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MARKED DEPENDENCE OF THE SELECTIVITY IN OXIDATION OF A PAIR OF ASSOCIATING THIOLS ON THE STRUCTURE OF COEXISTING THEIR DECEPTOR

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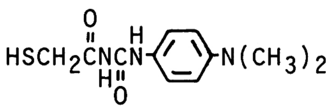
The selectivity in oxidation of a pair of associating thiols with oxygen, on addition of a deceptor structurally related to the thiol, changed remarkably with the structure of the substituent of the deceptor.

Enzyme activity is decreased by binding of an inhibitor to the enzyme. The structures of inhibitors are analogous to that of the specific substrate.[1)] This suggests that the presence of a "deceptor" — a substance similar in structure to the reacting molecule — in a nonenzymatic system may affect chemical events. However, detailed studies have scarcely been made on a correlation between the structures of the substituents of deceptors and chemical selectivity. In this paper we report that the selectivity in oxidation of a pair of associating thiols (**1** and **2**) depends largely on the structure of the substituent of coexisting their deceptor. The selectivity (r) is represented by the logarithmeric ratio of the yield of the unsymmetrical disulfide (**4**) to twice that of the symmetrical disulfide (**3**) $\{r = \ln([\mathbf{4}]/(2\,[\mathbf{3}]))\}$.

It has been shown, regarding the nature of the oxidation, that (i) thiols **1** and **2** associate strongly in benzene *via* two NH•••O intermolecular hydrogen bonds[2)] to form tetramers (reaction intermediates) such as **6** (Fig. 1) as well as dimers, (ii) the S-S bond formation occurs between the two proximate HS groups in the



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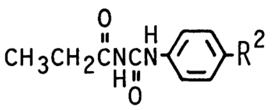

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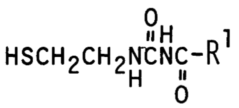
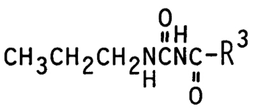


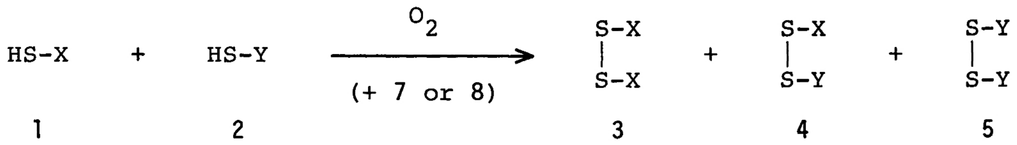
$\mathrm{HSCH_2CH_2}\underset{\mathrm{H}}{\mathrm{N}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\overset{\mathrm{H}}{\mathrm{N}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\text{-}\mathrm{R}^1$

2



$\mathrm{CH_3CH_2CH_2}\underset{\mathrm{H}}{\mathrm{N}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\overset{\mathrm{H}}{\mathrm{N}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\text{-}\mathrm{R}^3$

8

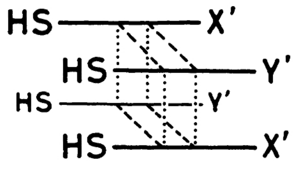


tetramers,[2)] and (iii) the product ratio in this type of oxidation is kinetically controlled.[2,3)]

If a deceptor (7 or 8)[4)] — a derivative having the methyl group instead of the HS group of thiol 1 or 2[4)] — is added to a 1:1 mixture of 1 and 2 in aqueous acetonitrile [mole fraction of acetonitrile (x_{MeCN}) = 0.58], the deceptor might be expected to replace 1 or 2 in the tetramers, resulting in changes in the selectivity. Indeed, this is the case with oxidation of 1 and 2a (R^1 = i-C_5H_{11}) in the presence of 7:[5)] the r value has decreased sharply from 2.4 (the value in the absence of 7) to 0.79, as shown in Fig. 2 where the selectivity is plotted against the A value[6)] — the free energy difference ΔG (= $-RT \ln K$) involved in the axial – equatorial equilibrium of substituted cyclohexanes — for R^2. It should be noted that the r value becomes lowest at R^2 = NMe_2 (the same group as the *para* substituent of 1) and that the r value for R^2 = i-Pr is similar to that for R^2 = NMe_2. In addition, the selectivity has decreased more markedly for R^2 = i-Pr (r = 0.97) than for R^2 = n-Pr (r = 1.8).

