C_4H_9, R^2=n-C_nH_{2n+1}) with oxygen, the selectivity (a measure of molecular recognition) at 35.0 °C reached a maximum for R^1=R^2 (=n-C_4H_9) both in aqueous acetonitrile (n=2 to 6) and in aqueous ethanol (n=3 to 5).

The elucidation of factors controlling specific biological recognition is very significant in chemistry as well as in biology. In order to solve this problem, we have studied (i) the dependence of the selectivity in oxidation of a pair of associating thiols (**1** and **2**) on the structures of R^1 and R^2,[1,2] (ii) the dependence of the crystalline 1 : 1 complex formation between a pair of acylurea derivatives on the structures of their substituents,[2,3] and (iii) the stacking mode of the substituents in the crystalline 1 : 1 complexes by X-ray diffraction.[2,3] From these studies using a pair of associating compounds, it has been 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.[2] In the above investigations on the selectivity, one of the substituents (R^1 and R^2) was an aryl group: (i) R^1=p-$Me_2NC_6H_4$ and R^2=Me_2CH-$(CH_2)_m$ (m=0 to 4)[1a] and (ii) R^1=p-$Me_2NC_6H_4$ and R^2=p-ZC_6H_4 (Z=$CHMe_2$, NO_2, Me, and Cl).[2] We report here the experimental evidence to support the above "similarity recognition hypothesis," using straight-chain alkyl groups as both substituents.



$$\mathrm{HSCH_2\underset{\underset{\displaystyle O}{\|}}{C}\overset{H}{N}\overset{\overset{\displaystyle O}{\|}}{C}\underset{\cdots H}{N}\text{-}R^1}$$

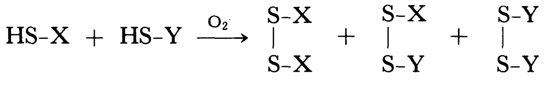
1a R^1=n-C_4H_9



$$\mathrm{HSCH_2CH_2\underset{H\cdots}{N}\overset{\overset{\displaystyle O}{\|}}{C}\overset{H}{N}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}R^2}$$

2a R^2=C_2H_5
b R^2=n-C_3H_7
c R^2=n-C_4H_9
d R^2=n-C_5H_{11}
e R^2=n-C_6H_{13}

Triethylamine-catalyzed oxidation of a pair of thiols (**1** and **2**) with oxygen gives one unsymmetrical (**4**) and two symmetrical disulfides (**3** and **5**). The selectivity (r, a measure of the degree of the recognition between **1** and **2**) is represented by the logarithmic ratio of the yield of **4** to twice that of **3**: r=ln([**4**]/(2[**3**])). The butyl group was chosen as R^1.



$$\mathrm{HS\text{-}X + HS\text{-}Y \xrightarrow{O_2} \begin{array}{c}S\text{-}X\\|\\S\text{-}X\end{array} + \begin{array}{c}S\text{-}X\\|\\S\text{-}Y\end{array} + \begin{array}{c}S\text{-}Y\\|\\S\text{-}Y\end{array}}$$

1 **2** **3** **4** **5**

Table 1 lists the yields of the disulfides (**4** and **3**) and the selectivity (r) in oxidation of **1a** and **2** at 35.0 °C in aqueous acetonitrile [mole fraction of water (x_w)=0.42]. In Fig. 1, r values are plotted against the structures of R^2. The selectivity (r) has proved to pass through a maximum at the butyl group, the same group used as R^1. Moreover, the selectivity was examined in another aqueous solvent, water-ethanol (x_w=0.75). The results are illustrated in Table 2 and Fig. 1.[4] Also in this case, the r has been found to reach a maximum for R^2=n-C_4H_9 (=R^1).

Table 1. Yields of Disulfides (**4** and **3**) and Selectivity (r) in Oxidation of **1a** and **2** at 35.0 °C in Aqueous MeCN (x_w=0.42)

R^2	Yield/%		r[a]
	4	**3**	
C_2H_5	18.4	32.9	−1.27±0.03
n-C_3H_7	76.8	9.2	1.4 ±0.1
n-C_4H_9	83.9	1.6	3.3 ±0.1
n-C_5H_{11}	85.5	2.6	2.8 ±0.1
n-C_6H_{13}	25.5	34.4	−0.99±0.06

a) Errors given are the standard deviations.

