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TETRAMERS AS INTERMEDIATES IN SPECIFIC OXIDATION OF A PAIR OF ASSOCIATING THIOLS

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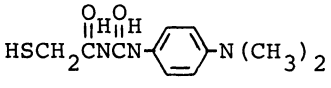
Tetramers composed of the associating thiols (1 and 2) were suggested to be intermediates in the specific oxidation of a 1:1 mixture of 1 and 2, based on spectroscopic studies, the behavior of the selectivity in this oxidation, the determination of degree of association, and so on.

High specificity of "chemical" reactions in living systems is now considered to result from the fact that these reactions occur in highly organized molecular aggregates such as enzyme-substrate, protein-protein, and protein-nucleic acid complexes. Thus, the relation of specific intermolecular association to reaction behavior should be elucidated in order to understand as yet unknown factors controlling chemical reactions, enzymatic or nonenzymatic. From this point of view, the selectivity was already investigated in the oxidation of a pair of associating thiols (1 and 2)[1], each having the binding site ($-\overset{O}{\overset{\|}{C}}\overset{H}{\underset{|}{N}}\overset{O}{\overset{\|}{C}}\overset{H}{\underset{|}{N}}-$) and the recognition site [$C_6H_4N(CH_3)_2$ or R^1].[2] We now report that this specific oxidation is suggested to proceed through tetramers composed of 1 and 2.

Spectroscopic studies of 1 and 2 were made by using the dilution technique. First, infrared spectra[3] in $CDCl_3$ showed the NH stretching vibration bands due to intermolecular hydrogen bond at 3266 cm^{-1} for 1, 3246 cm^{-1} for $2a_2$, and 3240 cm^{-1} for $2b_2$ as well as to intramolecular hydrogen bond at 3355 cm^{-1} for 1, 3316 cm^{-1} for $2a_2$, and 3308 cm^{-1} for $2b_2$. Second, ^1H NMR studies in $CDCl_3$ (Figure 1 and Table 1) have revealed that (i) on mixing of equimolar amounts of 1 and $2a_2$ (or $2b_2$), the NH^{α}



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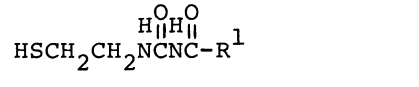
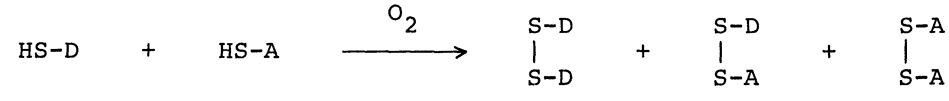


$2a_j$ $R^1 = (CH_2)_jCH(CH_3)_2$

$2b_k$ $R^1 = (CH_2)_kCH_2CH_2CH_3$

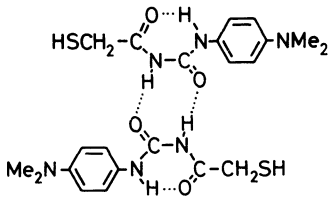


1 2 3 4 5

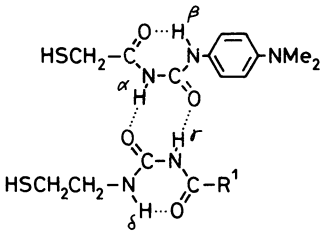
and NH^{γ} protons were largely shifted downfield, while the NH^{β} and NH^{δ} protons underwent small shifts and (ii) the concentration dependence of the chemical shifts of the NH^{α} and NH^{γ} resonances was less sharp when 1 and $2a_2$ (or $2b_2$) were dissolved individually than when they were mixed together. These data demonstrate that 1 and $2a_2$ (or $2b_2$) form weak complexes with each other as well as with themselves.

Further, the dependence of the selectivity (R), represented as the ratio of an unsymmetrical disulfide (4) to symmetrical one (3) (R = 4/3)[4], on the mole ratio of 1 to $2a_2$ (or $2b_2$) showed a maximum rise of R at a 1:1 mixture of 1 and $2a_2$ (or $2b_2$),[5] providing evidence for the 1:1 complex formation between 1 and $2a_2$ (or $2b_2$). This is consistent with the finding that thiol 2n or 2t having the p-nitrophenyl or p-tolyl group as R^1 forms a solid 1:1 complex[6] [mp 146-147 °C (dec) or 144-146 °C, respectively], when mixed with 1.