Further studies on the selectivity were made in the presence of 8 (Fig. 3).[5)] When a series of branched alkyl groups are used as R^3, the selectivity has proved to show a minimum at the isopentyl group (r = 0.30). The r value of 1.4 for R^3 = n-C_5H_{11} has been found to differ largely from that for R^3 = i-C_5H_{11}. These observations demonstrate that the more strongly the substituent R^3 of 8 resembles the isopentyl group of 2a in geometrical shape, the more remarkably the selectivity is lowered.

In an attempt to relate the observed dependence of the selectivity on the



6

Fig. 1. 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 $C_6H_4NMe_2$ and R^1, respectively.

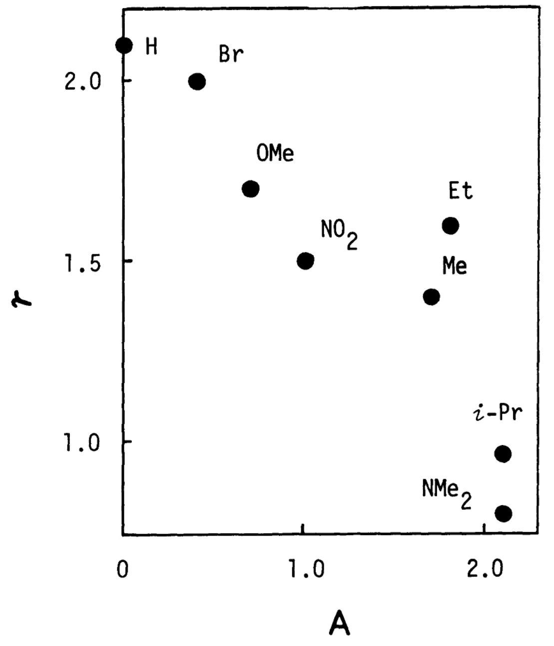


Fig. 2. Plot of the selectivity (r) in oxidation of 1 and 2a (R^1 = i-C_5H_{11}) in the presence of 7 against the A value for R^2. The point for R^2 = n-Pr (r = 1.8) is not shown, since its A value is unavailable.

structures of 8 to structural alterations of the tetramers in solution, ^1H NMR (270 MHz) spectra were measured at 35 °C for 1:1:1 mixtures of 1, 2a, and 8 $[R^3 = (CH_2)_jCHMe_2]$ both in $CDCl_3$ and in CD_3CN-H_2O $(x_{CD_3CN} = 0.58)$. However, the structural changes of 8 caused no appreciable changes in the chemical shift for the inner NH proton[7] of 1 participating in intermolecular hydrogen bond.[8]

It is interesting to note that the selectivity in the presence of 8 also reaches a minimum at the 2-phenylethyl group when a series of phenylalkyl groups are used as R^3 (Fig. 3). This finding, together with the selectivity data for oxidation of 1 and 2 $[R^1 = i\text{-}C_5H_{11}$ and $(CH_2)_nPh$ $(n = 1-3)]$[3,9] (Fig. 3), would suggest that the 2-phenylethyl group resembles the isopentyl group most closely among the phenylalkyl groups examined. This view would coincide with the results for the crystalline 1:1 complex formation between a pair of acylurea derivatives $[p\text{-}(Me_2N)C_6H_4N(H)C(=O)N(H)C(=O)\text{-}R^4$ (9) and $p\text{-}O_2NC_6H_4C(=O)N(H)C(=O)N(H)\text{-}R^5$ (10)];[4,10] the isopentyl, benzyl, 2-phenylethyl, and 3-phenylpropyl groups were used as R^4 (Fig. 4). Of the three phenylalkyl groups, the 2-phenylethyl group shows the closest similarity to the isopentyl group in the trend of the complex formation.

