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SPECIFIC RECOGNITION OF NONPOLAR GROUPS IN AQUEOUS MEDIA. LARGER SELECTIVITY DIFFERENCES IN OXIDATION OF ASSOCIATING THIOLS IN AQUEOUS MIXED SOLVENTS THAN IN NONAQUEOUS ONES

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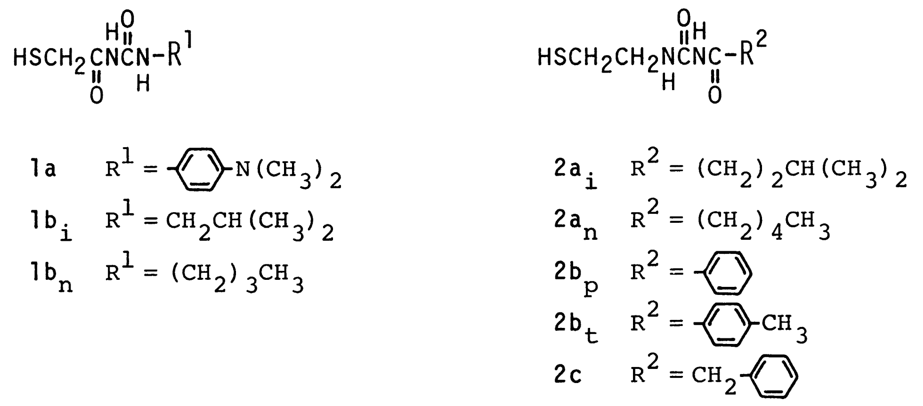
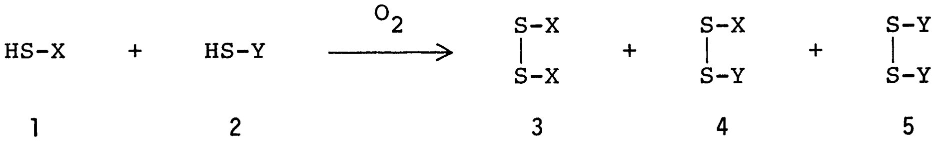
Environment dependence of the selectivity in oxidation of a pair of associating thiols was examined in binary solvent mixtures of an alcohol or acetonitrile with water and an organic cosolvent. The discrimination between the two nonpolar groups (n- and i-C_5H_{11} groups, phenyl and p-tolyl groups, or n- and i-C_4H_9 groups) of one of the thiols was found to occur more specifically in aqueous media than in the corresponding nonaqueous media.

There is much evidence that solvents markedly affect chemical selectivity[1,2] as well as chemical reactivity[3] and equilibrium.[1,4] As a continuing study on molecular recognition,[5,6] we examined the effect of aqueous solvents on the structure dependence of the selectivity in oxidation of a pair of associating thiols (**1** and **2**)[7]; the selectivity (r) is represented here by the logarithmeric ratio of the yield of the unsymmetrical disulfide (**4**) to twice that of the





$$\underset{\mathbf{1}}{\text{HS-X}} \quad + \quad \underset{\mathbf{2}}{\text{HS-Y}} \quad \xrightarrow{O_2} \quad \underset{\mathbf{3}}{\begin{array}{c}\text{S-X}\\ | \\ \text{S-X}\end{array}} \quad + \quad \underset{\mathbf{4}}{\begin{array}{c}\text{S-X}\\ | \\ \text{S-Y}\end{array}} \quad + \quad \underset{\mathbf{5}}{\begin{array}{c}\text{S-Y}\\ | \\ \text{S-Y}\end{array}}$$

Table 1. The selectivity ($r^{<5>}$) in oxidation of **1a** and **2a** in binary solvent systems containing EtOH ($x_{\mathrm{EtOH}} = 0.25$) at various temperatures

t/°C	$r_{\mathrm{i}}^{<5>}$		$r_{\mathrm{n}}^{<5>}$	
	H_2O – EtOH	DIO[a] – EtOH	H_2O – EtOH	DIO[a] – EtOH
20	2.6 (0.05)[b]	2.1 (0.04)	-4.1 (0.05)	1.4 (0.04)
35	2.5 (0.04)	0.41 (0.02)	-3.6 (0.05)	0.36 (0.03)
50	3.8 (0.07)	1.0 (0.02)	-3.0 (0.02)	0.93 (0.02)
70	2.9 (0.07)	1.2 (0.03)	0.34 (0.03)	1.6 (0.03)

a) DIO, 1,4-dioxane. b) The values in parentheses represent three times standard deviation.

symmetrical disulfide (**3**) $\{r = \ln([\mathbf{4}]/(2\,[\mathbf{3}]))\}$.

