

SIMILARITY IN THE STRUCTURE OF THE BINDING SITES BETWEEN A PAIR OF
REACTING MOLECULES: ITS EFFECT ON MOLECULAR RECOGNITION

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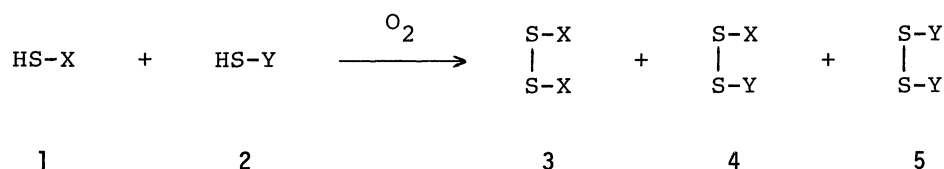
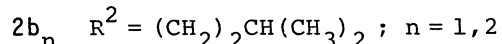
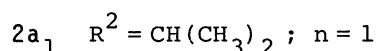
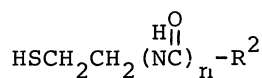
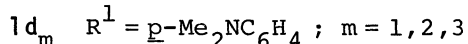
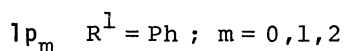
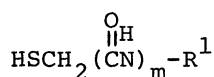
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Based on the selectivity [the ratio of an unsymmetrical disulfide (4) to symmetrical one (3)] in the oxidation of a pair of thiols (1 and 2) with O_2 , it is suggested that maximal recognition between 1 and 2 occurs when 1 and 2 are similar in the structure of the binding sites to each other.

Increasing attention has recently been focused on molecular recognition such as chiral recognition¹ and the recognition of linear triatomic species² by use of macrocyclic inclusion compounds. This paper describes the effect of similarity in the structure of the binding sites between a pair of thiols (1 and 2) on molecular recognition between them.

Thiols³ 1 and 2 generally have the binding sites $[-(\overset{O}{\parallel}C-NH)_k-$, $k=1, 2, \text{ or } 3$]. A 1:1 mixture of 1 and 2 is used as a reaction system, in which the structure of the binding site in 1 varies; this system is divided into system I ($1p_m$ and $2a_1$),



system II ($1p_m$ and $2b_1$), system III ($1p_m$ and $2b_2$), and system IV ($1d_m$ and $2b_2$). The oxidation of each of the four reaction systems with oxygen is used as a model reaction for molecular recognition.

The two thiols (1 and 2, 0.5 mmol each) were treated with O_2 in 12.5 ml of 80% (v/v) acetonitrile-20% water at 35.0 °C in the presence of a catalytic amount of Et_3N (5×10^{-2} mmol) to give an unsymmetrical (4) and two symmetrical disulfides (3 and 5). When the oxidation was completed, yields of 3 and 4 were determined by the use of their absorption at 310 nm after separation by tlc⁴ in the case of system IV ($m=2$ and 3), and determined gravimetrically after separation by preparative tlc in all the other cases. The selectivity (\underline{R}) in this oxidation, represented as the ratio of the yield of 4 to that of 3 ($\underline{R} = 4/3$), can be regarded as a measure of molecular recognition between 1 and 2.

Figure 1 shows a plot of the selectivity (\underline{R}) against " $m-n$ ", the difference in the number of amide-bond units ($-C(=O)NH-$) between 1 and 2. As is evident from Figure 1, \underline{R} reaches a maximal value when the numbers of amide-bond units in 1 and 2 are equal to each other (i.e., when $m-n=0$) in the four respective systems. Further,

