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N-Nitrosodimethylamine Formation catalyzed by Alkylthioureas. A Kinetic Study

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The catalytic efficiencies of several alkylthioureas in *N*-nitrosodimethylamine formation were compared in aqueous acetate buffer of pH 4.0. The rate law, $v_0=k_T$[dimethylamine]$_0$[nitrite]$_0$[alkylthiourea]$_0$, is suggested for the initial rate of the catalytic reaction, where the concentration terms represent initial stoichiometric concentrations of the indicated species. No clear-cut explanation could be given for the variation, within a factor of ten, of the k_T value with the structure of the thioureas. However, the overall catalytic efficiency of the thioureas, or the net rate of nitrosamine formation, is shown to depend not only on the k_T value but also on the rate of decomposition of the thioureas. Thus, the marked difference in the efficiency of thiourea and tetramethylthiourea, which have similar k_T values, is ascribed to the faster decomposition of thiourea as compared with its tetramethyl derivative.

Keywords——*N*-nitrosodimethylamine; kinetic study; thiourea; alkylthioureas; differential pulse polarography

Thioureas have been shown[1] to catalyze the nitrosation of dimethylamine more efficiently than thiocyanate ion, one of the most effective catalysts.[2] The reaction of nitrous acid with thiourea in acid solution has been reported to proceed through initial rapid formation of the unstable *S*-nitrososulfonium ion, $(NH_2)_2C=S^+-NO$,[3,4] which has recently been suggested as the active nitrosating agent in the nitrosation of morpholine.[5] The greater catalytic efficiency of thiourea as compared with other anionic nucleophiles such as SCN^- and Br^- has been ascribed[5] to the large equilibrium constant[4] for the formation of the sulfonium ion. Similarly, the rate accelerating effects of 1,3-dimethylthiourea, thiourea, and tetramethylthiourea observed in the nitrosation of dimethylamine[1] (the rates increased in that order) might at first glance be expected to be correlated with the equilibrium constants for sulfonium ion formation. However, another factor, the decomposition of thioureas by nitrous acid,[3,4] must also be taken into account in assessing the overall catalytic efficiency of thioureas in nitrosation reactions: not only the observed rate constant for the catalyzed reaction, which includes the equilibrium constant for sulfonium ion formation, but also the rate constant for the decomposition reaction will affect the net rate of nitrosamine formation. As an extension of our previous work,[1] we have compared the formation curves of *N*-nitrosodimethylamine in the presence of several alkylthioureas, and attempted to explain the results in terms of two parallel reactions of the nitrososulfonium ions, that is, decomposition[3,4] and reaction with dimethylamine.

An acetate buffer of pH 4.0 was selected as the reaction medium, because the rate of the uncatalyzed reaction, which is maximal between pH 3 and 4,[6] can be conveniently measured in the medium, and also because our previous studies were carried out at this pH.[1,7]

The following abbreviations are employed for the alkylthioureas used in the present study: TU, thiourea; MTU, 1-methylthiourea; 1,3-DMTU, 1,3-dimethylthiourea; 1,3-DETU, 1,3-diethylthiourea; TMTU, tetramethylthiourea; EthTU, ethylenethiourea.

Experimental

Materials——Thioureas were obtained commercially and recrystallized from ethanol or hexane. Reagent grade sodium nitrite was dried over phosphorus pentoxide under reduced pressure. Aqueous dimethylamine was prepared by dissolving the amine fractionated from commercial aqueous solution in purified water (see below), and standardized with hydrochloric acid. Sodium perchlorate was recrystallized from 95% ethanol. Deionized and distilled water was used throughout. Other chemicals were of reagent grade and were used without further purification.

Kinetic Measurements——All reactions were carried out at 30±0.01°C in a volumetric flask.

(a) Formation of *N*-Nitrosodimethylamine: The reaction was initiated by adding a freshly prepared solution of sodium nitrite (adjusted to pH 4.0 with perchloric acid) to an acetate buffer (2.0 M) of pH 4.0 containing dimethylamine, one of the thioureas, and a calculated amount of sodium perchlorate to keep the ionic strength of the reaction mixture unity. At appropriate intervals 1.0 ml of the reaction solution was pippetted into 1 ml of 1 M sulfamic acid in a 10 ml volumetric flask and diluted to volume with 0.1 M sulfuric acid. The mixture was subjected to differential pulse polarographic measurements with a Fuso polarograph, model-312. The amount of the nitrosamine was determined by comparing the value of the peak current (peak potential, −0.85 V *vs.* S.C.E.) with a calibration curve prepared with authentic samples. Since the reaction could not be analyzed in terms of simple integrated rate equations, the initial rate method was employed for its analysis. The initial rate was obtained from the concentration-time curve at time zero.

