The Effect of Intermolecular Association on Kinetic Behavior. Rate Acceleration with Time in Oxidation of a Pair of Thiols

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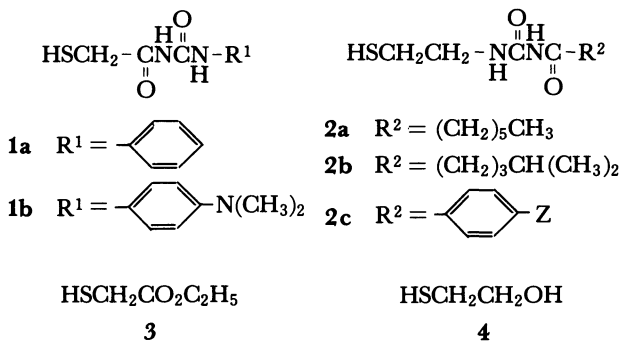
Synopsis. In base-catalyzed oxidation of a pair of associating thiols [$HSCH_2$-CONHCONH-Ph and $HSCH_2CH_2$-NHCONHCO-C_6H_{13}], rate enhancement with time occurred in protic media, whereas the rate was reduced with time in aprotic solvents. For a pair of nonassociating thiols [$HSCH_2CO_2C_2H_5$ and $HSCH_2CH_2OH$], the rate enhancement was neither observed in a protic solvent nor in an aprotic one.

Recently it has been shown that intermolecular association plays a significant role in chemical reactions.[1] In order to elucidate the effect of intermolecular association on kinetic behavior, we examined the rate of oxidation for pairs of associating (**1** and **2**, system A) and nonassociating thiols (**3** and **4**, system N) in various solvents, and report that the rate acceleration with time in the oxidation is only observed for the associating system.



$HSCH_2CO_2C_2H_5$ **3**

$HSCH_2CH_2OH$ **4**

The ln([RSH]/[RSH]$_0$) was plotted against time for oxidation of a pair of associating thiols **1a** and **2a,b** (systems A_{aa} and A_{ab}) in oxygen-saturated acetonitrile (MeCN) and H_2O-MeCN [mole fraction of water (x_w)=0.42], at 35.0 °C in the presence of triethylamine (Et_3N) as a catalyst (Fig. 1). In MeCN the oxidation follows pseudo first-order kinetics, as in the case of the oxidation in the presence of a large excess of a base.[2,3] On the other hand, sharp downward curvature is observed in aqueous MeCN,[4] suggesting that rate acceleration occurs with time. This has been confirmed by a plot of [RSH]/[RSH]$_0$ against time showing downward curvature (Fig. 2).

The [RSH]/[RSH]$_0$-time profiles were further investigated in various solvents for oxidation of system A_{aa} (Fig. 2). Also in H_2O-EtOH (x_w=0.20), the reaction has proved to be accelerated with time. This holds for the oxidation in nonaqueous protic solvents, EtOH and EtOH-MeCN (x_{EtOH}=0.42), but not in 1,4-dioxane even after 100 h. These observations suggest that rate acceleration with time in oxidation of system A occurs in protic media.[5]

Thiols **1** and **2** have been shown to associate strongly with each other in $CDCl_3$ via two NH···O intermolecular hydrogen bonds between the inner -NHCO-

