CHEMISTRY LETTERS, pp. 1291-1294, 1980. © The Chemical Society of Japan 1980

SPECIFIC WEAK INTERACTIONS RELATED TO GEOMETRICAL SHAPE OF ASSOCIATING THIOLS: THE FACTOR RESPONSIBLE FOR SELECTIVE MOLECULAR RECOGNITION IN THEIR OXIDATION

Tadashi ENDO, Yukiko TAKEDA, Toyohiko ORII, Tomoji MURATA, and Miyuki SAKAI
College of Science and Engineering, Aoyama Gakuin University,
Chitosedai, Setagaya, Tokyo 157

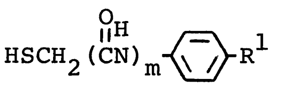
Naoya NAKAGAWA and Kunio NIKKI
The University of Electro-communications, Chofugaoka, Chofu, Tokyo 182

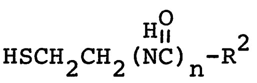
In oxidation of a pair of associating thiols (**1d** and **2**) with O_2, specific weak interactions related to their geometrical shape such as CH···N and CH···SH interactions are suggested to be responsible for selective molecular recognition.

We report here the experimental evidence to suggest that specific weak interactions related to geometrical shape of associating thiols are responsible for selective molecular recognition in their oxidation.

Two types of model systems were used: the associating system (system A) and non-associating system (system N).[1,2] System A consists of a pair of associating thiols (**1** and **2**)[1], each having the reaction site (SH), the binding site ($-\overset{O}{\overset{\|}{C}}\overset{H}{N}\overset{O}{\overset{\|}{C}}\overset{H}{N}-$), and the recognition site ($C_6H_4-R^1$ or R^2); this system is further divided into system A_d (**1d** and **2**), system A_i (**1i** and **2a**), and system A_p (**1p** and **2a**). System N consists of a pair of non-associating thiols (**3** and **4**)[1].

A 1:1 mixture of **1** and **2** (or of **3** and **4**, 0.5 mmol each) was treated with oxygen in the presence of a catalytic amount of Et_3N (0.05 mmol) at 35.0 °C in 12.5 ml of 80% (v/v) acetonitrile-20% water to give an unsymmetrical disulfide (**6**) and

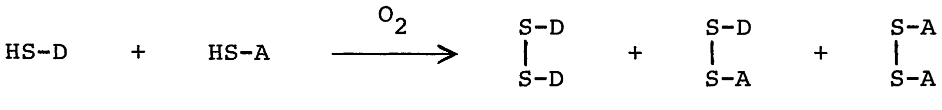




$HSCH_2CH_2(\overset{H}{N}\overset{O}{\overset{\|}{C}})_n-R^2$

1d $m = 2,\ R^1 = N(CH_3)_2$
1i $m = 2,\ R^1 = CH(CH_3)_2$
1p $m = 2,\ R^1 = H$
3 $m = 1,\ R^1 = H$

2a$_j$ $n = 2,\ R^2 = (CH_2)_jCH(CH_3)_2$
2b$_k$ $n = 2,\ R^2 = (CH_2)_kCH_2CH_2CH_3$
4a$_j$ $n = 1,\ R^2 = (CH_2)_jCH(CH_3)_2$
4b$_k$ $n = 1,\ R^2 = (CH_2)_kCH_2CH_2CH_3$



$$HS\text{-}D + HS\text{-}A \xrightarrow{O_2} \begin{matrix} S\text{-}D \\ | \\ S\text{-}D \end{matrix} + \begin{matrix} S\text{-}D \\ | \\ S\text{-}A \end{matrix} + \begin{matrix} S\text{-}A \\ | \\ S\text{-}A \end{matrix}$$

1 or **3**   **2** or **4**   **5**   **6**   **7**

two symmetrical ones (**5** and **7**). The selectivity ($\underline{R}$) in this oxidation is represented by the ratio of the yield[1] of **6** to that of **5** ($\underline{R}$ = **6**/**5**).[3]