(b) Decomposition of Alkylthioureas: The reaction was initiated and quenched as described above, except that dimethylamine was excluded from the reaction mixture and that water was used for dilution in place of 0.1 M sulfuric acid. The disappearance of thioureas was monitored spectrophotometrically at a suitable wavelength: TU, 237; MTU, 235; 1,3-DMTU, 233; 1,3-DETU, 235; TMTU, 249; EthTU, 233 nm.

Results and Discussion

Under the present experimental conditions, the initial rate of formation of *N*-nitrosodimethylamine (NDMA) in the absence of thioureas can be expressed by one kinetic term, first-order for dimethylamine (DMA) and second-order for nitrite.⁸⁾ In the presence of TU, the catalyzed reaction is first-order with respect to each reactant, DMA, nitrite, and TU (Fig. 1), as observed in the nitrosation reactions catalyzed by anionic nucleophiles.⁹⁾ Thus, the overall initial rate for NDMA formation will be given by equation (1),¹⁰⁾

$$(\mathrm{d[NDMA]}/\mathrm{d}t)_{t=0} = k_0[\mathrm{DMA}]_0[\mathrm{nitrite}]_0^2 + k_\mathrm{T}[\mathrm{DMA}]_0[\mathrm{nitrite}]_0[\mathrm{TU}]_0 \tag{1}$$

where $[\mathrm{DMA}]_0$, $[\mathrm{nitrite}]_0$, and $[\mathrm{TU}]_0$ represent the initial stoichiometric concentrations of the respective species. A similar rate law has been demonstrated in the *p*-nitrosophenol-catalyzed nitrosation of diethylamine in aqueous buffer solutions of pH 2—6,¹¹⁾ and the formation of *N*-nitrosomorpholine catalyzed by TU in aqueous sulfuric acid has been reported to be first-order with respect to the total concentration of each substrate.⁵⁾ Since the reactions of nitrous acid with the other thioureas used in the present study also give the corresponding *S*-nitrososulfonium ions,⁴⁾ it seems reasonable that NDMA formation in the presence of these thioureas obeys equation (1). Thus, on the basis of the work of Stedman³,⁴⁾ and Williams⁵,¹²,¹³⁾ and their co-workers, the fate of the thioureas can be represented as shown in Chart 1.

The values of rate constants, k_T, for the catalyzed reaction estimated from equation (1) are as follows: EthTU, 1.5; 1,3-DMTU, 3.9; TU, 12; MTU, 8.8; TMTU, 15; 1,3-DETU, 5.9 $\mathrm{M}^{-2}\,\mathrm{min}^{-1}$—here the thioureas are arranged in increasing order of the equilibrium constant, K_X, for sulfonium ion formation.¹⁴⁾ Under the present experimental conditions (pH 4.0, *cf.* Fig. 2), k_T is given by equation (2),¹⁵⁾

$$k_\mathrm{T} = k_\mathrm{N}K_\mathrm{X}K_\mathrm{DMA}[\mathrm{H}^+]/(K_\mathrm{nit}+[\mathrm{H}^+]) \tag{2}$$

where k_N is the rate constant defined in Chart 1 and K_DMA and K_nit are the acid dissociation constants of DMA and nitrous acid, respectively. The k_N value for TU evaluated from equation (2) is $7\times10^8\ \mathrm{M}^{-1}\,\mathrm{min}^{-1}$, which is comparable to that calculated for the reaction of morpholine with the sulphonium ion ($7\times10^6\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$ at 31°C, that is, $4._2\times10^8\ \mathrm{M}^{-1}\,\mathrm{min}^{-1}$);⁵⁾ for the other thioureas, the k_N values are 4×10^8 (EthTU), $3._5\times10^8$ (1,3-DMTU), 3×10^8 (MTU), $5._5\times10^8$ (TMTU), and $2\times10^8\ \mathrm{M}^{-1}\,\mathrm{min}^{-1}$ (1,3-DETU). At the present stage, however, no clear-cut explanation can be offered for the observed variation of the k_T values (see above) with different thioureas, except that the value for EthTU may reflect the fact that it has the smallest K_X value.¹⁴⁾

