

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.

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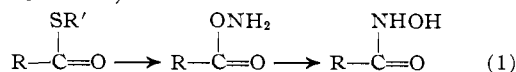
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RECEIVED NOVEMBER 30, 1963

### 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 ( $\text{CH}_3\text{CONHOH}$ ). However, it is generally recognized<sup>1-3</sup> 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.<sup>4</sup> 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 reaction<sup>2</sup>).



(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)].

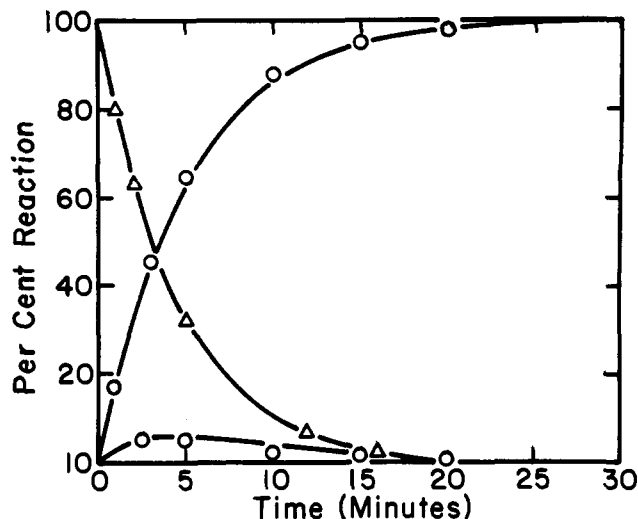
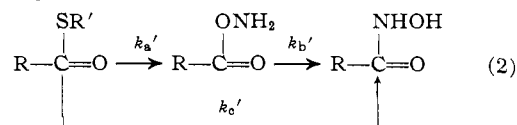


Fig. 1.—Disappearance of ester and appearance and disappearance of O-acetylhydroxylamine and appearance of hydroxamic acid with time (pH 5.42, total hydroxylamine concentration 0.5 M).

Under the pseudo-first-order conditions employed (see previous communication) scheme 1 amounts kinetically to a simple  $A \rightarrow B \rightarrow C$  problem.<sup>5</sup> 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  $A \rightarrow B \rightarrow C$  problem<sup>5</sup> 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.

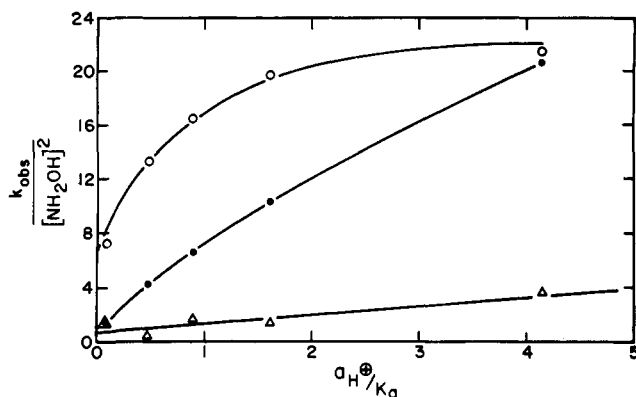


Fig. 2.—Plots of the pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) divided by the square of the concentration of free hydroxylamine vs. the hydrogen ion activity divided by the acid dissociation constant of hydroxylamine where  $k_{\text{obsd}} = k_e'$  (O),  $k_{\text{obsd}} = k_b'$  (●), and  $k_{\text{obsd}} = k_a'$  (▲).

In Fig. 2 the values of  $k_a'/(NH_2OH)^2$ ,  $k_b'/(NH_2OH)^2$ , and  $k_e'/(NH_2OH)^2$  have been plotted vs.  $a_H/K_a'$ . Inspection of Fig. 2 reveals that the value of  $k_e'/(NH_2OH)^2$ , as opposed to the functions of  $k_a'$  and  $k_b'$ , exhibits the same dependency on  $a_H/K_a'$  as the disappearance of ester (Fig. 1 of previous communication). Therefore, the mechanism leading directly from ester to acethydroxamic acid is that which undergoes a change in the rate-limiting step with increase in acidity justifying the assumptions leading to the postulated mechanism of the previous communication.

In separate experiments the reactions of *n*-butylmercaptan with acethydroxamic acid and *O*-acetylhydroxylamine were investigated. The inability to realize these back reactions under the conditions of the hydroxylaminolysis reaction assures us that the dependence of the rate constant on acidity could not be due to any conceivable equilibrium situation. Additional experiments have shown the reactions discussed to be rather insensitive to changes in ionic strength.

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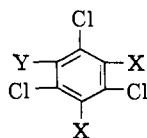
RECEIVED NOVEMBER 30, 1963

### Reduction of Nitroaromatic Compounds with Sodium Borohydride

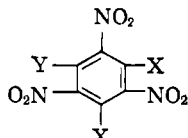
Sir:

Severin<sup>1,2</sup> demonstrated that the reduction of nitroaromatic compounds with sodium borohydride under alkaline conditions formed the corresponding dihydro or polyhydro product. Thus, *sym*-trinitrobenzene and 1-*X*-2,4-dinitrobenzene (*X* = Cl, CH<sub>3</sub>, COOH, and CH=CHC<sub>6</sub>H<sub>5</sub>) gave *sym*-trinitrocyclohexane and 1-*X*-4,6-dinitrocyclohex-1-ene.

