B. **Aza-9,10-anthraquinone.**—An experiment similar to that described above with equimolar amounts of quinone and copper salt and excess ethanol gave neither acetaldehyde nor ethyl ester after 100 hours at reflux. Another experiment with the quinone, cupric tosylate and benzhydrol in dimethyl sulfoxide solution gave no benzophenone (infrared analysis) after 5 days at room temperature; benzhydrol was recovered nearly quantitatively.

C. **1,10-Phenanthroline-5,6-quinone** in experiments identical to those described under B was completely ineffective in causing oxidation or acylation, although a green cupric complex is readily formed.

[CONTRIBUTION FROM THE JAMES BRYANT CONANT LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE, MASS., AND THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

Imidazole Catalysis of the Hydrolysis of δ-Thiovalerolactone

BY F. H. WESTHEIMER AND MYRON L. BENDER

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Bruice and Bruno recently published a study of the hydrolysis of δ-thiovalerolactone, catalyzed by imidazole. They reported a maximum in the *p*H-rate profile, determined two apparent *pK* values, which can account for the maximum, and proposed a mechanism for the reaction. They derived equations directed toward showing how one of the apparent *pK*'s can be represented as a complex kinetic quantity, rather than as the *pK* of any particular group present in the reactants or intermediates. However, their kinetic analysis is here shown to be inconsistent with the principles of dynamic equilibrium. An alternative mechanism, consistent with their data, is proposed.

In a recent issue, Bruice and Bruno[1] published a kinetic study of the hydrolysis of δ-thiovalerolactone, catalyzed by imidazole. They reported a *p*H–rate maximum near 7.8, and analyzed the *p*H–rate profile according to eq. 1 in terms of two ionization constants: that of imidazole, K_1, and an apparent constant, $\bar{K}$, to which they assigned the value 4.78×10^{-9}. They proposed the mechanistic scheme shown in Chart I, and derived kinetic equations which were intended to account for $\bar{K}$. Unfortunately, their kinetic analysis is unsound. An alternative mechanism, presented in Chart II, is in agreement with their data.

$$k_{obs} = \frac{k}{[(\bar{K}/(H^+)) + 1][((H^+)/K_1) + 1]} \quad (1)$$

The published study[1] shows two pathways by which an intermediate is formed from imidazole and thiolactone (Chart I). The various rate and equilibrium constants along these two pathways leading to IH″ are necessarily related, since the same thermodynamic equilibrium for the intermediate must be achieved without regard to path. The required relationship (see Appendix) is expressed by eq. 2.

$$k_1k_4K_3K_4 = k_2k_5K_2 \quad (2)$$

The approximations essential to Bruice and Bruno's argument are in direct conflict with this equation. From the scheme of Chart I, Bruice and Bruno derive eq. 3 (their eq. 5) for the disappearance of thiolactone L.

$$-d(L)/dt = \frac{k_3[k_1(H^+) + k_5K_2]}{(H^+)\left(k_3 + \frac{k_2}{K_2}\right) + k_4K_4}(L)(ImH) \quad (3)$$