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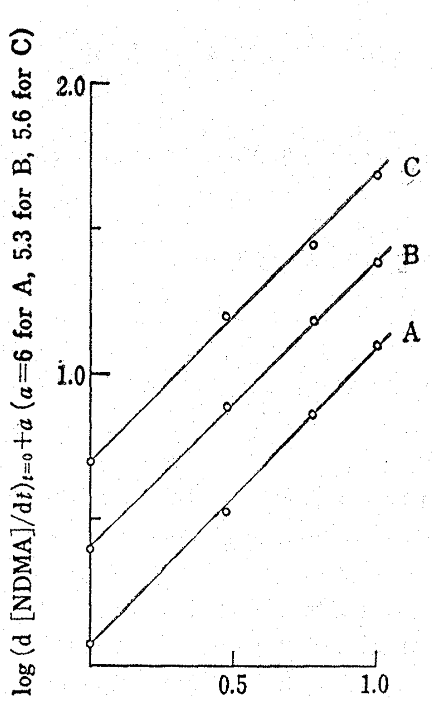

A : $\log[\text{DMA}]_0+2$;
B : $\log[\text{TU}]_0+3$;
C : $\log[\text{nitrite}]_0+2$.

Fig. 1. Dependence of the Initial Rate of NDMA Formation on the Concentration of (A) DMA,[a] (B) TU,[b] and (C) Nitrite[c]

pH 4.0 (2.0 M acetate), 30°C, $\mu=1.0$.
a) $[\text{nitrite}]_0=0.010$ M, $[\text{TU}]_0=0.0010$ M, slope=1.03.
b) $[\text{DMA}]_0=0.10$ M, $[\text{nitrite}]_0=0.010$ M, slope=0.98.
c) $[\text{DMA}]_0=0.10$ M, $[\text{TU}]_0=0.0010$ M, slope=1.01.

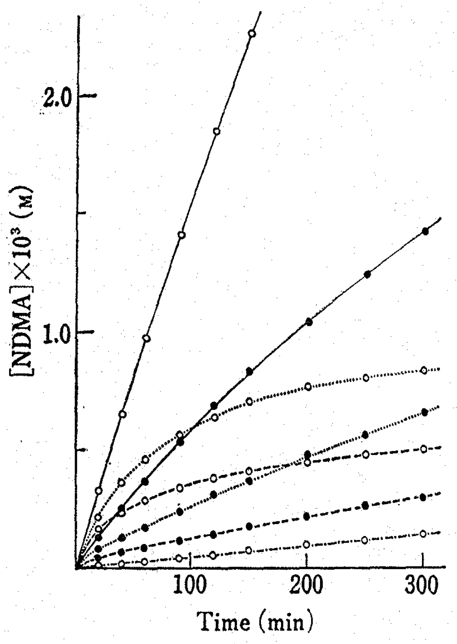

Fig. 2. Concentration-time Curve for NDMA Formation at pH 4.0 (2.0 M Acetate) and 30°C, $\mu=1.0$

○—○, with TMTU; ●—●, with 1,3-DETU; ○---○, with TU; ●---●, with 1,3-DMTU; ○----○, with MTU; ●----●, with EthTU; ○-·-·-○, without an alkylthiourea: $[\text{DMA}]_0=0.10$ M, $[\text{nitrite}]_0=0.010$ M, $[\text{alkylthiourea}]_0=0.0010$ M.