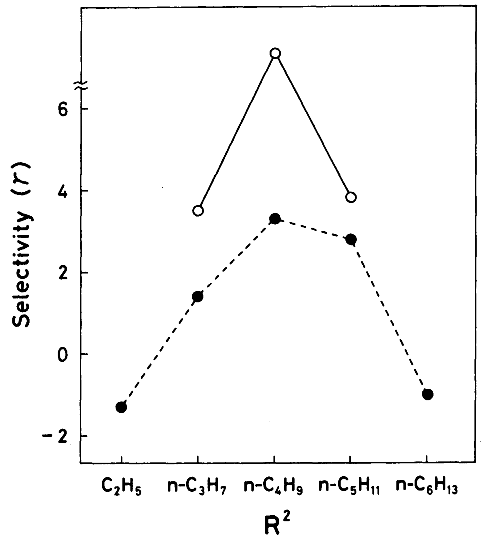
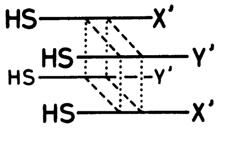


Fig. 1. Dependence of the selectivity (r) in oxidation of a pair of thiols (**1a** and **2**) on the structures of R^2 at 35.0 °C. ●, In aqueous acetonitrile [mole fraction of water (x_w)=0.42]; ○, in aqueous ethanol (x_w=0.75).

Table 2. Yields of Disulfides (**4** and **3**) and Selectivity (r) in Oxidation of **1a** and **2b**—**d** at 35.0 °C in Aqueous EtOH ($x_w=0.75$)

R^2	Yield/%		r[a)]
	4	**3**	
n-C_3H_7	91.8	1.5	3.4±0.1
n-C_4H_9	88.1	<0.1	>6
n-C_5H_{11}	94.0	1.1	3.8±0.2

a) Errors given are the standard deviations.



6

Fig. 2. Association scheme in a typical tetramer **6**. -----, Hydrogen bonds in dimers; ·····, noncovalent weak interactions responsible for stabilization of tetramers. The symbols X′ and Y′ represent R^1 and R^2, respectively.

In connection with the observations that the selectivity in the oxidation is sensitive to temperature,[1)] we examined the temperature dependence of r values (R^1=n-C_4H_9) in aqueous acetonitrile (x_w=0.42). Unexpectedly, the r values at 20.0 °C remain almost unchanged with the structures of R^2: 3.7±0.1 (n-C_3H_7), 3.6±0.1 (n-C_4H_9), and 3.8±0.1 (n-C_5H_{11}). Furthermore, at a higher temperature (i.e., 50.0 °C), r values increase progressively with increasing number of carbon atoms in R^2: −0.59±0.04 (n-C_3H_7), 2.2±0.1 (n-C_4H_9), and 3.0±0.1 (n-C_5H_{11}).[5)]

The findings shown in Fig. 1 are not understandable in terms of the following factors influencing chemical selectivity. First, electronic effects of R^2 fail to account for the selectivity data, because the order of σ_p values[7)] for R^2 [−0.15 (C_2H_5), −0.13 (n-C_3H_7), −0.16 (n-C_4H_9), and −0.15 (n-C_5H_{11})] differs sharply from that of the corresponding r values (Fig. 1). Second, steric effects cannot explain the observed selectivity, because the order of E_s values for R^2 [−0.07 (C_2H_5), −0.36 (n-C_3H_7), −0.39 (n-C_4H_9), and −0.40 (n-C_5H_{11})][8)] differs essentially from that of the corresponding r values (Fig. 1).[9)] Third, the hydrophobic effect is not responsible for the selectivity data, because π values[11)] increase with increasing number of carbon atoms in straight-chain alkyl groups, the π being a measure of the hydrophobic effect. Fourth, the reactivity differences between thiols **1a** and **2** cannot explain the selectivity. This is because r values should be negative, regardless of the structures of R^2, if the selectivity depends upon the reactivity differences: r values are largely positive for R^2=n-C_3H_7, n-C_4H_9, and n-C_5H_{11} (Fig. 1).

It has been shown that (i) the oxidation proceeds through tetramers (reaction intermediates) such as **6** (Fig. 2), which are formed by dimerization of dimers produced from **1** and **2** through two NH···O intermolecular hydrogen bonds between the inner -NHCO- units in the -CONHCONH- groups[12)] and (ii) the product ratio in this type of oxidation is kinetically controlled.[1)]

In conclusion, the experimental results and discussions presented here demonstrate that the similarity recognition hypothesis holds true for straight-chain alkyl groups at temperatures around 35 °C.

Experimental

The melting points were uncorrected. ^{1}H NMR (270 MHz) spectra were measured on a JEOL GX-270 spectrometer using tetramethylsilane as an internal standard. The mass spectra were taken on a Hitachi RMU-6M mass spectrometer.

Materials. Acetonitrile was dried, purified by distillation from calcium hydride and phosphorus pentaoxide, and stored over molecular sieves. Water was distilled after deionization. Ethanol was dried, purified by distillation from magnesium ethoxide,[13)] and stored over molecular sieves.

