Unusual Concentration-Rate Profiles for Oxidation of a Pair of Associating Thiols

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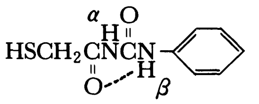
Synopsis. In base-catalyzed oxidation of a pair of associating thiols [$HSCH_2$-CONHCONH-Ph and $HSCH_2CH_2$-NHCONHCO-C_6H_{13}] with oxygen, there are concentration regions where initial rates decrease with increasing concentrations of the thiols. For a pair of nonassociating thiols [$HSCH_2CO_2C_2H_5$ and $HSCH_2CH_2OH$], initial rates increase linearly with concentrations of the thiols.

Intermolecular association plays a very important role in controlling chemical reactions.[1-3] Recently, it has been found that, in oxidation of a pair of associating thiols (**1** and **2**), rate enhancement with time occurs in protic media.[4] We report here the unusual behavior of initial rates toward concentrations of the associating thiols in their oxidation.



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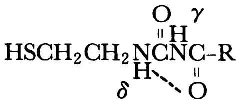

2a R = $(CH_2)_3CH_2CH_2CH_3$

b R = $(CH_2)_3CH(CH_3)_2$

c R =

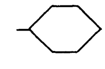

Figure 1 plots the overall initial rates (v_0) — average rates until 5% consumption of thiols — for oxidation of 1:1 mixtures of **1** and **2** against the initial concentrations of the thiols ($[RSH]_0$) in oxygen-saturated acetonitrile (MeCN) at the fixed concentration of triethylamine (Et_3N) as a catalyst (35.0 °C). The v_0 for a cyclohexyl (c-C_6H_{11}) group used as R increases linearly with increasing $[RSH]_0$. On the other hand, for n-hexyl and isohexyl groups as R there exist concentration regions where the v_0 remains almost unaltered with $[RSH]_0$ (0.02—0.04 M (1 M=1 mol dm^{-3})) and decreases with increasing $[RSH]_0$ (0.03—0.04 M), respectively.

The concentration–initial rate profiles were further investigated in ethanol (Fig. 2). The v_0 for R=n-C_6H_{13} has proved to decrease with increasing $[RSH]_0$ in the 0.02—0.03 M range. In contrast, for R=c-C_6H_{11} the v_0 seems not to show appreciable changes in the 0.02—0.04 M range.

It appears that a deviation from a straight line in the concentration–initial rate profiles (Figs. 1 and 2) becomes more remarkable in EtOH than in MeCN: for R=c-C_6H_{11} a "normal linear" profile in MeCN changes into a "plateau" one in EtOH, for R=n-C_6H_{13} a "plateau" profile in MeCN changing into a "decrease" one in EtOH.

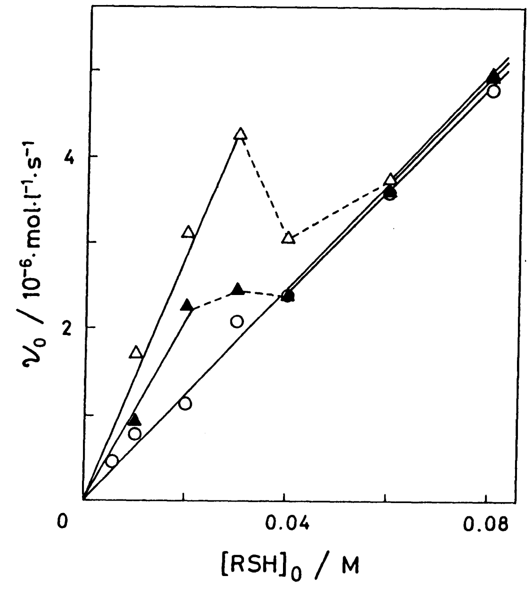

Fig. 1. Dependence of overall initial rates (v_0) for oxidation of 1:1 mixtures of **1** and **2** on initial concentrations of the thiols ($[RSH]_0$) in MeCN at 35.0 °C. $[RSH]_0=[\mathbf{1}]_0+[\mathbf{2}]_0$; $[Et_3N]=2.0\times10^{-3}$ M. ▲, **1** and **2a**; △, **1** and **2b**; ○, **1** and **2c**.