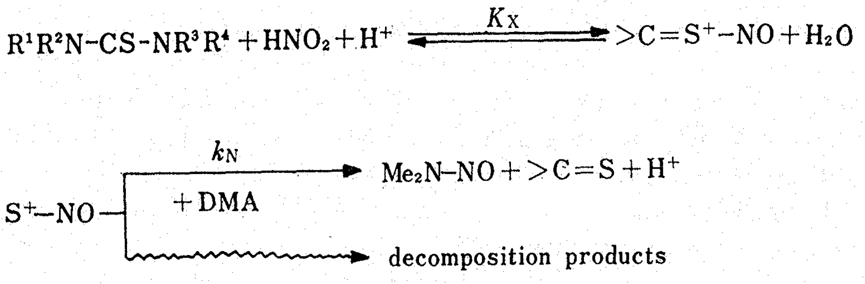

Chart 1

Although the k_T values for TU and TMTU are similar in magnitude, the overall catalytic efficiency of TMTU is considerably larger than that of TU, as illustrated in Fig. 2 where the following order of the efficiency holds for reaction times of up to 6 h: TMTU>1,3-DETU>TU>1,3-DMTU>MTU>EthTU. The observed difference between the efficiency of TU and TMTU will be ascribed to the difference in the stability of these thioureas (*cf.* Chart 1). Under the conditions where the k_T values were obtained (see Fig. 2), the decompositions of TU and TMTU obeyed pseudo-first-order kinetics with respect to the thioureas.[16] For TU, the reaction was also confirmed to be first-order with respect to nitrite.[17] The second-order rate constant, k_D, defined by equation (3) was calculated from the observed pseudo-first-order rate constant (equal to $k_D[\text{nitrite}]_0$), and values of 3.08×10^{-2} and 1.71 $\text{M}^{-1}\,\text{min}^{-1}$ were obtained for TMTU and TU, respectively.

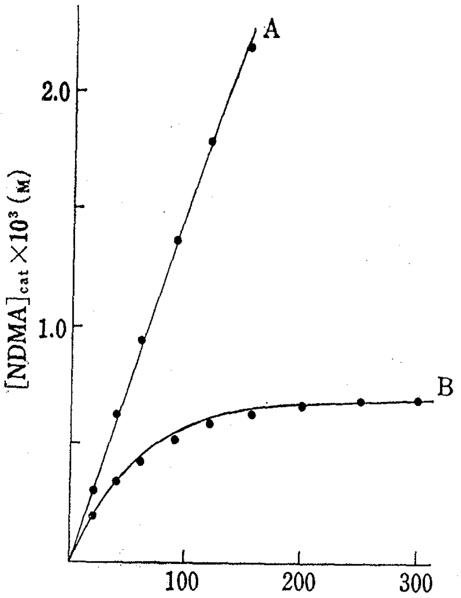

Fig. 3. [NDMA]$_{cat}$ (definition, see text) *vs.* Time Plot for (A) TMTU-catalyzed and (B) TU-catalyzed Reactions

Solid lines represent theoretical curves calculated by the use of equation (4) and solid circles represent experimental points. Conditions: pH 4.0 (2.0 M acetate), 30°C, μ=1.0, [DMA]$_0$=0.10 M, [nitrite]$_0$=0.010 M, [alkylthiourea]$_0$=0.0010 M.

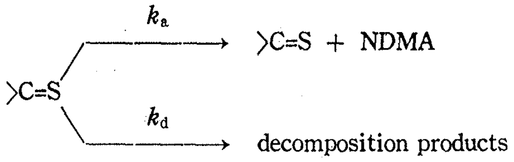

Chart 2

$$-\mathrm{d[TU]/d}t = k_\mathrm{D}[\mathrm{nitrite}]_0[\mathrm{TU}] \qquad (3)$$

Under the conditions given in Fig. 2, [alkylthiourea]$\gg$[*S*-nitrososulfonium ion] is valid,[15] and the reactions of the thioureas, TU and TMTU, can be simplified as shown in Chart 2, where $k_a=k_T$[DMA][nitrite] and $k_d=k_D$[nitrite] (*cf.* equations (1) and (3)). Since the conditions [DMA]$_0$=100[alkylthiourea]$_0$ and [nitrite]$_0$=10[alkylthiourea]$_0$ are employed in the present study, $k_a=k_T$[DMA]$_0$[nitrite]$_0$ and $k_d=k_D$[nitrite]$_0$ are expected to hold roughly until the amount of NDMA formed by the catalyzed and the uncatalyzed reactions (*cf.* equation (1)) becomes significant as compared to [nitrite]$_0$. Thus, in the early stage of the reaction, the concentration of NDMA formed *via* the catalyzed reaction, [NDMA]$_{cat}$, will be given by equation (4).[18]

$$[\mathrm{NDMA}]_\mathrm{cat} = (k_a/k_d)[\mathrm{alkylthiourea}]_0\{1-\exp(-k_d t)\} \qquad (4)$$

Experimentally, [NDMA]$_{cat}$ can be estimated by subtracting the NDMA concentration formed by the uncatalyzed reaction from the overall concentration of NDMA produced. The former can be estimated approximately from the reaction carried out in the absence of the thioureas as long as equation (4) is applicable. As shown in Fig. 3, the experimental values of [NDMA]$_{cat}$ for the TU- and the TMTU-catalyzed reactions agree well with the theoretical curves calculated by the use of equation (4) and the rate constants, k_T and k_D (see above).