Previously we have reported that the selectivity in oxidation of system A_d depends sharply on the structure of R^2:[2,3] (i) in the case of **1d** and **2a** maximal selectivity ($\underline{R}$ = 21) occurs at $\mathbf{2a}_2$ (j = 2), $\underline{R}$ being 0.84, 1.2, 21, 13, and 11 for j = 0, 1, 2, 3, and 4, respectively, and (ii) with **1d** and **2b** alternation in the selectivity is clearly observed, $\underline{R}$ being 4.5, 0.28, 0.53, 0.29, and 0.40 for k = 0, 1, 2, 3, and 4, respectively. In order to elucidate a factor governing these radical changes in $\underline{R}$, some attempts were made.[4]

Oxidation of system N clarified that with **3** and **4a** (j = 0 to 3) the selectivity showed almost no changes ($\underline{R}$ = 1.8 to 1.9) and that with **3** and **4b** (k = 0 to 3) $\underline{R}$ decreased progressively from 2.0 to 0.50 with "k", thus demonstrating that intermolecular association between a pair of thiols is first required for the sharp response of $\underline{R}$ to the structure of R^2 —— selective molecular recognition. Further, the rate of the oxidation remained almost unaltered with R^2 under conditions similar to those described above (at 0.010 M): (i) in system A_d the time required for 50% oxidation ($\tau_{0.5}$) was 76 ± 6, 62 ± 5, and 64 ± 5 min for j = 0, 2, and 4, respectively, and (ii) in system N the $\tau_{0.5}$ value was 28 ± 2 and 27 ± 2 min for j = 0 and 2, respectively.[5] These results suggest that the dependence of chemical reactivity difference between **1d** and **2** on the structure of R^2 is not related to the sharp structure dependence of $\underline{R}$ for system A_d.

Our previous work has shown that tetramers (**8**-**12**) composed of **1d** and **2** (Figure 1) are intermediates of their oxidation.[6] Each of these tetramers would give the corresponding disulfide(s) selectively when treated with oxygen —— (i) heterotetramer **8** gives **5**, **6**, or **7**, (ii) heterotetramers **9** and **10** exclusively give **6**, and (iii) homotetramers **11** and **12** exclusively give **5** and **7**, respectively. This

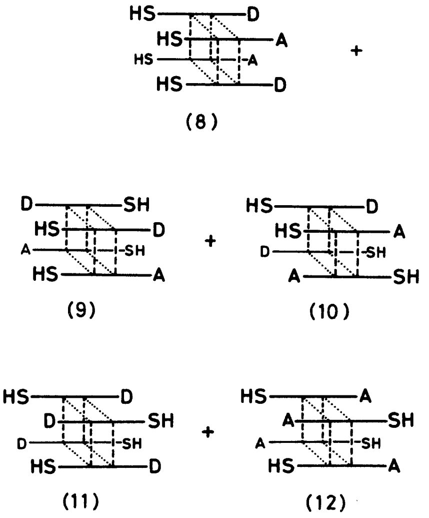


Figure 1. Schematic drawings of the conformations of tetramers (**8**-**12**) formed by dimerization of dimers. ······, Hydrogen bond responsible for stabilization of dimers; -----, non-covalent interactions responsible for stabilization of tetramers.

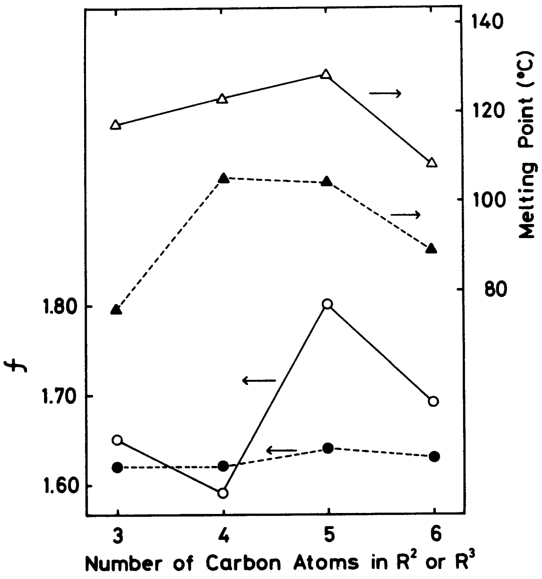
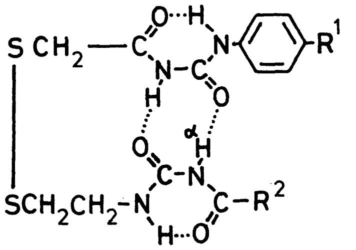


Figure 2. Dependence of $\underline{f}$ and melting point for **2a** or **13a** on the structure of R^2 or R^3. ○, $\underline{f}$ of **2a**; ●, $\underline{f}$ of **13a**; △, melting point of **2a**; ▲, melting point of **13a**.