Thiol **1a** was prepared as described before,[14)] recrystallized from ether-hexane, and had the following properties: Mp 104—105 °C; ^{1}H NMR ($CDCl_3$) δ=0.94 (3H, t, J=7 Hz), 1.31—1.60 (4H, m), 2.09 (1H, t, J=9 Hz), 3.27—3.34 (4H, m), 8.29 (1H, s), 9.57 (1H, s). Found: C, 44.09; H, 7.56; N, 14.54; S, 17.30%; M$^+$, 190. Calcd for $C_7H_{14}N_2O_2S$: C, 44.19; H, 7.42; N, 14.72; S, 16.85%; M, 190.

Thiols **2** were synthesized as described before,[1b)] recrystallized from ether-hexane, and had the following properties.

2a: Mp 117.5—119.0 °C; ^{1}H NMR ($CDCl_3$) δ=1.19 (3H, t, J=7 Hz), 1.43 (1H, t, J=8 Hz), 2.38 (2H, q, J=7 Hz), 2.67—2.75 (2H, m), 3.47—3.54 (2H, m), 8.79 (2H, s). Found: C, 41.16; H, 6.79; N, 15.98; S, 18.17%; M$^+$, 176. Calcd for $C_6H_{12}N_2O_2S$: C, 40.90; H, 6.87; N, 15.90; S, 18.17%; M, 176.

2b: Mp 119—120 °C; ^{1}H NMR ($CDCl_3$) δ=0.98 (3H, t, J=7 Hz), 1.42 (1H, t, J=9 Hz), 1.63—1.74 (2H, m), 2.31 (2H, t, J=7 Hz), 2.66—2.75 (2H, m), 3.46—3.53 (2H, m), 8.76 (2H, s). Found: C, 44.12; H, 7.51; N, 14.56; S, 17.11%; M$^+$, 190. Calcd for $C_7H_{14}N_2O_2S$: C, 44.19; H, 7.42; N, 14.72; S, 16.85%; M, 190.

2c: Mp 105.5—106.0 °C; ^{1}H NMR ($CDCl_3$) δ=0.94 (3H, t, J=7 Hz), 1.31—1.45 (3H, m), 1.59—1.70 (2H, m), 2.33 (2H, t, J=7 Hz), 2.66—2.74 (2H, m), 3.46—3.53 (2H, m), 8.79 (2H, s). Found: C, 47.18; H, 7.74; N, 13.66; S, 15.85%; M$^+$, 204. Calcd for $C_8H_{16}N_2O_2S$: C, 47.05; H, 7.90; N, 13.73; S, 15.67%; M, 204.

2d: Mp 107.5—108.5 °C; ^{1}H NMR ($CDCl_3$) δ=0.91 (3H, t, J=7 Hz), 1.30—1.45 (5H, m), 1.61—1.69 (2H, m), 2.32 (2H, t, J=8 Hz), 2.66—2.86 (2H, m), 3.46—3.53 (2H, m), 8.79 (2H, s). Found: C, 49.26; H, 8.38; N, 12.76; S, 14.74%; M$^+$, 218. Calcd for $C_9H_{18}N_2O_2S$: C, 49.52; H, 8.31; N, 12.83; S, 14.69%; M, 218.

2e: Mp 102—103 °C; ^{1}H NMR ($CDCl_3$) δ=0.86—0.91 (3H, m), 1.30—1.45 (7H, m), 1.60—1.68 (2H, m), 2.32 (2H, t, J=7 Hz), 2.66—2.74 (2H, m), 3.46—3.53 (2H, m), 8.73 (2H, s). Found: C, 51.89; H, 8.67; N, 12.08; S, 14.01%; M$^+$, 232. Calcd for $C_{10}H_{20}N_2O_2S$: C, 51.70; H, 8.68; N, 12.06; S, 13.78%; M, 232.

Symmetrical disulfide **3** (R^1=n-C_4H_9) was prepared as described before,[1b)] and had the following properties: Mp 195—197 °C [tetrahydrofuran (THF)]; ^{1}H NMR (dimethyl-d_6 sulfoxide) δ=1.20 (6H, t, J=7 Hz), 1.56—1.79 (8H, m), 3.4—3.5 (4H, m), 3.97 (4H, s), 8.49 (2H, s), 10.75 (2H, s). Found: m/z 378.1380. Calcd for $C_{14}H_{26}N_4O_4S_2$: M, 378.1398.

Unsymmetrical disulfides **4** (R^1=n-C_4H_9) were synthesized as described before,[15)] and had the following properties.

