

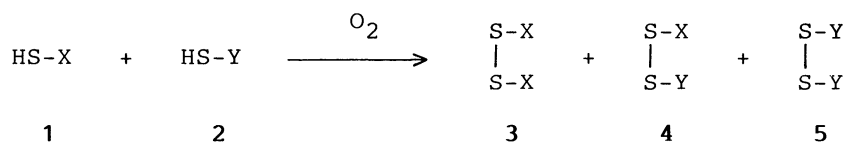
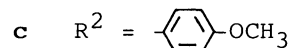
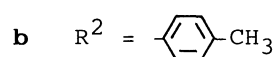
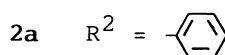
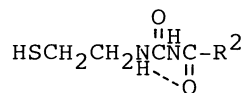
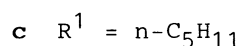
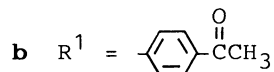
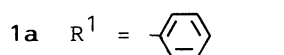
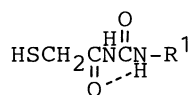
Control of Chemical Selectivity by Specific Weak Interactions  
between Groups in Reacting Molecules

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In oxidation of a pair of associating thiols, each having a phenyl or a given group (R), it has been found that the order of the selectivity agrees with that of the strength of specific R-Ph interactions for each of two sets of R [(i)  $p\text{-MeC}_6\text{H}_4 < \text{Ph} < p\text{-MeOC}_6\text{H}_4$  and (ii)  $n\text{-C}_5\text{H}_{11} < \text{Ph} < p\text{-MeCOC}_6\text{H}_4$ ].

The selectivity in organic reactions has mainly been controlled by electronic effects,<sup>1)</sup> steric effects,<sup>2)</sup> and proximity effects through chelation,<sup>2)</sup> micelle formation,<sup>3)</sup> inclusion,<sup>4)</sup> and hydrogen bonds.<sup>5)</sup> If weak interactions whose energies are smaller than those for hydrogen bonds operate specifically between groups in reacting molecules, they also would control chemical selectivity. With this in mind, we have been studying the structure dependence of the selectivity<sup>6)</sup> in oxidation of a pair of associating thiols (1 and 2) each having a phenyl (Ph) or a given group, and report here that the selectivity depends upon the strength of specific weak interaction of a Ph group with a given group.

Triethylamine-catalyzed oxidation of a pair of associating thiols<sup>7)</sup> 1 and 2 with oxygen gives one unsymmetrical (4) and two symmetrical disulfides (3 and 5).<sup>8)</sup> The selectivity ( $\underline{r}$ ) is represented by the logarithmic ratio of the yield of



the unsymmetrical disulfide (4) to twice that of the symmetrical disulfide (3):  $\underline{r} = \ln\{[4]/(2[3])\}$ .

Figure 1 shows the temperature dependence of the selectivity ( $\underline{r}$ ) in oxidation of 1a and 2a-c ( $R^2 = p\text{-ZC}_6\text{H}_4$ ) in aqueous acetonitrile [mole fraction of water ( $x_w$ ) = 0.42]. The  $\underline{r}$  values for  $R^2$  increase in the order  $p\text{-MeC}_6\text{H}_4 < \text{Ph} < p\text{-MeOC}_6\text{H}_4$  in the 20–70 °C range. The selectivity in aqueous ethanol ( $x_w = 0.50$ ) at 35.0 °C increases in the same order as in the above mixed solvent:  $\underline{r}$  values are 2.57, 3.39, and 3.64 for  $R^2 = p\text{-MeC}_6\text{H}_4$ , Ph, and  $p\text{-MeOC}_6\text{H}_4$ , respectively.

The structure–selectivity relationship was further investigated using another set of substituents [ $R^1 = \text{Ph}$ ,  $p\text{-MeCOC}_6\text{H}_4$ , and  $n\text{-C}_5\text{H}_{11}$  ( $R^2 = \text{Ph}$ )] in pure acetonitrile (Fig. 2). The selectivity for  $R^1$  has been found to increase in the order  $n\text{-C}_5\text{H}_{11} < \text{Ph} < p\text{-MeCOC}_6\text{H}_4$  in the 35–50 °C range.