A similar explanation should be applicable to the overall catalytic efficiency of the other thioureas examined, but the decomposition of these thioureas did not obey simple pseudo-first-order kinetics under the present experimental conditions.[16] In addition, preliminary results on NDMA formation at pH 3.0 (2.0 M phosphate) suggested that the decomposition products of 1,3-dialkylthioureas (1,3-DMTU, 1,3-DETU, and EthTU) also have some catalytic activities, though smaller than those of the parent thioureas,[19] making the overall kinetics more complex. Since the nature of the decomposition products seems not to have been elucidated in detail,[4] we are now investigating them with a view to explaining the overall kinetic efficiency of these thioureas.

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References and Notes

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8) The logarithmic plots of the initial rate against the concentration of DMA ($[\text{nitrite}]_0 = 0.010\,\text{M}$, $[\text{DMA}]_0 = 0.010$—$0.10\,\text{M}$) and against that of nitrite ($[\text{DMA}]_0 = 0.10\,\text{M}$, $[\text{nitrite}]_0 = 0.010$—$0.10\,\text{M}$) gave straight lines with slopes of 1.10 and 1.98, respectively. In our previous paper (ref. 7) the latter slope was obtained as 1.82 and the reaction was analyzed as the sum of two concurrent reactions, first- and second-order with respect to nitrite. This discrepancy probably arose from the difference in the concentration of buffer components.

9) For a review, see J.H. Ridd, *Quart. Rev.*, **15**, 418 (1961).

10) Acetate buffer catalysis has been demonstrated for the k_0-term of equation (1) (ref. 7), and there may be a contribution of buffer catalysis to the k_T-term. In the present study, however, the experiments were carried out at a constant buffer concentration and inclusion of the buffer catalysis in the rate constants, k_0 and k_T, should not lead to an erroneous explanation of the results.

11) E.A. Walker, B. Pignatelli, and M. Castegnaro, *J. Agric. Food Chem.*, **27**, 393 (1979).

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14) In ref. 4 the following values are reported for the equilibrium constant, $K_X = [S\text{-nitrososulfonium ion}]/[\text{H}^+][\text{HNO}_2][\text{alkylthiourea}]$: EthTU, 1190; 1,3-DMTU, 3300; TU, 5000; MTU, 9340; TMTU, 8200; 1,3-DETU, $10300\,\text{M}^{-2}$ at 25°C.

15) Acid dissociation constants of the alkylthioureas (M.J. Janssen, *Rec. Trav. Chim.*, **81**, 650 (1962)) and of dimethylamine indicate that [protonated alkylthiourea] and [free DMA] are negligible compared to the concentrations of the corresponding conjugate base and acid, respectively. From the K_X values (note 14), the ratio [*S*-nitrososulfonium ion]/[alkylthiourea] is estimated to be less than 10^{-2}. These conditions make the expression for k_T rather simple.

16) The plots of log $(A - A_\infty)$ against time for the reactions of TU and TMTU were linear up to 80% completion, where A and A_∞ represent the absorbances at time t and infinite time, respectively. With the other thioureas such plots did not give straight lines.

17) A logarithmic plot of the initial rate of the decomposition of TU against the concentration of nitrite gave a straight line with a slope of 0.99 ($[\text{TU}]_0 = 0.0010\,\text{M}$, $[\text{nitrite}]_0 = 0.0010$—$0.010\,\text{M}$).

18) In Chart 2, $d[\text{NDMA}]/dt = k_a[{>}\text{C=S}]$ and $d[{>}\text{C=S}]/dt = -k_d[{>}\text{C=S}]$. From these equations, $d[\text{NDMA}]/d[{>}\text{C=S}] = -k_a/k_d$. Provided that k_a and k_d can be regarded as constant, the latter equation is easily integrated to give $[\text{NDMA}] = (k_a/k_d)\{[{>}\text{C=S}]_0 - [{>}\text{C=S}]\}$, which gives equation (4) because $[{>}\text{C=S}] = [{>}\text{C=S}]_0\exp(-k_dt)$ is valid at the same time.

19) For example, the concentration-time curve for NDMA formation catalyzed by 1,3-DMTU at pH 3 showed a break. An initial rapid formation of NDMA, probably following equation (4), was followed by a slower, linear increase of NDMA concentration. The slope of the latter line was more than twice that for the uncatalyzed reaction: as can be seen in Fig. 2, the concentration-time curve for the uncatalyzed reaction was also almost linear at pH 3 within the time-scale of the experiment (60 min). The decomposition of the thioureas at pH 3 was faster than that at pH 4.

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