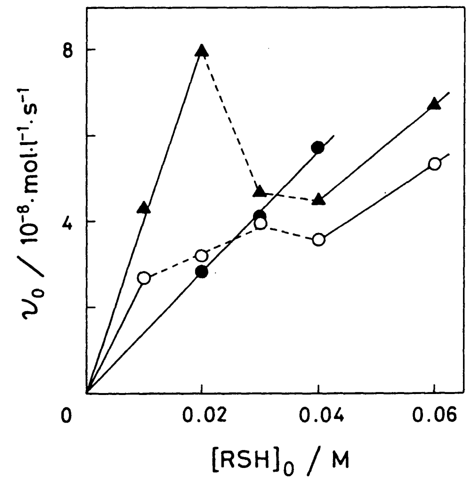

Fig. 2. Dependence of overall initial rates (v_0) for oxidation of 1:1 mixtures of **1** and **2** (or **3** and **4**) on initial concentrations of the thiols ($[RSH]_0$) in EtOH at 35.0°C. $[RSH]_0=[\mathbf{1}]_0+[\mathbf{2}]_0$ (or $[\mathbf{3}]_0+[\mathbf{4}]_0$); $[Et_3N]=2.0\times10^{-3}$ M. ▲, **1** and **2a**; ○, **1** and **2c**; ●, **3** and **4**.

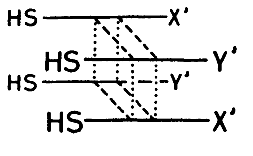

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Fig. 3. Association scheme in a typical tetramer **5**. ----, Hydrogen bonds in dimers; ······, noncovalent weak interactions responsible for stabilization of tetramers. The symbols X′ and Y′ represent Ph and R, respectively.

The $[RSH]_0$-v_0 plot for a pair of nonassociating thiols (**3** and **4**) shows a straight line in EtOH (Fig. 2). This control experiment demonstrates that "rate decrease" occurs for the associating thiols (**1** and **2**).

$HSCH_2CO_2C_2H_5$ **3** $HSCH_2CH_2OH$ **4**

Thiols **1** and **2** have been shown to associate strongly with each other as well as with themselves in $CDCl_3$ via two NH···O intermolecular hydrogen bonds between the inner -NHCO- units in the -CONHCONH- group to form tetramers (reaction intermediates) such as **5** (Fig. 3).[1b,1c,5)] In an attempt to elucidate the relationship between intermolecular association and the observed kinetic behavior, the following two experiments were carried out. First, NMR spectra of 1 : 1 mixtures of thiols **1** and **2b** were measured under nearly the same conditions as for the oxidation [i.e., at total concentrations of **1** and **2b** ([RSH])=0.020, 0.030, and 0.040 M in CD_3CN at 35 °C].[6)] The chemical shifts for the NH^β and NH^δ protons, which participate in intramolecular hydrogen bonds, remain constant [δ 10.28 (H^β) and 8.54 (H^δ)] with [RSH], whereas the NH^α and NH^γ protons, which participate in intermolecular hydrogen bonds, undergo slight downfield shifts with increasing [RSH] from δ 8.69 to 8.74 (H^α) and from 8.27 to 8.33 (H^γ). Second, plots of $\ln([RSH]/[RSH]_0)$ against time in MeCN at 35.0 °C (Fig. 4) have revealed that oxidation of **1** and **2b** at $[RSH]_0$=0.020[4)] and 0.030 M follows pseudo first-order kinetics, whereas at $[RSH]_0$=0.040 M an upward curvature is observed.[7)] Though these results appear to be related to the unusual kinetic behavior mentioned above, it is difficult to explain the behavior by them.

