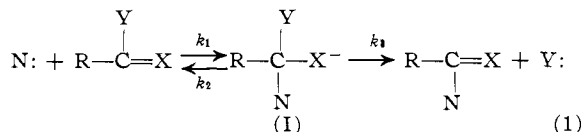


The Kinetic Demonstration of a Metastable Intermediate in a Nucleophilic Displacement at a Thiol-Ester Bond

Sir:

Nucleophilic displacement reactions on compounds of general structure $R-C(Y)=X$ have commonly been assumed to proceed *via* the intermediate formation of metastable tetrahedral intermediates (I). However,



few examples are available in the literature which provide evidence of the intermediate existence of compounds of type I.^{1,2} We report herein the kinetic results of a study of the reaction of hydroxylamine with *n*-butyl thiolacetate (eq. 2) which establishes the first instance of a tetrahedral intermediate in a

$NH_2OH + C_4H_9SCOCH_3 \rightarrow C_4H_9SH + CH_3CONHOH$ (2)
displacement reaction on a thiol-ester bond and the only case for a tetrahedral intermediate in a nucleophilic displacement reaction on an ester bond when the nucleophile is other than a water lyate species. The hydroxylaminolysis reactions were carried out under a N_2 atmosphere at 30°, $\mu = 1.0 M$ (with KCl), employing a large excess of hydroxylamine over ester (NH_2OH

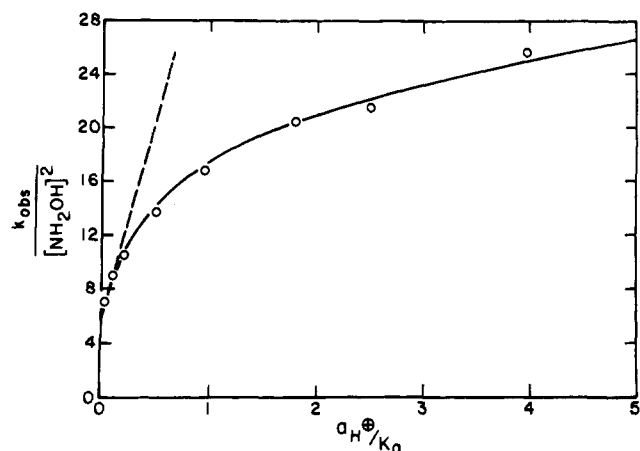


Fig. 1.—Plot of the pseudo-first-order rate constants for hydroxylaminolysis (k_{obs}) divided by the square of the concentration of free hydroxylamine *vs.* the hydrogen ion activity divided by the acid dissociation constant of hydroxylamine. The value of $k_{obs}/(NH_2OH)^2$ is seen to approach linearity in a_H/K_a at high acidity.

+ NH_3^+OH at 0.025 to 0.8 *M* and ester at $\sim 10^{-4}$ *M*). In all reactions buffer capacity was supplied entirely by the reacting base and its conjugate acid (*i.e.*, H_2NOH/H_3^+NOH). The reactions were found to be pseudo-first order for three to five half-lives at all acidities investigated (pH 5.4 to 7.5). The pseudo-first-order rate constants (k_{obs}) for the disappearance of thiol-ester (as determined spectrophotometrically at 234 $m\mu$) at any constant pH were found to be linearly dependent upon the second power of the hydroxylamine concentration. At all acidities investigated no measurable rate of ester disappearance was observed in the absence of hydroxylamine. The hydroxylaminolysis reaction, therefore, requires one mole of free hydroxylamine base as a reactant plus a second mole of either the free base or its conjugate acid as catalyst. At any constant pH where $N_T = N + H_3^+OH + NH_2OH$.

(1) M. L. Bender, *Chem. Rev.*, **59**, 53 (1959).

(2) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 3505 (1962);

$$-\frac{d(\text{ester})}{dt} = k_3(\text{ester})(NH_2OH)(N_T) \quad (3)$$

$$k_3 = \frac{k_{obs}}{(NH_2OH)(N_T)}$$

A plot of $k_{obs}/(H_2NOH)^2$ *vs.* a_H/K_a' (where a_H is the hydrogen ion activity as measured with the glass electrode and K_a' the acid dissociation constant of hydroxylamine) is provided in Fig. 1. In Fig. 1, when $a_H/K_a' = 0$ then $(NH_3^+OH) = 0$ and the limiting rate constant for the general base-catalyzed hydroxylaminolysis reaction (k_{gb}) is provided by the intercept on the $k_{obs}/(NH_2OH)^2$ axis.