From all the results presented here, it seems reasonable to conclude

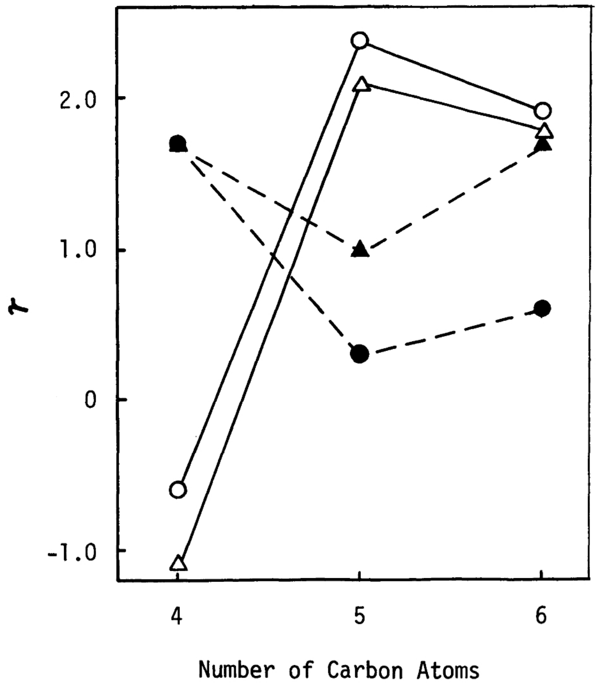
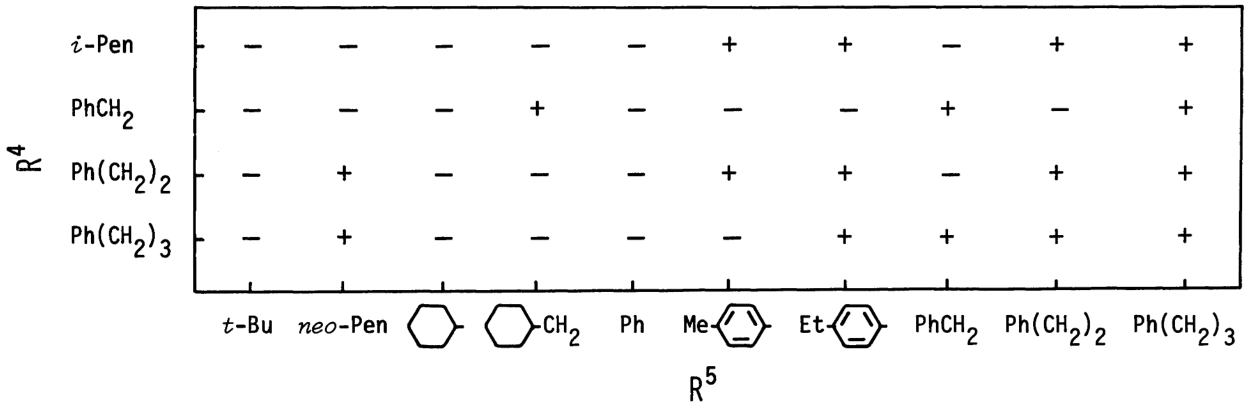


Fig. 3. Dependence of the selectivity (r) in oxidation of 1 and 2a $[R^1 = (CH_2)_2CHMe_2]$ in the presence of 8 $[R^3 = (CH_2)_jCHMe_2$ (●) and $(CH_2)_kPh$ (▲)] and in oxidation of 1 and 2 $[R^1 = (CH_2)_mCHMe_2$ (○) and $(CH_2)_nPh$ (△)] on the number of carbon atoms in R^3 and R^1. With the $(CH_2)_xPh$ groups, the number of carbon atoms is counted as "x+3".