In connection with other studies, this procedure<sup>1,2</sup> was applied to I and II. Instead of the expected ring



I, *X* = *Y* = NO<sub>2</sub>  
II, *X* = NO<sub>2</sub>; *Y* = H  
III, *X* = H; *Y* = NO<sub>2</sub>



IV, *X* = H; *Y* = Cl  
V, *X* = Cl; *Y* = H  
VI, *X* = OCH<sub>3</sub>; *Y* = H  
VII, *X* = Br; *X* = OCH<sub>3</sub>; *Y* = H

reduction products, *sym*-trichlorotrinitrocyclohexane and 4,6-dinitro-1,3,5-trichlorocyclohexene, benzenoid derivatives were obtained. Reduction of I afforded II (45%), m.p. 129.5–30.5° (no depression with authentic II, m.p. 129–130°, infrared spectrum identical with authentic II) as the only isolable product. The reduction of II under these conditions gave III in somewhat lower yields, m.p. 72–73° (lit.<sup>3</sup> 71°); infrared spectrum: 1362 and 1545 cm.<sup>-1</sup> (Ar-NO<sub>2</sub>), 3060 cm.<sup>-1</sup> (C-H stretch), 1560 cm.<sup>-1</sup> (C=C stretch), 728 cm.<sup>-1</sup> (C-Cl); mol. wt. 226.5 (calcd.), 221 (found).<sup>4</sup> By carrying out the reduction of I at elevated temperatures, some of the mononitro derivative (III) was obtained together with the dinitro derivative (II), thus indicating that this denitration reaction was occurring in a stepwise fashion.

When the symmetrical chlorine substitution was replaced by nitro groups and one or two of the remaining ring positions substituted, the reaction apparently followed still a different path. The reduction of picryl chloride (IV) and styphnyl chloride (V) under conditions identical with those above yielded *sym*-trinitrocyclohexane (infrared spectrum and X-ray powder pattern identical with that of a sample, m.p. 124–125°, prepared by the reduction of *sym*-trinitrobenzene) and not the mono- and dichloro-*sym*-trinitrocyclohexanes.

The replacement of one or both of the chlorine atoms in V by methoxyl groups did not alter the results. The dimethoxy derivative (VI) and the bromomethoxy derivative (VII) were both converted to *sym*-trinitrocyclohexane when treated with sodium borohydride under the above conditions.

The products obtained in these reductions are either hydride displacement products or *sym*-trinitrocyclohexane. The former apparently arise from the nucleophilic displacement of one or more nitro groups as nitrite ion by hydride from borohydride ion. This reaction path prevails when the O-N-O plane of each of the nitro groups in the substrate is closer to being normal to than coplanar with the benzene ring; *i.e.*, minimal or zero resonance interaction between the nitro groups and the benzene ring. The confirmation of all the nitro groups in I, II, and III should closely approximate that of the C-2 nitro group of dichloro compound V. A crystal structure determination has shown that the O-N-O plane of this nitro group is rotated 76° out of the plane of the benzene ring.<sup>5</sup> Nucleophilic displacement by hydride of the *nonconjugated* nitro groups in I, II, and III would be expected since the nitro group has been shown to be a better leaving group than chlorine in nucleophilic displacements on the benzene ring.<sup>6</sup>

The formation of *sym*-trinitrocyclohexane from the mono- and disubstituted *sym*-trinitrobenzenes apparently depends upon having some resonance interaction between at least one of the nitro substituents and the benzene ring. In monochloro compound IV, the C-4 nitro group is only 3.6° out of the plane of the benzene ring<sup>7</sup> and in dichloro compound V, the C-4 and C-6 nitro groups are only 37° out of the plane of the benzene ring.<sup>5</sup> The dihedral angle made by the O-N-O plane of the C-4 and C-6 nitro groups with the plane of the benzene ring in VI and VII has not been measured, but it probably does not differ too much

(3) J. D. Loudon, *J. Chem. Soc.*, 1525 (1940).

(4) Determined in chloroform solution with a Mechrolab vapor pressure osmometer.

(5) Private communication, Dr. J. R. Holden of these laboratories.

(6) The reaction of aniline with 1,2,3,5-tetranitrobenzene is about 2000 times faster than with 1-chloro-2,4,6-trinitrobenzene [R. E. Parker and T. O. Read, *J. Chem. Soc.*, 9 (1962)]. See also, J. F. Bunnett, *Quart. Rev. (London)*, **12**, 1 (1958).

(7) Private communication, Dr. J. M. Stewart, University of Maryland.

(1) T. Severin and R. Schmitz, *Chem. Ber.*, **95**, 1417 (1962).

(2) T. Severin and M. Adam, *ibid.*, **96**, 448 (1963).