Control of the Degree of Molecular Recognition by Shape-specific Weak Interactions between Nonpolar Groups

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In oxidation of a pair of associating thiols [(**1**) and (**2**)], each having a phenyl or a hexyl group (R = n-C_6H_{13}, i-C_6H_{13}, cyclo-C_6H_{11}), it has been shown that the order of the selectivity [a measure of the degree of the recognition between (**1**) and (**2**)] for R (*i.e.*, n-C_6H_{13} < i-C_6H_{13} < cyclo-C_6H_{11}) depends upon the strength of the phenyl–R interactions.

Noncovalent stereospecific interactions are suggested to be responsible for selective biological recognition.[1] This view led us to examine whether or not the degree of the discrimination between a pair of associating model compounds [(**1**) and (**2**)], each having a phenyl or a hexyl group R as the recognition site, correlated with the strength of 'shape-specific weak interactions'[2] between the recognition sites. We report here the first example in which specific molecular recognition is controlled by shape-specific weak interactions between nonpolar groups in the respective molecules.

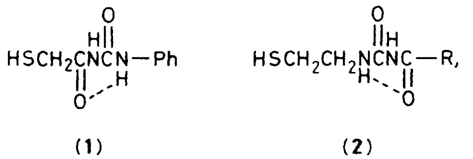
The degree of the discrimination between associating thiols [(**1**) and (**2**)]† was examined in their oxidation‡ with oxygen. The selectivity [*r*, a measure of the degree of the recognition between (**1**) and (**2**)] is represented by the logarithmic ratio of the yield of the unsymmetrical disulphide (**4**) to twice that of the symmetrical disulphide (**3**): $r = \ln\{(\mathbf{4})/[2 \times (\mathbf{3})]\}$.

Figure 1 shows the dependence of the selectivity (*r*) on the structures of R in (**2**) in several aqueous mixed solvents (mole fraction of water = x_w). The *r* values for R have been found to increase in the order n-C_6H_{13} < i-C_6H_{13} < cyclo-C_6H_{11}, regardless of the solvents employed.

The structure (R)–selectivity (*r*) relationship was further investigated in aqueous acetonitrile (x_w = 0.42) at various temperatures. In the 20—70 °C range, *r* values for R increase in the same order as in Figure 1.

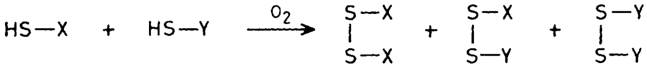
The overall initial rates (average rates until 5% consumption of thiols)[3] for oxidation of 1 : 1 mixtures of (**1**) and (**2**) in aqueous acetonitrile (x_w = 0.42) at 35.0 °C are nearly equal to one another: [(1.2 ± 0.2), (1.3 ± 0.4), and (1.1 ± 0.1)] × 10^{-6} mol dm^{-3} s^{-1} for R = n-C_6H_{13}, i-C_6H_{13}, and cyclo-C_6H_{11}, respectively. This suggests that the changes in *r* values with the structures of R cannot be explained by the changes in relative rates for oxidation of the 1 : 1 mixtures with R.§

Since the order of υ (a steric parameter)[5] for R [i-C_6H_{13} (0.68) < n-C_6H_{13} (0.73) < cyclo-C_6H_{11} (0.87)] does not agree with that of the corresponding *r* values, steric effects are not responsible for the observed selectivity (Figure 1). Moreover, in aqueous acetonitrile (x_w = 0.42), *r* values for R = n-C_6H_{13} increase from −3.8 (20 °C) to 0.27 (70 °C) with temperature, whereas those for R = i-C_6H_{13} decrease from 4.4 (20 °C) to 1.2 (70 °C) with temperature. This finding cannot be interpreted by hydrophobic interaction, because hydrophobicity[6] is repor-



(**1**) (**2**)