4a (R^2=C_2H_5): Mp 161.5—162.5 °C (MeCN); ^{1}H NMR ($CDCl_3$) δ=0.93 (3H, t, J=7 Hz), 1.18 (3H, t, J=8 Hz), 1.39—1.57 (4H, m), 2.36—2.41 (2H, m), 2.87—2.92 (2H, m), 3.28—3.30 (2H, m), 3.58 (2H, s), 3.61—3.70 (2H, m), 8.37 (1H, s), 8.74 (1H, s), 9.39 (1H, s), 9.83 (1H, s). Found: m/z 364.1205. Calcd for $C_{13}H_{24}N_4O_4S_2$: M, 364.1241.

4b (R^2=n-C_3H_7): Mp 171.0—173.5 °C (THF); ^{1}H NMR ($CDCl_3$) δ=0.91—1.00 (6H, m), 1.33—1.42 (2H, m), 1.50—1.58 (2H, m), 1.65—1.73 (2H, m), 2.34 (2H, t, J=7 Hz), 2.91 (2H, t, J=6 Hz), 3.27—3.34 (2H, m), 3.52 (2H, s), 3.65—3.72 (2H, m), 8.36 (1H, s), 8.76 (1H, s), 9.50 (1H, s), 10.18 (1H, s). Found: m/z 378.1410. Calcd for $C_{14}H_{26}N_4O_4S_2$: M, 378.1398.

4c (R^2=n-C_4H_9): Mp 174—176 °C (THF); ^{1}H NMR ($CDCl_3$) δ=0.91—0.96 (6H, m), 1.33—1.64 (8H, m), 2.36 (2H, t, J=7 Hz), 2.91 (2H, t, J=6 Hz), 3.29—3.31 (2H, m), 3.52 (2H, s), 3.69—3.71 (2H, m), 8.34 (1H, s), 8.73 (1H, s), 9.34 (1H, s), 10.08 (1H, s). Found: m/z 392.1567. Calcd for $C_{15}H_{28}N_4O_4S_2$: M, 392.1554.

4d (R^2=n-C_5H_{11}): Mp 168.0—169.5 °C (THF); ^{1}H NMR ($CDCl_3$) δ=0.88—0.96 (6H, m), 1.32—1.66 (10H, m), 2.35 (2H, t, J=7 Hz), 2.91 (2H, t, J=6 Hz), 3.29—3.31 (2H, m), 3.51 (2H, s), 3.68—3.70 (2H, m), 8.35 (1H, s), 8.76 (1H, s), 9.54 (1H, s), 10.24 (1H, s). Found: m/z 406.1725. Calcd for $C_{16}H_{30}N_4O_4S_2$: M, 406.1711.

4e (R^2=n-C_6H_{13}): Mp 174—175 °C (MeCN); ^{1}H NMR ($CDCl_3$) δ=0.89—0.96 (6H, m), 1.2—1.7 (12H, m), 2.3—2.4 (2H, m), 2.8—3.0 (2H, m), 3.2—3.4 (2H, m), 3.53 (2H, s), 3.6—3.8 (2H, m), 8.35 (1H, s), 8.73 (1H, s), 9.25 (1H, s), 9.99 (1H, s). Found: m/z 420.1859. Calcd for $C_{17}H_{32}N_4O_4S_2$: M, 420.1868.

Oxidation of a Pair of Thiols. A mixture of **1a** (0.50 mmol) and **2** (0.50 mmol) in 12.5 ml of the solvent was stirred vigorously under oxygen for 15 min in a well-stirred water bath which was thermostated to ±0.1 °C. To this mixture was added Et_3N (0.05 mmol), and vigorous stirring was continued for the time required to complete the oxidation. When the oxidation was completed, the reaction mixture was evaporated to dryness. The yields of **3** and **4** in the reaction mixture were determined exactly by an integrator after separation by HPLC using LiChrosorb CN [hexane-isopropyl alcohol (94 : 6—97 : 3)]. The r values are reproducible in two or more experiments within the errors described in Tables 1 and 2.

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4) The r value of larger than 6 implies that the oxidation gives **4** exclusively to such an extent that the yield of **3** exceeds the limitations of the determination.

5) Our previous work[6] showed that, in oxidation of **1** (R^1=n-C_5H_{11}) and **2c—e**, r values at 35.0 °C in aqueous acetonitrile (x_w=0.42) became positive (r=3.6 to 4.1) with a maximum for R^2=n-C_5H_{11} (=R^1).

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9) Another measure of steric effects, the v, also is not responsible for the data in Fig. 1, since v values [0.56 (C_2H_5), 0.68 (n-C_3H_7), 0.68 (n-C_4H_9), 0.68 (n-C_5H_{11}), and 0.73 (n-C_6H_{13})][10] slightly increase with increasing number of carbon atoms in straight-chain alkyl groups used as R^2.

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