The observed selectivity is not understandable by the following factors influencing chemical selectivity. First, electronic effects of  $R^2$  fail to explain the selectivity (Fig. 1), because the order of  $\sigma_p$  values for Z (*para*-substituents of  $R^2$ ) [ $-0.27$  (OMe)  $< -0.17$  (Me)  $< 0$  (H)]<sup>9)</sup> differs essentially from that of the corresponding  $\underline{r}$  values. Second, steric effects cannot account for the selectivity (Fig. 1), because the order of the A (a steric parameter)—which is defined as

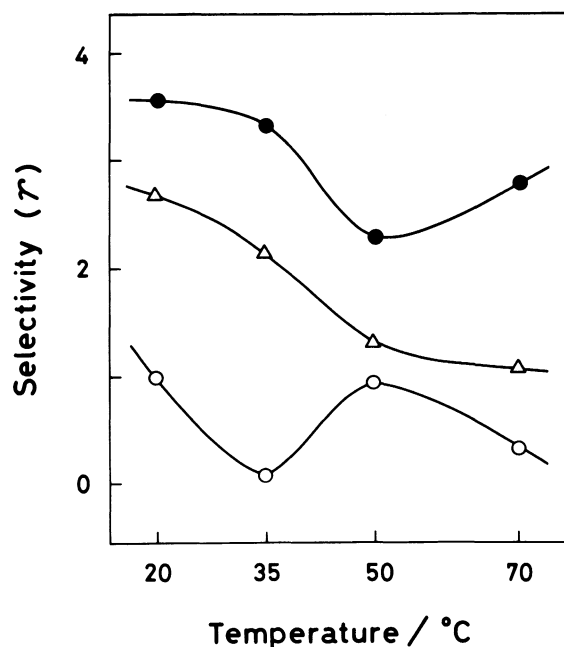


Fig. 1. Temperature dependence of the selectivity ( $\underline{r}$ ) for 1a and 2a-c in aqueous MeCN ( $x_w = 0.42$ ). Errors (the standard deviations) in the  $\underline{r}$  range from  $\pm 0.01$  to  $\pm 0.04$ , except for  $R^2 = \text{Ph}$  [ $\pm 0.11$  (20 °C) and  $\pm 0.06$  (35 °C)] and  $p\text{-MeC}_6\text{H}_4$  [ $\pm 0.08$  (35 °C) and  $\pm 0.07$  (70 °C)]. ●,  $R^2 = p\text{-MeOC}_6\text{H}_4$ ; △,  $R^2 = \text{Ph}$ ; ○,  $R^2 = p\text{-MeC}_6\text{H}_4$ .

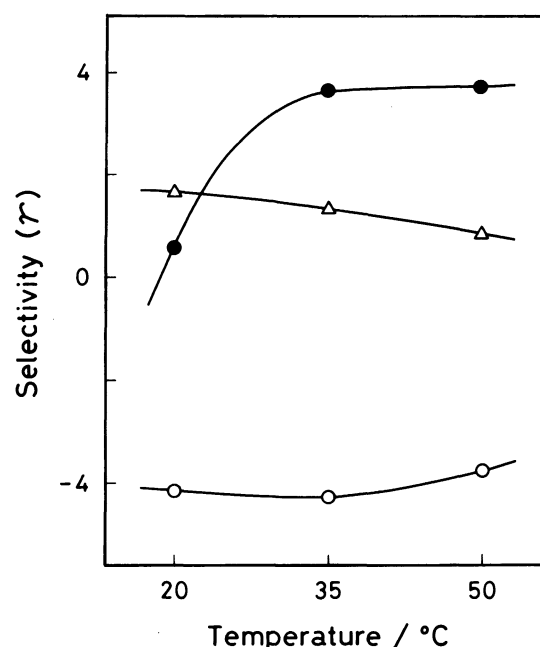


Fig. 2. Temperature dependence of the selectivity ( $\underline{r}$ ) for 1a-c and 2a in MeCN. Errors (the standard deviations) in the  $\underline{r}$  range from  $\pm 0.01$  to  $\pm 0.04$  except for  $R^1 = p\text{-MeCOC}_6\text{H}_4$  [ $\pm 0.05$  (35 °C)]. ●,  $R^1 = p\text{-MeCOC}_6\text{H}_4$ ; △,  $R^1 = \text{Ph}$ ; ○,  $R^1 = n\text{-C}_5\text{H}_{11}$ .