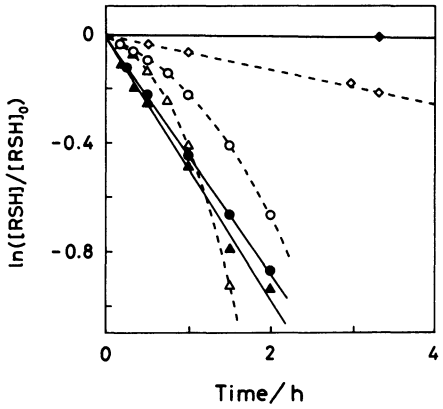


Fig. 1. First-order kinetic plots for oxidation of **1a** and **2a** (system A_{aa}), of **1a** and **2b** (system A_{ab}), and of **3** and **4** (system N) at 35.0 °C. [RSH]$_0$=2.00×10^{-2} M, [Et_3N]=2.0×10^{-3} M. ●, System A_{aa} in MeCN; ○, system A_{aa} in H_2O-MeCN (x_w=0.42); ▲, system A_{ab} in MeCN; △, system A_{ab} in H_2O-MeCN (x_w=0.42); ◆, system N in MeCN; ◇, system N in H_2O-MeCN (x_w=0.42). Linear relationship for system N in aqueous MeCN is shown only until ca. 20% conversion in this figure.

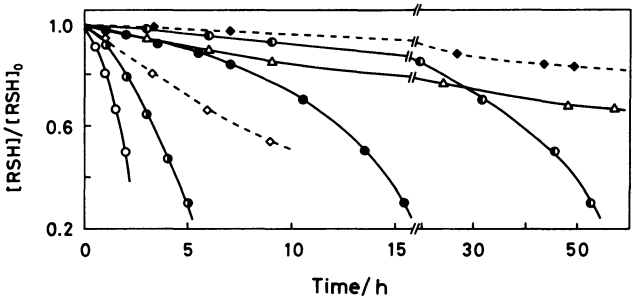


Fig. 2. Kinetic plots for oxidation of **1a** and **2a** (system A_{aa}) and **3** and **4** (system N) at 35.0 °C. [RSH]$_0$=2.00×10^{-2} M, [Et_3N]=2.0×10^{-3} M. ○, System A_{aa} in H_2O-MeCN (x_w=0.42); ◑, system A_{aa} in MeCN-EtOH (x_{EtOH}=0.42); ●, system A_{aa} in H_2O-EtOH (x_{EtOH}=0.80); ◐, system A_{aa} in EtOH; △, system A_{aa} in 1,4-dioxane; ◇, system N in H_2O-MeCN (x_w=0.42); ◆, system N in MeCN.

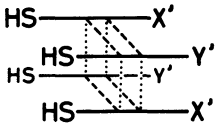


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Fig. 3. Association scheme in a typical tetramer **5**. -----, Hydrogen bonds in dimers; ·····, noncovalent weak interactions responsible for stabilization of tetramers. The symbols X′ and Y′ represent R^1 and R^2, respectively.

units in the -CONHCONH- group to form tetramers (reaction intermediates) such as **5** (Fig. 3).[6]

Control experiments were performed using a pair of nonassociating thiols (**3** and **4**, system N) (Figs. 1 and 2). In H_2O–MeCN (x_w=0.42), the reaction follows pseudo first-order kinetics until at least 50% conversion (Fig. 1). In MeCN, the rate appears to follow second-order kinetics. These findings indicate that no rate enhancement occurs for system N regardless of the solvents employed.

From the results presented here, it seems reasonable to conclude that intermolecular association is responsible for the rate acceleration with time in the oxidation. Our work suggests the possibility that intermolecular association affects another aspect of kinetic behavior in chemical reactions.

Experimental

Materials. Thiols **1a** and **2a,b** were prepared as described previously.[3] Other thiols and Et_3N were purified by distillation through a fractionating column. Organic solvents were dried by proper procedures,[7] and purified by distillation. Water was purified through Millipore Milli-Q water purification system followed by distillation. The iodine solution (0.001 M (1 M=1 mol dm^{-3})) containing potassium iodide (0.005 M) was titrated with 1.00×10^{-3} M aqueous sodium arsenite standard solution before use.

Kinetics. The two thiols (**1** and **2** or **3** and **4**, 1.00×10^{-4} mol each) were weighed into a two-necked flask, and dissolved in 10.00 ml of the reaction solvent. The solution was stirred under an oxygen atmosphere for at least 4 h in a well-stirred water bath thermostated to ±0.1 °C. Oxidation of thiols was negligible in the absence of Et_3N. At time zero, 2.0×10^{-5} mol of Et_3N was added to the solution with a microsyringe, and time measurement was begun. At appropriate time intervals, a 0.50 ml portion of the reaction mixture was pipetted out, and quenched in 5 ml of a 1:9 mixture of 3 M hydrochloric acid with MeCN. The amount of remaining thiols in the quenched solution was then determined by titration with the 0.001 M iodine solution. Each plot in Figs. 1 and 2 represents the average of at least three, generally five, or more runs.