Table 1 lists the selectivity in oxidation of **1a** and **2a** for $R^2 = i\text{-}C_5H_{11}$ ($r_{\mathrm{i}}^{<5>}$) and for $R^2 = n\text{-}C_5H_{11}$ ($r_{\mathrm{n}}^{<5>}$) in binary mixed solvents of ethanol (EtOH) with water and 1,4-dioxane [the mole fraction of EtOH (x_{EtOH}) = 0.25][8] in the 20 – 70 °C range. The $|r^{<5>}|$ values in aqueous EtOH are larger than those in dioxane – EtOH except near 70 °C. The temperature dependence of the difference between $r_{\mathrm{i}}^{<5>}$ and $r_{\mathrm{n}}^{<5>}$ ($\Delta r_{\mathrm{i-n}}^{<5>} = r_{\mathrm{i}}^{<5>} - r_{\mathrm{n}}^{<5>}$) in aqueous EtOH was then compared with that in dioxane – EtOH (Table 2), the $\Delta r_{\mathrm{i-n}}^{<5>}$ being regarded as a measure of the recognition between the i- and n-pentyl groups in **2a** by **1a**. The $\Delta r_{\mathrm{i-n}}^{<5>}$ in aqueous EtOH becomes far larger than that in dioxane – EtOH.

Similar trends are observed for oxidation of **1a** and **2b**. The differences between the selectivity for $R^2 = Ph$ and that for $R^2 = p\text{-}CH_3C_6H_4$ ($\Delta r_{\mathrm{p-t}} = r_{\mathrm{p}} - r_{\mathrm{t}}$) in water – EtOH ($x_{\mathrm{EtOH}} = 0.25$) are 1.3, 4.7, and 1.7 at 20, 35, and 50 °C, respectively, those in MeCN – EtOH ($x_{\mathrm{EtOH}} = 0.25$) being -0.28, 1.5, and -0.04 at 20, 35, and 50 °C, respectively.[9]

The "aqueous media effect" on the recognition was further investigated in oxidation of **1a** and **2a** (Table 3) and in oxidation of **1b** and **2c** (Table 4).[10] In both cases, the $|\Delta r_{\mathrm{i-n}}|$ values become larger in aqueous mixed solvents than in the corresponding nonaqueous solvents.

The importance of intermolecular association in molecular recognition[5] was also shown in the present case.

Table 2. The $\Delta r_{\mathrm{i-n}}^{<5>}$ in oxidation of **1a** and **2a** in a pair of binary solvent systems containing EtOH ($x_{\mathrm{EtOH}} = 0.25$) at various temperatures

t/°C	$\Delta r_{\mathrm{i-n}}^{<5>}$	
	H_2O – EtOH	DIO[a] – EtOH
20	6.7	0.7
35	6.1	0.05
50	6.8	0.07
70	2.6	-0.4

a) DIO, 1,4-dioxane.

Table 3. The $\Delta r_{i-n}^{<5>}$ in oxidation of **1a** and **2a** at 35.0 °C in binary solvent systems containing isopropyl alcohol (IPA)

x_{IPA}	$\Delta r_{i-n}^{<5>}$	
	H_2O – IPA	DIO[a] – IPA
0.20	5.4	0.44
0.50	4.1	-0.55
0.75	4.9	-0.31

a) DIO, 1,4-dioxane.

Table 4. The $\Delta r_{n-i}^{<4>}$ ($= r_n^{<4>} - r_i^{<4>}$) in oxidation of **1b** and **2c** at 35.0 °C in binary solvent systems containing MeCN

x_{MeCN}	$\Delta r_{n-i}^{<4>}$		
	H_2O – MeCN	DIO[a] – MeCN	MeOH – MeCN
0.25	6.6	2.0	2.4
0.58	3.8	3.1	3.3

a) DIO, 1,4-dioxane.

The r values in oxidation of a 1:1 mixture of the nonassociating thiols [p-$(CH_3)_2NC_6H_4NHCOCH_2SH$ and i-$C_5H_{11}CONHCH_2CH_2SH$] are much closer to zero [-0.55 at 35.0 °C and -0.25 at 50.0 °C in aqueous EtOH ($x_{EtOH} = 0.25$)], the value statistically expected, than those for the corresponding associating thiols (**1a** and **2a**$_i$) (Table 1).[11-13]

On the basis of the results presented here, we propose that the recognition of nonpolar groups such as biologically important alkyl groups can be achieved more specifically in aqueous media than in nonaqueous organic media. Our work would suggest the significance of an aqueous environment in specific molecular recognition in chemical and biological systems.