$$-\frac{d(\text{ester})}{dt} = k_{gb}(NH_2OH)^2(\text{ester}) \quad (4)$$

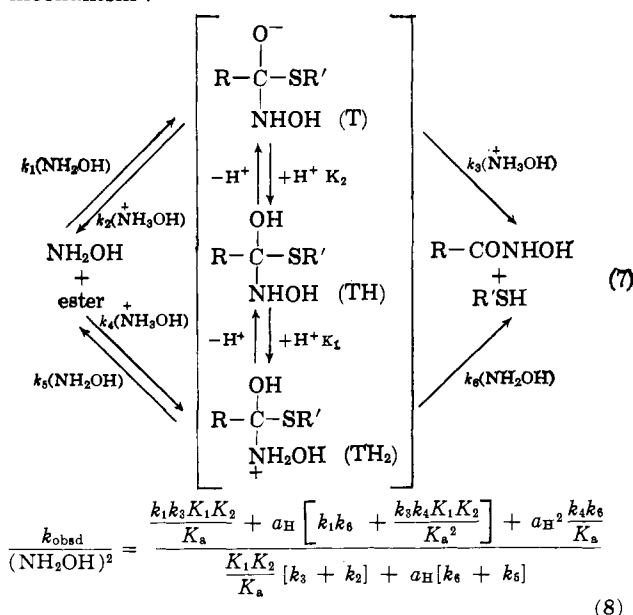
As the value of a_H/K_a' increases from 0 the value of $k_{obs}/(NH_2OH)^2$ does not increase in a linear fashion as anticipated for a reaction undergoing simultaneous general base and general acid catalysis (*i.e.*, eq. 5; see dashed line in Fig. 1).

$$-\frac{d(\text{ester})}{dt} = (k_{gb} + \frac{k_{ga}}{K_a'} a_H)(NH_2OH)^2(\text{ester}) \quad (5)$$

Instead, as the values of a_H/K_a' increase from 0, the value of $k_{obs}/(NH_2OH)^2$ first increases rapidly and then slowly, becoming a linear function of the acidity only at the higher acid concentrations. Clearly, as the acidity increases the rate changes from one strongly dependent on acidity to one which is less dependent. A change of this nature is convincing evidence for the existence of intermediates which must be in acid-base equilibria and whose formation and partitioning is singularly general base-catalyzed at very low acidity and whose formation and partitioning is singularly general acid-catalyzed at high acidity. The reaction differs from previous examples of reactions exhibiting parallel general acid and general base catalysis in that at intermediate pH values equilibrium between the two paths of catalysis appears to be important. The points on the plot of Fig. 1 are experimental and the curve theoretical, being derived from eq. 6.

$$\frac{k_{obs}}{(NH_2OH)^2} = \frac{2.77 \times 10^{-6} + 22.44 a_H + 1.35 \times 10^6 a_H^2}{4.8 \times 10^{-7} + a_H} \quad (6)$$

Assuming steady state in the intermediates T, TH, and TH_2 the following expression can be derived for mechanism 7



The general form of eq. 8 is more meaningfully expressed as shown in eq. 9 since it is quite impossible to separate the various constants and it is seen that eq. 9

possesses the same mathematical form as eq. 6. From eq. 8 it is seen that the rate expressions under the limiting

$$\frac{k_{\text{obsd}}}{(\text{NH}_2\text{OH})^2} = \frac{k_1 + a_{\text{H}}k_{11} + a_{\text{H}}^2k_{111}}{k_{1v} + k_{va_{\text{H}}}} \quad (9)$$

conditions of $a_{\text{H}} = 0$ and $a_{\text{H}} = \infty$ are provided by (9a) and (9b), respectively, which are the classical expressions for general base and general acid catalysis.

$$\frac{k_{\text{obsd}}}{(\text{NH}_2\text{OH})^2} = \frac{k_1k_3}{k_3 + k_2} \quad (9a)$$

$$\frac{k_{\text{obsd}}}{(\text{NH}_2\text{OH})^2} = \frac{a_{\text{H}}k_4k_6}{K_a(k_6 + k_5)} \text{ or } \frac{k_{\text{obsd}}}{(\text{NH}_2\text{OH})(\text{NH}_3^+\text{OH})} = \frac{k_4k_6}{k_6 + k_5} \quad (9b)$$

The mechanism of eq. 7 is of course not the only possible one that may be written which will fit the determined kinetics. It is, however, the only scheme in which microscopic reversibility is followed and in which both the general acid- and general base-catalyzed step are symmetrical, and it is, therefore, probably the most reasonable and simple of the various possibilities. The intimate details will be discussed in a forthcoming paper where other examples of the types of kinetic phenomena reported in this communication will be provided. However, regardless of the mechanistic scheme which one might wish to propose, the important point we wish to establish herein is that any scheme proposed must accommodate metastable intermediates which are in acid-base equilibria.

Acknowledgment.—We wish to thank Professors Westheimer, Bunnett, Jencks, and Bunton for reading preprints of this article and providing us with their comments.

(3) Career Investigator of the National Institutes of Health.