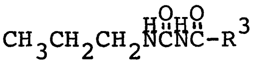
consideration together with the results mentioned above leads us to assume that selective molecular recognition would be ascribed to the dependence of relative concentration of the tetramers on the structure of R^2. This assumption is supported by NMR results that the NH proton of **2** participating in intermolecular hydrogen bonding underwent a considerably larger downfield shift[7] (0.2 ppm) for a 1:1 mixture of **1d** and **$2a_2$** than for a 1:1 mixture of **1d** and **$2b_2$** in $CDCl_3$ at 0.01 M and 32 °C.

Since the solvent used in this oxidation was aqueous acetonitrile, hydrophobic interaction may be associated with the control of molecular recognition. However, the following data cannot be explained by hydrophobic contribution to the selectivity for system A_d: (i) plots of *R* in oxidation of **1d** and **$2a_2$** against the volume percent of water in acetonitrile-water mixtures showed a maximum at 20% of water, but not a progressive increase with increasing volume percent of water,[3,8] and (ii) the increasing (or decreasing) order of the π value[9] of an alkyl group employed as R^2 in **2** is quite different from the increasing (or decreasing) order of *R* in oxidation of system A_d for the corresponding alkyl group. Therefore, selective molecular recognition in oxidation of system A_d would best be attributed to specific weak interactions related to geometrical shape of the recognition sites and the reaction sites in tetramers. Possible candidates for weak interactions are $CH\cdots N$[10], $CH\cdots SH$, $SH\cdots SH$[11], and $SH\cdots N$[11] interactions,[12] the first two interactions[13] mainly contributing to the selectivity *R*.

Thiol **2t** ($n = 2$, $R^2 = p\text{-}CH_3C_6H_4$) formed a solid 1:1 complex[6] with **1d**, but not with **1p**, suggesting the contribution of $CH\cdots N$ interaction between an alkyl group in R^2 and the amino group in R^1 to the stabilization of the solid complex. The contribution of $CH\cdots N$ interaction to selective molecular recognition is suggested by the finding that the structure dependence of *R* was less sharp for systems A_i and A_p than for system A_d —— (i) with system A_i the *R* value was 5 both for $j = 0$ and 2, and (ii) with system A_p the *R* value was 2.6 and 6.2 for $j = 0$ and 2, respectively. Moreover, ^1H NMR studies of unsymmetrical disulfides derived from **1d** and **$2a_2$** [**6d** ($j = 2$)], **1d** and **$2b_2$** [**6d** ($k = 2$)], and **1p** and **$2a_2$** [**6p** ($j = 2$)] in $CDCl_3$ at 0.005 M and 34 °C revealed that the NH^{α} proton underwent a downfield shift of 0.19 or 0.18 ppm in going from **6p** ($j = 2$) to **6d** ($j = 2$) or from **6d** ($k = 2$) to **6d** ($j = 2$), respectively; these results indicate that $CH\cdots N$ interaction is attractive and specific, and thus makes the $NH^{\alpha}\cdots O$ hydrogen bonding stronger.



6

Figure 2 shows that degree of association[2] (*f*) in benzene at 0.04 M is larger for **2a** than for its derivative,  $CH_3CH_2CH_2\overset{H}{N}\overset{O}{C}\overset{H}{N}\overset{O}{C}\text{-}R^3$ [**13a**; $R^3 = (CH_2)_jCH(CH_3)_2$], except in the case of $R^2 = R^3 = isoC_4H_9$ and that the melting point[14] of **2a** is higher than that of **13a** by 20 to 40 °C. Higher *f* and melting point of **2a** would be viewed as being due to attractive $CH\cdots SH$ interaction between an alkyl and the SH groups.

From all of the data presented here, it may be concluded that specific weak interactions related to geometrical shape of the recognition sites are responsible for selective molecular recognition in oxidation of system A_d.