the free energy difference  $\Delta G$  ( $= -RT \ln K$ ) involved in the axial—equatorial equilibrium of substituted cyclohexanes — for  $Z$  [ $0$  (H)  $< 0.7$  (OMe)  $< 1.7$  (Me)]<sup>10</sup>) does not agree with that of the corresponding  $\underline{r}$  values.<sup>11</sup>) Third, the hydrophobic effect cannot explain the temperature—selectivity plot (Fig. 1) where there are extrema, since hydrophobicity<sup>13</sup>) increases progressively with increasing temperature. Fourth, the reactivity difference between thiols<sup>14</sup>) 1 and 2 is not responsible for the observed selectivity. This is because  $\underline{r}$  values should be negative regardless of the structures of  $R^1$  or  $R^2$ , if the selectivity depends upon the reactivity difference; however, the  $\underline{r}$  shows large positive values (Figs. 1 and 2).<sup>16</sup>)

Our gas-chromatographic studies demonstrated that the  $\Delta\Delta H^{\ddagger}$  — a measure of specific weak interactions with a Ph group — values for  $R^1$  and  $R^2$  were (i)  $-1.18$  (*p*-MeC<sub>6</sub>H<sub>4</sub>),  $-1.32$  (Ph), and  $-1.51$  kcal mol<sup>-1</sup> (*p*-MeOC<sub>6</sub>H<sub>4</sub>)<sup>17</sup>) and (ii)  $-0.08$  (*n*-C<sub>5</sub>H<sub>11</sub>),  $-1.32$  (Ph), and  $-1.92$  (*p*-MeCOC<sub>6</sub>H<sub>4</sub>) kcal mol<sup>-1</sup>.<sup>18</sup>) Therefore, the order of the  $\underline{r}$  for  $R^1$  or  $R^2$  has proved to be the same as that of the strength of the R—Ph interactions for  $R^1$  or  $R^2$ .

It has been shown that (i) the oxidation proceeds through tetramers<sup>6b,c</sup>) (reaction intermediates) such as 6 (Fig. 3), which are formed by dimerization 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 and (ii) the selectivity depends upon the relative concentration<sup>15</sup>) of the tetramers which is considered to reflect the strength of the interactions between substituents ( $R^1$  and  $R^2$ ).<sup>19</sup>)

On the basis of the experimental results and discussions presented here, we propose that the selectivity in organic reactions can be controlled by specific weak interactions between groups in reacting molecules. This work suggests a novel method for the control of chemical selectivity.

We thank Mr. Takashi Isago for valuable assistance.

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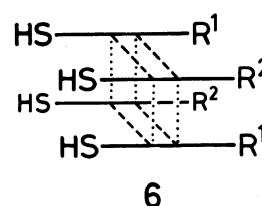


Fig. 3. Association scheme in a typical tetramer 6. -----, Hydrogen bonds; ·····, noncovalent interactions responsible for tetramer formation.

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  - 7) Thiols 1 and 2 were readily prepared as described previously.<sup>6b)</sup> All new compounds had satisfactory spectroscopic data.
  - 8) The two thiols (1 and 2, 0.50 mmol each) were treated with oxygen in the presence of Et<sub>3</sub>N (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 HPLC using LiChrosorb CN and  $\mu$  Bondasphere C<sub>18</sub>. The  $r$  values in Figs. 1 and 2 were reproducible in two or more experiments within the errors described therein.
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  - 14) Initial rates — average rates until 10% consumption of thiols — for 1 are considered to be about 100 times larger than those for 2 in aqueous acetonitrile ( $x_w = 0.42$ ) at 35.0 °C.<sup>15)</sup>
  - 15) T. Endo, M. Hashimoto, T. Orii, and M. M. Ito, *Bull. Chem. Soc. Jpn.*, 57, 1562 (1984) and the references cited therein.
  - 16) Since the  $\sigma_p$  for *p*-MeCOC<sub>6</sub>H<sub>4</sub> and the A for *n*-C<sub>5</sub>H<sub>11</sub> and *p*-MeCOC<sub>6</sub>H<sub>4</sub> are unavailable, the correlation of the selectivity for R<sup>1</sup> (Fig. 2) with electronic and steric effects for R<sup>1</sup> cannot be discussed.
  - 17) 1 kcal = 4.184 kJ.
  - 18) M. M. Ito, J. Kato, S. Takagi, E. Nakashiro, T. Sato, Y. Yamada, H. Saito, T. Namiki, I. Takamura, K. Wakatsuki, T. Suzuki, and T. Endo, *J. Am. Chem. Soc.*, 110, 5147 (1988). The  $\Delta\Delta H^\ddagger$  for *n*-pentane is not published.
  - 19) The product ratio in this type of oxidation is shown to be kinetically controlled.<sup>6a,b)</sup> The rate-determining step of base-catalyzed oxidation of thiols is reported to be either the formation of thiolate anions or their oxidation to the corresponding thiyl radicals.<sup>15)</sup>

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