References

1) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Hashimoto, and T. Ishigami, *Nature*, **268**, 74 (1977); T. Endo, Y. Takeda, H. Kamada, S. Kayama, and H. Tasai, *Chem. Lett.*, **1980**, 417; T. Endo, Y. Takeda, T. Orii, A. Kuwahara, M. Ohta, M. Sakai, R. Okada, and M. Hashimoto, *Bull. Chem. Soc. Jpn.*, **53**, 2687 (1980).

2) T. J. Wallace, A. Schriesheim, and W. Bartok, *J. Org. Chem.*, **26**, 1311 (1963).

3) T. Endo, M. Hashimoto, T. Orii, and M. M. Ito, *Bull. Chem. Soc. Jpn.*, **57**, 1562 (1984) and the references cited therein.

4) Similar rate profiles were observed for oxidation of **1b** and **2c** (Z=H, Me, and Et) in H_2O–MeCN (x_w=0.42) at 35.0 °C.[3]

5) The rate-determining step is generally regarded as that given by Eq. 1 or 2 [G. Capozzi and G. Modena, "Oxidation of Thiols," in "The Chemistry of the Thiol Group," ed by S. Patai, Wiley, London (1974), Part 2, Chap. 17]. One

$$RSH + Et_3N \overset{K}{\rightleftharpoons} RS^- + Et_3NH^+ \quad (1)$$

$$RS^- + O_2 \longrightarrow RS\cdot + O_2^{\cdot-} \qquad k_2 \quad (2)$$

possible explanation for the rate profiles in Figs. 1 and 2 is associated with the behavior of superoxide anion ($O_2^{\cdot-}$) in solvents.

First, in aprotic solvents such as MeCN, the steady state assumption can be applied to $O_2^{\cdot-}$, since the $O_2^{\cdot-}$ (the other oxidant) formed in situ is known to oxidize thiols readily

$$RSH + O_2^{\cdot-} \longrightarrow RS\cdot + O_2H^- \quad (3)$$

(Eq. 3) to disulfides [S. Oae, T. Takata, and Y. H. Kim, *Bull. Chem. Soc. Jpn.*, **54**, 2712 (1981)]. If the step shown by Eq. 2 is rate-determining, the rate for the oxidation may be expressed as

$$-d[RSH]/dt = 2k_2'[RSH] \quad (4)$$

where $k_2'=k_2[O_2]K[Et_3N]/[Et_3NH^+]$. Thus, the oxidation will follow pseudo first-order kinetics (Fig. 1).[2]

Second, in protic solvents, the $O_2^{\cdot-}$ reacts with solvent molecules to give the other oxidants (Ox·), such as $HO_2\cdot$ [J. Rabani and S. O. Nielsen, *J. Phys. Chem.*, **73**, 3736 (1969)], which may also oxidize thiols (Eq. 5) to disulfides. If the

$$RSH + Ox\cdot \longrightarrow RS\cdot + OxH \qquad k_5 \quad (5)$$

step shown by Eq. 2 is rate-determining, the rate for the oxidation may follow the expression

$$-d[RSH]/dt = k_2'[RSH] + k_5[RSH][Ox\cdot] \quad (6)$$

Rate acceleration will occur at least when $k_2'<k_5[RSH]_0$.

Similar results are obtained, even if the rate-determining step is given by Eq. 1.

6) T. Endo, Y. Takeda, T. Orii, Y. Kaneko, and M. Kondo, *Chem. Lett.*, **1979**, 1455.

7) J. A. Riddick and W. B. Bunger, "Organic Solvents," 3rd ed, Wiley, New York (1970).