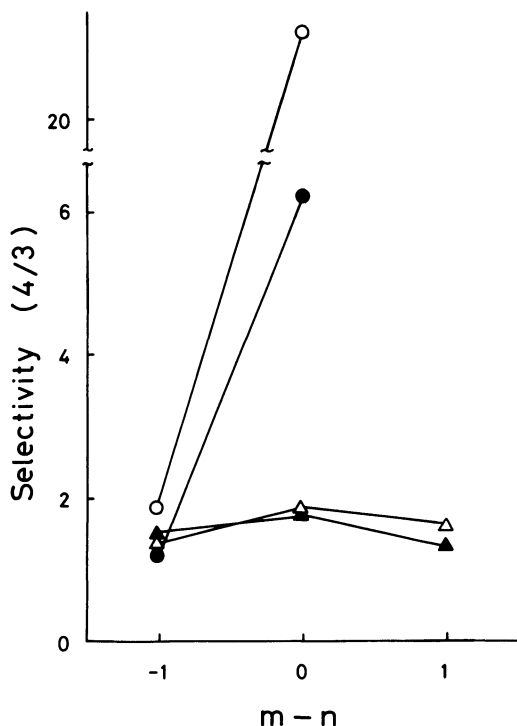


Figure 1. Dependence of selectivity ($\underline{R} = 4/3$) in oxidation of 1 and 2 on " $m-n$ ". ▲, System I; △, system II; ●, system III; ○, system IV.

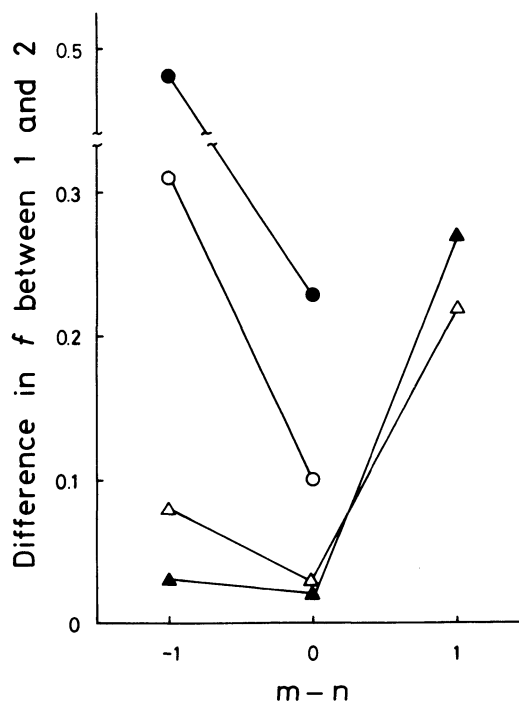


Figure 2. Dependence of difference in \underline{f} between 1 and 2 on " $m-n$ ". ▲, System I; △, system II; ●, system III; ○, system IV.

this relationship appears to hold also for $m = 3$ in system IV.⁵

Since amide-bond units are known to form $\text{NH}\cdots\text{O}$ hydrogen bonding,⁶ the degree of association (\underline{f})⁷ of thiols was measured in benzene⁸ at 36.0 °C. The difference in \underline{f} between 1 and 2 was plotted against " $m - n$ " (Figure 2).⁹ The data in Figure 2 would suggest that similarity in the structure of the binding sites between thiols 1 and 2 corresponds to similarity in \underline{f} between 1 and 2.

Preliminary kinetic data on the oxidation of thiols¹⁰ have revealed that (i) the rate of the oxidation of 1 ($m = 1$ and 2) is much faster than that of 2, (ii) with systems II ($m = 1$) and IV ($m = 2$) the thiol radical initially generated by reaction with O_2 would be that from thiol 1 ($m = 1$ and 2), and (iii) the basic mechanisms for the oxidation of the above two systems are the same, as indicated by similar rate profiles for them.

It has already been demonstrated that the product ratio (\underline{R}) in the oxidation of system IV ($m = 2$) is kinetically controlled.¹¹ With systems I ($m = 1$) and II ($m = 1$) the selectivity in the disulfide-disulfide exchange reaction¹² between 3 and 5 ($\underline{R} = 2.1$ for $\text{R}^2 = \text{isoC}_3\text{H}_7$ and 2.2 for $\text{R}^2 = \text{isoC}_5\text{H}_{11}$) differed from that in the corresponding oxidation, suggesting that the result obtained with the oxidation of the two respective systems represents kinetic control. Moreover, the selectivity was found not to be controlled by solubility differences between thiols 1 and 2 in all the systems.¹³

From the experimental data presented in this paper, it may be concluded that maximal recognition between a pair of reacting molecules occurs when they are similar in the structure of the binding sites to each other. This conclusion would be applied to a reaction system where the sites other than the binding sites are fixed. It is hoped that our work will serve to stimulate experiments which may clarify the factors responsible for molecular recognition.