R = n-C_6H_{13}
i-C_6H_{13}
cyclo-C_6H_{11}



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

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

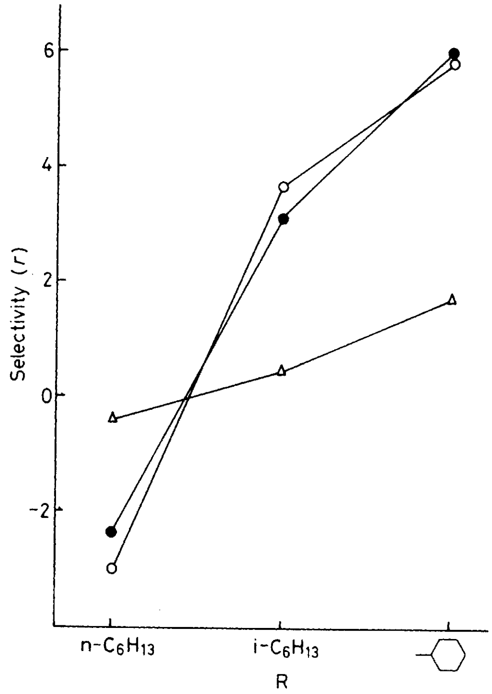


Figure 1. Dependence of the selectivity (*r*) in oxidation of a pair of thiols [(**1**) and (**2**)] on the structures of R (n-C_6H_{13}, i-C_6H_{13}, and cyclo-C_6H_{11}) in several aqueous mixed solvents at 35.0 °C. ●, In aqueous acetonitrile [mole fraction of water (x_w) = 0.42]; ○, in aqueous isopropyl alcohol (x_w = 0.50); △, in aqueous 1,4-dioxane (x_w = 0.54). Errors (the standard deviations) for *r* values range from ±0.10 to ±0.16 ($r > 5$), from ±0.04 to ±0.10 ($5 > |r| > 3$), and from ±0.04 to ±0.06 ($3 > |r|$). The *r* values are reproducible within the errors described above.

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† The thiols were prepared as described previously.[3] All new compounds had satisfactory spectroscopic data.

‡ The two thiols [(**1**) and (**2**), 0.50 mmol each] were treated with O_2 in the presence of Et_3N (0.05 mmol) as a catalyst in 12.5 ml of the solvent in a constant-temperature bath until the oxidation was complete. The yields of (**3**) and (**4**) were determined by h.p.l.c. using LiChrosorb CN.

§ The initial rate for oxidation of thiol (**1**) is approximately 100 times larger than that for oxidation of (**2**) in aqueous MeCN.[3,4] If the selectivity depends on the reactivity differences between (**1**) and (**2**), *r* values should become negative, regardless of the structures of R. This is not the case with R = i-C_6H_{13} and cyclo-C_6 H_{11} (Figure 1).

ted to increase progressively with increasing temperature. Also electronic effects fail to account for the selectivity data.¶

Our gas-chromatographic studies demonstrated that the strength of weak interactions of a Ph group with hexyl groups increased in the order n-C_6H_{13} < i-C_6H_{13} < cyclo-C_6H_{11}, the enthalpies of the interactions for the i-C_6H_{13} and cyclo-C_6H_{11} groups being smaller than that for the n-C_6H_{13} group by *ca.* 0.1 and 0.5 kcal mol^{-1} (1 kcal = 4.184 kJ), respectively.[9] Therefore, the order of *r* values for R has proved to be the same as that of the strength of the above Ph–R interactions for R.

The selectivity has been suggested to depend on the relative concentration of the tetramers (reaction intermediates)‖ which is considered to reflect the strength of the above interactions between the recognition sites.[3] On the basis of the experimental evidence and discussions presented here, we propose that the degree of the recognition between molecules each having a nonpolar group can be controlled by the strength of shape-specific weak interactions between the nonpolar groups in the respective molecules. This hypothesis would aid our understanding of the specific recognition between molecules having nonpolar groups in chemical and biological systems.

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¶ This is because the difference between *r* values for R = $(CH_2)_nCHMe_2$ and $(CH_2)_nCH_2CH_2Me$ (in aqueous MeCN at 35.0 °C) increases greatly from −0.1 ($n = 1$) to 5.5 ($n = 3$, Figure 1), whereas that between the σ_p[7] (or σ^*[8]) values for the pair of groups will decrease on changing *n* from 1 to 3 [σ_p (or σ^*) (an electronic parameter) for R is unavailable].

‖ The oxidation proceeds through tetramers formed by dimerisation of dimers produced from (**1**) and (**2**) through two NH···O intermolecular hydrogen bonds between the inner –NHC(=O)– units in the –C(=O)NHC(=O)NH– group.[3]

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