Considering that the two acylurea bonds (-CNCN-) in 1 and 2 extend in the opposite direction to each other, these results indicate that if weak complexes present in solution consist of dimers alone (Figure 1), the conformations of homodimers (6 and 8) are of the head-to-tail type, that of heterodimer (7) being of the head-to-head type. However, homodimers of head-to-tail conformation cannot explain the selective formation of the symmetrical disulfides (i.e., R of lower than 2, the value statistically expected) in some cases:[7] R was 0.84 for $2a_0$ and 1.2 for $2a_1$, and 0.28 for $2b_1$, 0.53 for $2b_2$, 0.29 for $2b_3$, and 0.40 for $2b_4$. Moreover, the degree of association (f), obtained by dividing the stoichiometric mole fraction of the solute by the effective mole fraction of the solute, for 0.06 M CCl_4 solution of $2a_2$ proved to be as large as 1.95 at 36.0 °C; f of 2.00 can be interpreted as



(6)



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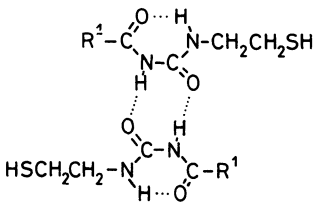


(8)

Figure 1. Scheme of conformations of dimers (6-8).

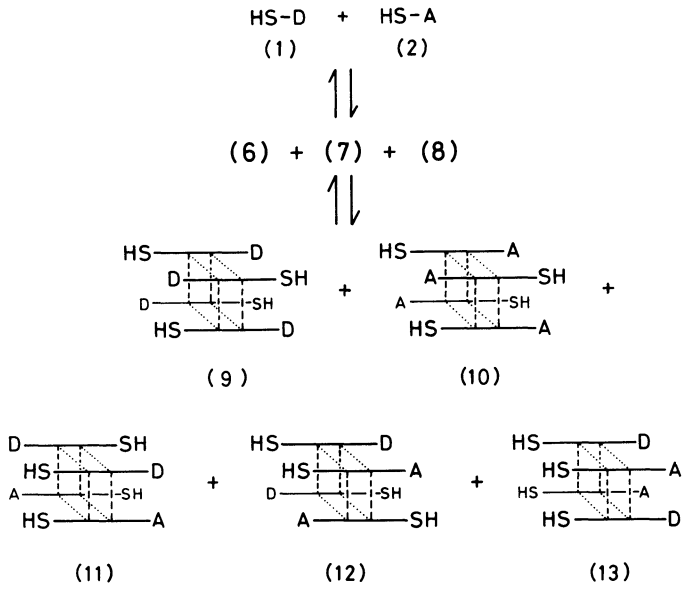


Figure 2. Scheme of conformations of tetramers (9-13). ·····, Intermolecular hydrogen bond responsible for stabilization of dimers; -----, attractive non-covalent interactions responsible for stabilization of tetramers.

Table 1. Chemical shifts in 1, 2, and their 1:1 mixtures in $CDCl_3$[a)]

Concn, M			Chemical shifts[b)]			
1	$2a_2$	$2b_2$	NH^{α}	NH^{β}	NH^{γ}	NH^{δ}
0.020			9.39	10.13		
0.005			8.89	10.16		
0.001			8.78	10.54[c)]		
	0.020				8.70	8.70
	0.005				7.86	8.68
	0.001				7.48	8.62
		0.020			8.60	8.74
		0.005			7.83	8.67
		0.001			7.44	8.61
0.020	0.020		9.74	10.18	8.99	8.77
0.005	0.005		9.07	10.08	8.10	8.60
0.001	0.001		8.78	10.55[c)]	ca. 7.5	8.57
0.020		0.020	9.79	10.18	8.94	8.77
0.005		0.005	9.16	10.20	8.08	8.67
0.001		0.001	8.83	10.54[c)]	ca. 7.5	8.60

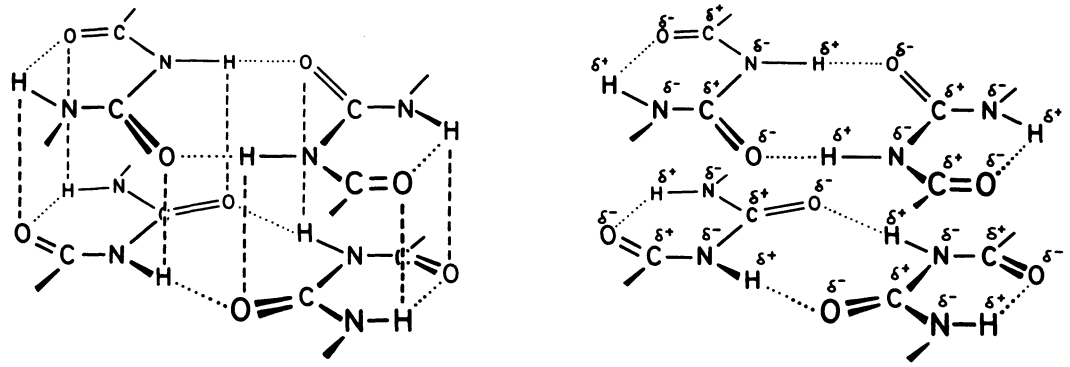
a) Spectra were measured at 32 °C on a Varian XL-100A spectrometer using Fourier transform. Greek letters (α, β, γ, and δ) indicate assignments as given in Figure 1. b) Expressed in ppm downfield from TMS. c) Large downfield shifts for NH^{β} proton on dilution would be due to acidic substances produced from $CDCl_3$.