Acknowledgment. We thank Drs. Motohiro Nishio and Michio Kondo for helpful discussions, Mr. Yuji Kaneko for valuable assistance, and the Ministry of Education, Japan, for financial support.

References and Notes

1) The preparation of thiols **1**-**4** and the determination of the yields of **5** and **6** were made as described before (T. Endo, Y. Takeda, H. Kamada, S. Kayama, and H. Tasai, Chem. Lett., *1980*, 417). All new compounds had satisfactory spectral data.
2) The degree of association (*f*), obtained by dividing the stoichiometric mole fraction of the solute by the effective mole fraction of the solute, was measured at 36.0 °C in benzene. The *f* value at 0.01 M was less than 1.05 for **3** and **4**, and ranged from 1.3 to 1.5 for **1** and **2** except that *f* of **1p** was 1.30 at 0.02 M.
3) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Hashimoto, and T. Ishigami, Nature, *268*, 74 (1977).
4) It has been confirmed with oxidation of system A_d that (i) the product ratio *R* is kinetically controlled and (ii) the selectivity is not controlled by solubility differences between thiols (**1d** and **2**) and between disulfides (**5**-**7**).[3]
5) The time required for 10% oxidation of **2a** alone was all *ca*. 10 h.
6) T. Endo, Y. Takeda, T. Orii, Y. Kaneko, and M. Kondo, Chem. Lett., *1979*, 1455.
7) A downfield shift of the NH proton implies that NH···O hydrogen bonding becomes stronger.
8) The dielectric constant and surface tension of acetonitrile-water mixtures are known to increase progressively with increasing volume percent of water.
9) The π value (an excellent parameter of hydrophobicity) is reported to increase in the order isoC_3H_7 < n-C_3H_7 < isoC_4H_9 < n-C_4H_9 < n-C_5H_{11} < n-C_6H_{13} < n-C_7H_{15} (C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, Mol. Pharmacol., *1*, 205 (1965)).
10) The presence of this interaction was suggested by the fact that *ab initio* SCF MO calculations showed the total interaction energy for a complex of CH_4 with NH_3 to be -1.1 kcal/mol (K. Morokuma, Acc. Chem. Res., *10*, 294 (1977)).
11) The SH···SH and SH···N interactions are regarded as weak hydrogen bonding (N. L. Allinger, M. P. Cava, D. C. De Jongh, C. R. Johnson, N. A. Lebel, and C. L. Stevens, "Organic Chemistry", Worth, New York, 1971), and appear to be relatively unimportant as weak interactions affecting changes in *R* with R^2.
12) The CH···CH interaction of an alkyl group in R^2 with itself (or of an alkyl group in R^2 with the methyl group in $N(CH_3)_2$) would also affect the selectivity, as suggested by the finding that the melting point of **13a** showed a small maximum at R^3 = isoC_4H_9 (Figure 2). This interaction would appear to play a major role in the predominance of a rotamer in 1,3,5-trineopentylbenzene with all three neopentyl groups on the same side of the benzene ring in $CDCl_3$ (R. E. Carter and P. Stilbs, J. Am. Chem. Soc., *98*, 7515 (1976)).
13) These two interactions are assumed to possess the following features: (i) they have energies smaller than that for hydrogen bond, (ii) they are interactions between groups, between a group and an atom, or between atoms, which reflect the nature of the interacting groups or atoms, and (iii) they have high specificity (*e.g.*, as to directionality); they may be generally involved in van der Waals interaction.
14) Considering that intermolecularly hydrogen-bonded materials have higher melting points than the corresponding similar sized compounds (G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond", Freeman, San Francisco, 1960, p 35), it seems reasonable to consider that melting points would also be raised by specific weak interactions discussed here. Since homodimers in solution adopt the head-to-tail conformations, also in the solid state **2** would adopt the head-to-tail conformation. Recently, a relationship was found to exist between the selectivity *R* in oxidation of system A_d and the melting point of **2** (T. Endo, Y. Takeda, T. Orii, A. Kuwahara, M. Ohta, M. Sakai, R. Okada, and M. Hashimoto, Bull. Chem. Soc. Jpn., in press). This correlation may be explained by assuming that specific weak interactions between **1d** and **2** are similar, in the dependence on R^2, to those of **2** with itself.

(Received July 1, 1980)