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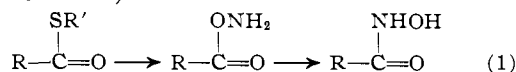
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O- vs. N-Attack of Hydroxylamine on *n*-Butyl Thiolacetate and the Establishment that N-Attack Passes through a Metastable Intermediate

Sir:

In the preceding communication the reaction product has been assumed to be acethydroxamic acid (CH_3CONHOH). However, it is generally recognized¹⁻³ that hydroxylamine may act as either an oxygen or a nitrogen nucleophile to yield as the initial product, from acyl derivatives, either hydroxamic acids or O-acyl hydroxylamines. As a means of ascertaining the validity of our assumptions which are implicit in eq. 7 of the previous communication, the rate of acethydroxamic acid formation from ester was determined in reactions covering the pH range of 5.4 to 7.0.⁴ In all instances the ester was found to be completely converted to hydroxamic acid but the rate of hydroxamic acid formation was found to be less than the rate of ester disappearance. This result suggests the intermediate formation of O-acetylhydroxylamine and its conversion, by reaction with additional hydroxylamine, to acethydroxamic acid (a well-known and rapid reaction²).



(1) A. W. Scott and B. L. Wood, *J. Org. Chem.*, **7**, 508 (1942).

(2) W. P. Jencks, *J. Am. Chem. Soc.*, **80**, 4581, 4485 (1958).

(3) T. C. Bruice and J. J. Bruno, *ibid.*, **83**, 3494 (1961).

(4) The formation of acethydroxamic acid was followed quantitatively by a modification of the procedures of F. Lipmann and L. C. Tuttle [*J. Biol. Chem.*, **159**, 21 (1945)].

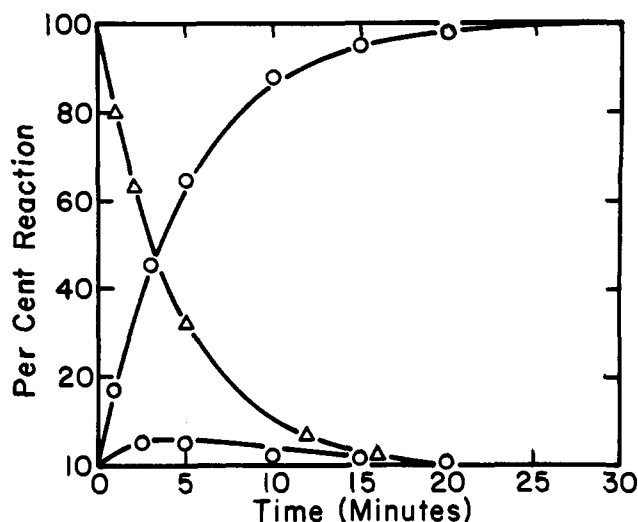
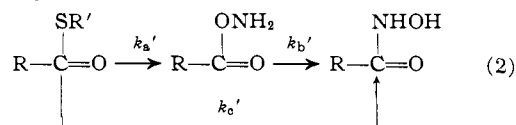


Fig. 1.—Disappearance of ester and appearance and disappearance of O-acetylhydroxylamine and appearance of hydroxamic acid with time (pH 5.42, total hydroxylamine concentration 0.5 M).

Under the pseudo-first-order conditions employed (see previous communication) scheme 1 amounts kinetically to a simple $A \rightarrow B \rightarrow C$ problem.⁵ Since the concentration of A and C are known with time the concentration of B is also known. At all the pH values employed B was found to amount to no more than 15% of A_0 at the time of its maximum concentration (as an example see Fig. 1). However, by employing the simple integrated equations for the $A \rightarrow B \rightarrow C$ problem⁵ and solving for the maximum, B should approach 40–70% of A_0 over the pH range studied based on the calculated constants for the disappearance of A and appearance of C . Therefore, all of C does not arise through B , a fact also shown by the lack of a lag period in the production of C . We must, therefore, postulate that hydroxylamine reacts with the thiol ester to produce acethydroxamic acid directly as well as O-acetylhydroxylamine which is then converted to acethydroxamic acid *via* reaction with the excess hydroxylamine.



For purposes of employing eq. 2 the rate constants k_b' were determined by studying the reaction of hydroxylamine with O-acetylhydroxylamine as a function of pH and hydroxylamine concentration. The rate constant for the disappearance of ester equals $(k_a' + k_c')$. Integration of the rate expression for appearance and disappearance of A , B , and C in terms of $(k_a' + k_c')$ is readily accomplished

$$\begin{aligned} A &= A_0 e^{-(k_a' + k_c')t} \\ B &= \frac{A_0 k_a'}{k_b' - (k_a' + k_c')} [e^{-(k_a' + k_c')t} - e^{-k_b't}] \\ C &= A_0 - A - B \end{aligned} \quad (3)$$

providing separate solutions to k_a' , k_b' , and k_c' at all acidities. The determined concentrations of A , B , and C are within experimental error quantitatively provided by the determined values of the rate constants. The curves of Fig. 1 have been constructed from these determined constants. The fit of the experimental points to the calculated curves at other pH values are as good or better than indicated in Fig. 1.

(5) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd Ed., John Wiley and Sons, New York, N. Y., 1962, p. 166.