implying either the complete formation of dimers or the presence of higher aggregates in addition to dimers. From the experimental data in this paper, it seems reasonable to conclude that there exist tetramers —— two homotetramers (9 and 10) and three heterotetramers (11, 12, and 13) —— in equilibrium with dimers (6, 7, and 8) and monomers (1 and 2) as shown in Figure 2. Among many possibilities, five tetramers were chosen so that (i) the ratio of 1 to 2 in heterotetramers might be 1:1 and (ii) the stabilization of tetramers might become strongest.

The stabilization energy of tetramers (stacking energy of dimers) would come from attractive non-covalent interactions, "vertical" N-H···O hydrogen bond (Figure 3a) and/or electrostatic interactions between multipoles[8] (Figure 3b). This type of hydrogen bond in Figure 3a (i.e., bifurcated hydrogen bond) that the hydrogen bond capacity of each hydrogen atom is divided between two oxygen atoms is known to exist in solid aliphatic peracids[9] and in the solid 1:1 complex between crown ether and thiourea[10].

The presence of tetramers is not unusual phenomenon: (i) tetramer formation is shown for Et_2NH in cyclohexane[11]; (ii) the hemoglobins of higher animals are tetrameric proteins, composed of two pairs of unlike polypeptide chains[12]; and (iii) pyrimidine-purine complexes [i.e., $d(TC)_n \cdot d(GA)_n$] with repeating sequences are transformed to a new tetra-stranded complex on lowering the pH[13].

Based on the tetramer intermediates described here, the sharp dependence of the



(a) (b)

Figure 3. Schematic drawing of a possible model for attractive non-covalent interactions: "vertical" hydrogen bond (a,-----) and electrostatic interactions (b). Dotted lines (·····) in Figures 1 and 3 represent both intermolecular hydrogen bond responsible for the stabilization of dimers and intramolecular one.

selectivity in the oxidation of 1 and 2 on the structures of R^1 or on the environment reported previously[2] appears to be explained by specific weak chemical interactions between the recognition sites in 1 and 2. This study is now in progress.

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References and Notes

1) Thiol 1 was prepared as described before (T. Endo, K. Oda, and T. Mukaiyama, Chem. Lett., 443 (1974)). Thiol 2 was prepared in good yield by addition of cysteamine to an acyl isocyanate in tetrahydrofuran at 0 °C under argon. All new compounds gave satisfactory elemental analyses and spectral data.

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

3) The wave numbers are at 0.010 M.

4) The R value is based on the yields of the disulfides (3 and 4) obtained by treatment of a 1:1 mixture of 1 and 2 with oxygen; see also T. Endo, A. Kuwahara, H. Tasai, and T. Ishigami, J. Chromatogr., 140, 263 (1977).

5) R was 6.0, 21, and 12 for $1/2a_2 = 2$, 1, and 0.5, respectively, and was 0.2, 0.53, and ca. 0 for $1/2b_2 = 2$, 1, and 0.5, respectively.

6) This type of 1:1 complex formation was not observed for 2a (j = 0 to 4) and 2b (k = 0 to 4), when mixed with 1. Detailed results will be published elsewhere.

7) It was found that (i) with 2a (j = 0 to 4) maximal selectivity (R = 21) occurs at j = 2, with 2b (k = 0 to 4) alternation in the selectivity being clearly observed and (ii) the selectivity is neither controlled by solubility differences between thiols (1 and 2) [T. Endo, T. Orii, T. Murata, and M. Hashimoto, unpublished results] and between disulfides (3, 4, and 5) nor by whether the reaction is heterogeneous or homogeneous; see reference 2.

8) N. Nakagawa, personal communication.

9) D. Swern, L. P. Witnauer, C. R. Eddy, and W. E. Parker, J. Amer. Chem. Soc., 77, 5537 (1955).

10) I. Suh and W. Saenger, Angew. Chem. Int. Ed. Engl., 17, 534 (1978).

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12) R. Benesch and R. E. Benesch, Science, 185, 905 (1974).

13) D. Johnson and A. R. Morgan, Proc. Natl. Acad. Sci. U.S.A., 75, 1637 (1978).

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