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References and Notes

- 1) D. J. Cram in "Applications of Biochemical Systems in Organic Chemistry", Part II, J. B. Jones, C. J. Sih, and D. Perlman, Eds., Wiley-Interscience, New York, 1976, chapter V.
- 2) J. M. Lehn, E. Sonveaux, and A. K. Willard, J. Am. Chem. Soc., 100, 4914 (1978), and references cited therein.
- 3) Thiol 1 was prepared as described before (T. Endo, K. Oda, and T. Mukaiyama,

- Chem. Lett., 443 (1974)). Thiols $2a_1$ and $2b_1$ were synthesized according to the method previously reported (R. Kuhn and G. Quadbeck, Chem. Ber., 84, 844 (1951)). Thiol $2b_2$ was prepared in good yield by addition of cysteamine to 4-methyl-pentanoyl isocyanate in THF at 0 °C under argon. Satisfactory spectral data were used to support the assignment of all new compounds.
- 4) T. Endo, A. Kuwahara, H. Tasai, and T. Ishigami, J. Chromatogr., 140, 263 (1977).
 - 5) In the reaction mixture for system IV ($m=3$), the formation of 3 derived from $1d_3$ could not be detected as one of the main products, whereas the presence of 4 and 5 was confirmed by tlc. Thus, with system IV the yields of the unsymmetrical disulfides 4 for $m=1$ to 3, instead of the selectivity (R), can be compared with one another as a measure of molecular recognition: 43% for $m=1$, 87% for $m=2$, and 33% for $m=3$.
 - 6) The concentration dependence of NH proton chemical shifts in $CDCl_3$ at 32 °C has clarified that $1d_2$ and $2b_2$ form strong intermolecular hydrogen bonding with each other as well as with themselves (T. Endo, Y. Takeda, T. Orii, Y. Kaneko, and M. Kondo, Chem. Lett., 1455 (1979)).
 - 7) The degree of association (f) was obtained by dividing the stoichiometric mole fraction of the solute by the effective mole fraction of the solute using differential vapor pressure method. The determination of f was made at 0.02 M for $1p$, $2a_1$, and $2b$, and at 0.01 M for $1d$ and $2b_2$ depending on their solubilities. The degree of association f of 1 and 2 at 0.01 M ranged from 1.3 to 1.5 for $m=n=2$, and was less than 1.05 for $m=n=1$.
 - 8) Benzene was chosen as a solvent, because (i) aqueous organic solvents cannot be used for the apparatus employed for the determination of differential vapor pressure and (ii) in acetonitrile f of thiols 1 and 2 was too insensitive to their structures to be compared with one another, as evidenced by the finding that f is 1.04 for $1d_2$ (0.02 M) and 1.08 for $2b_2$ (0.04 M).¹¹
 - 9) The degree of association f of $1d_3$ was 1.00 even in saturated (ca. 2×10^{-4} M) benzene solution. The difference in f between $1p_0$ and $2a_1$ (or $2b_1$) was calculated on the assumption that f of $1p_0$ is 1.00.
 - 10) T. Endo, T. Orii, M. Hashimoto, and Y. Takeda, unpublished results.
 - 11) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Hashimoto, and T. Ishigami, Nature, 268, 74 (1977).
 - 12) Disulfides 3 and 5 employed were those derived from $1p_1$ and $2a_1$ (or $2b_1$), respectively. The exchange reaction was carried out in 80% (v/v) acetonitrile-20% water at 35.0 °C in the presence of a catalytic amount of both Et_3N and thiol $1p_1$ under argon for the same reaction time (3 h) as with the corresponding oxidation.
 - 13) The selectivity also proved not to be controlled by solubility differences between disulfides 3, 4, and 5 in the oxidation of systems I ($m=0$ and 1), II ($m=0$ and 1), and IV ($m=2$).

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