R^4 \ R^5	t-Bu	neo-Pen	C_6H_{11}	$C_6H_{11}CH_2$	Ph	Me-C_6H_4	Et-C_6H_4	$PhCH_2$	$Ph(CH_2)_2$	$Ph(CH_2)_3$
i-Pen	−	−	−	−	−	+	+	−	+	+
$PhCH_2$	−	−	−	+	−	−	−	+	−	+
$Ph(CH_2)_2$	−	+	−	−	−	+	+	−	+	+
$Ph(CH_2)_3$	−	+	−	−	−	−	+	+	+	+

Fig. 4. Crystalline 1:1 molecular complex formation between 9 and 10 for various combinations of R^4 and R^5. The + indicates complex formation and the − indicates no complex formation. Pen represents the pentyl group.

that the more closely the substituent of a deceptor resembles that of the reacting molecule in geometrical shape, the more markedly the selectivity is reduced. Our work suggests that weak interactions related to the nonpolar groups of reacting molecules and the corresponding deceptors are specific for their three-dimensional shape.11)

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1) M. A. Ondetti, B. Rubin, and D. W. Cushman, *Science*, 196, 441 (1977); O. W. Griffith and A. Meister, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 3330 (1977); A. A. Patchett, *et al.*, *Nature*, 288, 280 (1980).

2) T. Endo, A. Okubo, Y. Kaneko, M. Uehara, H. Tasai, A. Sato, K. Nikki, N. Nakagawa, and S. Kamei, *Bull. Chem. Soc. Jpn.*, 55, 2224 (1982).

3) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Hashimoto, and T. Ishigami, *Nature*, 268, 74 (1977).

4) The acylurea derivatives **1**, **2**, and **7**–**10** were readily prepared as described previously.2) Satisfactory spectroscopic data were obtained for all new compounds.

5) The oxidation was carried out by treating **1** and **2a** (0.50 mmol each) with O_2 in the presence of **7** or **8** (0.50 mmol) and Et_3N (0.05 mmol) at 35.0 °C in 12.5 ml of MeCN–water ($x_{MeCN} = 0.58$) until the thiols were completely consumed. The yields of **3** and **4** were determined as described previously.2)

6) Among the five substituent constants σ [D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958)], π [C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacol.*, 1, 205 (1965)], v [M. Charton, *J. Am. Chem. Soc.*, 97, 1552 (1975)], A [E. L. Eliel, *Angew. Chem. Int. Ed. Engl.*, 4, 761 (1965)], and R_m [C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973)], the A value had the closest correlation with the selectivity.

7) The NH proton chemical shift for **1** remained almost unaltered (δ *ca.* 10.01) with the structures of R^3 in $CDCl_3$. The concentrations of **1**, **2a**, and **8** were each 0.020 M in $CDCl_3$ and 0.040 M in CD_3CN–water.

8) The deshielding of the inner NH proton of **8** was larger for $R^3 = i\text{-}C_5H_{11}$ (δ 9.19) than for the other branched alkyl groups used as R^3 (δ *ca.* 9.10) in $CDCl_3$, leading to an apparent correlation with the selectivity. However, the highest degree of association of **8** for $R^3 = i\text{-}C_5H_{11}$ among the branched alkyl groups (T. Endo, Y. Takeda, T. Orii, T. Murata, and M. Sakai, *Chem. Lett.*, 1980, 1291) may cause the observed downfield shift.

9) T. Endo, Y. Takeda, T. Orii, A. Kuwahara, M. Ohta, M. Sakai, R. Okada, and M. Hashimoto, *Bull. Chem. Soc. Jpn.*, 53, 2687 (1980).

10) The crystalline 1:1 complex formation was carried out as described previously: T. Endo, K. Miyazawa, M. Endo, A. Uchida, Y. Ohashi, and Y. Sasada, *Chem. Lett.*, 1982, 1989. The complexes have the very characteristic color, which is not shown in this paper. The complex formation was performed in MeCN except in the case of $R^5 = p\text{-}MeC_6H_4$ and $p\text{-}EtC_6H_4$ where *N*,*N*-dimethylformamide was used as a solvent owing to the very low solubility of **10** in MeCN.

11) Recently, experimental evidence has been given for such specificity of weak interactions: T. Endo, M. M. Ito, Y. Yamada, H. Saito, K. Miyazawa, and M. Nishio, *J. Chem. Soc., Chem. Commun.*, 1983, 1430.

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