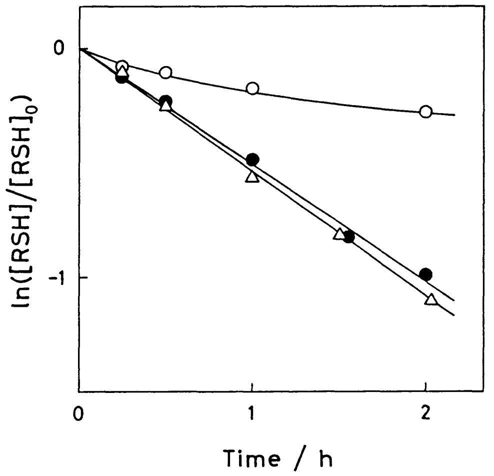

Fig. 4. First-order kinetic plots for oxidation of 1:1 mixtures of **1** and **2b** in MeCN at 35.0 °C. $[RSH]_0$= $[\mathbf{1}]_0+[\mathbf{2}]_0$; $[Et_3N]=2.0\times10^{-3}$ M. △, $[RSH]_0=2.0\times10^{-2}$ M; ●, $[RSH]_0=3.0\times10^{-2}$ M; ○, $[RSH]_0=4.0\times10^{-2}$ M.

From the experimental evidence presented here, it seems reasonable to conclude that intermolecular association is responsible for the unusual concentration-initial rate profiles for the oxidation.

Experimental

The melting points were uncorrected. ^1H NMR (270 MHz) spectra were measured on a JEOL GX-270 spectrometer using tetramethylsilane as an internal standard. The mass spectra were taken on a Hitachi RMU-6M mass spectrometer.

Materials. Organic solvents were dried by proper procedures,[8)] and purified by distillation. Water was purified through Millipore Milli-Q water purification system followed by distillation. The iodine solution (0.001 M) containing potassium iodide (0.005 M) was titrated with 1.00×10^{-3} M aqueous sodium arsenite standard solution before use.

Thiol **1** was prepared as described previously,[1b)] recrystallized from benzene-hexane, and had the following properties: Mp 127—128 °C; ^1H NMR (CD_3CN) δ=2.34 (1H, s), 3.34 (2H, s), 7.11 (1H, t, J=7 Hz), 7.33 (2H, dd, J=7 and 8 Hz), 7.51 (2H, d, J=8 Hz), 8.70 (1H, s, NH^α), 10.27 (1H, s, NH^β). Found: C, 51.32; H, 4.77; N, 13.21; S, 15.24%; M^+, 210. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25%; M, 210.

Thiols **2** were prepared as described before,[1b,9)] and had the following properties.

2b: Mp 102.5—103.0°C (hexane-ether); ^1H NMR (CD_3CN) δ=0.88 (6H, d, J=6 Hz), 1.15—1.24 (2H, m), 1.50—1.65 (4H, m), 2.27 (2H, t, J=7 Hz), 2.60—2.68 (2H, m), 3.35—3.42 (2H, m), 8.38 (1H, s, NH^γ), 8.53 (1H, s, NH^δ). Found: C, 51.98; H, 8.55; N, 12.09; S, 13.99%; M^+, 232. Calcd for $C_{10}H_{20}N_2O_2S$: C, 51.70; H, 8.68; N, 12.06; S, 13.78%; M, 232.

2c: Mp 147—148 °C (ether); ^1H NMR (CD_3CN) δ=1.23—2.30 (11H, m), 2.60—2.68 (2H, m), 3.34—3.42 (2H, m), 8.34 (1H, s), 8.58 (1H, s). Found: C, 52.22; H, 7.94; N, 12.14; S, 13.80%; M^+, 230. Calcd for $C_{10}H_{18}N_2O_2S$: C, 52.15; H, 7.88; N, 12.16; S, 13.92%; M, 230.

Other thiols and Et_3N were purified by distillation through a fractionating column.

Kinetics. Equimolar amounts of the two thiols [**1** and **2** (or **3** and **4**)] 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 the solvent. 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 generally six, or more runs.

References

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6) The NH protons were assigned on the basis of (i) comparison between chemical shifts for the NH protons of the 1 : 1 mixture and those of **1** and **2b** themselves (experimental section) and (ii) comparison of the concentration dependence of chemical shifts for the NH protons of the 1 : 1 mixtures with one another.

7) The rate of this type of Et_3N-catalyzed oxidation is shown to follow the equation $v=k_{1.7}[RSH][Et_3N]^{0.7}$ in aqueous MeCN (mole fraction of water=0.42) at 35.0 °C: T. Endo, M. Hashimoto, T. Orii, and M. M. Ito, *Bull. Chem. Soc. Jpn.*, **57**, 1562 (1984).

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