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7) Thiols **1** and **2** (0.50 mmol each) in 12.5 ml of a solvent were treated with O_2 in the presence of Et_3N (0.05 mmol) in a constant-temperature bath until the oxidation was complete. The yields of **3** and **4** were determined by HPLC [μBONDAPAK CN, *n*-hexane – isopropyl alcohol (85:15 for oxidation of **1a** and **2a–b** and 93:7 for oxidation of **1b** and **2c**)].

8) The reason for using this mole fraction of EtOH is that, among the solvents so far studied for oxidation of **1a** and **2a**$_\mathrm{i}$ at 35.0 °C, aqueous EtOH ($x_\mathrm{EtOH} = 0.25$) gave the very high r value of 2.5.

9) The $|\Delta r_\mathrm{p\text{-}t}|$ values have also been larger in water – MeCN ($x_\mathrm{MeCN} = 0.58$)$^{6)}$, which corresponds to 20% (v/v) water – 80% MeCN, than in 1,4-dioxane – MeCN ($x_\mathrm{MeCN} = 0.58$) except near 20 °C.

10) Thiols **1b** and the corresponding disulfides were readily prepared as described previously.$^{6)}$ All new compounds had satisfactory spectroscopic data.

11) It has been shown that (i) the oxidation proceeds through tetramers formed by dimerization of dimers$^{6)}$ produced, through two NH···O intermolecular hydrogen bonds$^{6)}$ between the inner -N(H)C(=O)- units in the -C(=O)N(H)C(=O)N(H)- group, from **1** and **2**, and (ii) the selectivity depends upon relative concentration of the tetramers, which would reflect weak interactions specific for the shape of the nonpolar groups as the recognition sites (R^1 and R^2) of **1** and **2** [T. Endo, M. Hashimoto, T. Orii, and M. M. Ito, *Bull. Chem. Soc. Jpn.*, 57, 1562 (1984)]. In an attempt to relate the observed selectivity changes with R^2 and the solvents (Table 3) to the changes in the mode of association of thiols **1a** and **2a**, ^{1}H NMR (270 MHz) spectra were measured at 35 °C for 1:1 mixtures of the thiols (0.007 M each) in a pair of binary solvent systems containing 0.50 mole fraction of isopropyl alcohol-d_8. In going from the mixture of **1a** and **2a**$_\mathrm{i}$ to the mixture of **1a** and **2a**$_\mathrm{n}$ in water – isopropyl alcohol-d_8, the intermolecularly hydrogen-bonded NH proton of **2a** underwent a small upfield shift from δ 10.11 [(2725.5 ± 0.5) Hz] to 10.09 [(2720.6 ± 1.5) Hz], the r value decreasing from 1.6 to -2.5; with the above-mentioned structural change in dioxane – isopropyl alcohol-d_8, this NH resonance was not shifted appreciably.

12) That the product ratio in this type of oxidation is kinetically controlled is demonstrated in water – MeCN ($x_\mathrm{MeCN} = 0.58$).$^{5,6)}$ This was also examined in other mixed solvents by carrying out thiol – disulfide exchange reaction between **2a**$_\mathrm{i}$ and **3** [$R^1 = p\text{-}(CH_3)_2NC_6H_4$] at 35.0 °C in the presence of a catalytic amount of Et_3N under argon; r values at the same reaction time as with the corresponding oxidation become -1.8 in water – EtOH ($x_\mathrm{EtOH} = 0.25$) and -1.5 in water – isopropyl alcohol ($x_\mathrm{IPA} = 0.20$). These observations indicate that the product ratio in the exchange reaction differs entirely from that in oxidation of **1a** and **2a**$_\mathrm{i}$ at 35.0 °C [$r = 2.5$ in water – EtOH ($x_\mathrm{EtOH} = 0.25$) and 2.2 in water – isopropyl alcohol ($x_\mathrm{IPA} = 0.20$)], suggesting that the results for the oxidation in these two solvents represent kinetic control.

13) In this type of oxidation, the product ratio is not attributed to differential solubilities of thiols **1** and **2**.$^{5,6)}$

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