Then they assume that "k_5K_2 may be ignored," *i.e.*, that in eq. 3

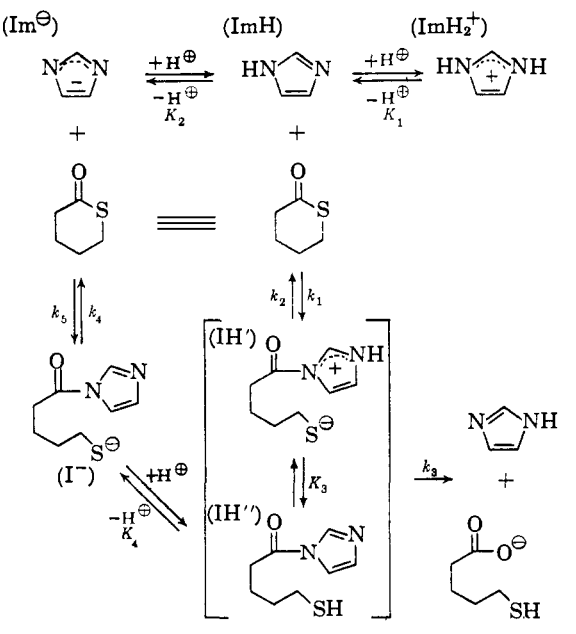
$$k_5K_2 << k_1(H^+) \quad (4)$$

But if the inequality of eq. 4 is assumed, then, from eq. 2

$$k_4K_4 << (k_2/K_2)(H^+) \quad (5)$$

This comparison appears in the denominator of eq. 3. If k_5K_2 in the numerator of eq. 3 is neglected, then, k_4K_4 in the denominator of eq. 3 *must* also be neglected. This algebraic requirement is equivalent to the statement that if the forward reaction to the intermediate *via* k_5 is negligible, then the reverse reaction *via* k_4 is likewise negligible. The presentation may be considered an example of the principle of microscopic reversibility; the violation of this principle is shown even without this algebraic demonstration by eq. 9 of Bruice and Bruno.[1]

CHART I



The inclusion of the product-forming step with rate constant k_3 in the kinetic eq. 3 does not in any way change these conclusions. The value of k_3 will not affect the free energy of any of the reactants, or the equilibrium constant for the formation of the intermediate which would obtain if k_3 were zero; therefore k_3 cannot affect the validity of eq. 2. Further, inspection of eq. 3 shows that the introduction of k_3 can only further reduce the importance of the product k_4K_4. If this term must be neglected

(1) T. C. Bruice and J. J. Bruno, *J. Am. Chem. Soc.*, **84**, 2128 (1962).

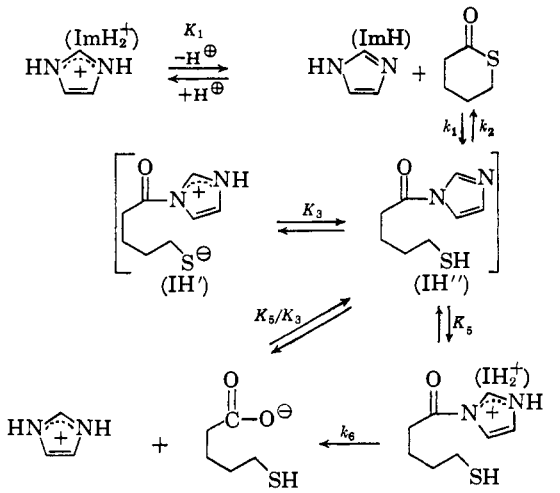
when k_3 is small, *a fortiori* it is negligible when k_3 is large.

Bruice and Bruno's eq. 7 and 8 were intended to account for the second pK deduced from the pH–rate profile. However, the significance of these equations depends critically on the product k_4K_4, and this term must be neglected if k_5K_2 is neglected.

The pH–rate profile can, however, be correlated with the mechanism shown in Chart II, and a kinetic analysis similar to that of Zerner and Bender.[2] Here the reactive intermediate postulated for the hydrolysis is an acylimidazolium ion, rather than a neutral acyl imidazole molecule, or a zwitterionic derivative. The mechanism is thus similar to that for the hydrolysis of acetylimidazole,[3] and is in accord with the acid catalysis for the hydrolysis of benzenesulfonylimidazole[4] and of some derivatives of phosphorylimidazole.[5] As shown in the Appendix, the mechanism of Chart II leads to eq. 6.

$$k_{obs} = \frac{k_1}{\left[\frac{k_2K_5}{k_5K_3(H^+)} + 1\right]\left[\frac{(H^+)}{K_1} + 1\right]} \qquad (6)$$

CHART II



A comparison of eq. 1 and 6 shows that the apparent ionization constant, $\bar{K}$, is equal to k_2K_5/k_5K_3. In this expression, the quotient K_5/K_3 is the ionization constant of the thiol group in the zwitterionic intermediate, IH′. Since the positive charge is far removed from the site of the ionization, the constant will probably not differ much from 1×10^{-10}, the value found[1] for δ-thiovaleramide. If this ionization constant is accepted as a first approximation to K_5/K_3, and if $\bar{K} = 4.78 \times 10^{-9}$, then k_2/k_5 should be in the neighborhood of 50. That is to say, the apparent pK of 8.3 in the pH–rate profile can be accounted for if the ratio of the rate constant for the return to starting materials from the zwitterionic intermediate, IH′, is about 50 times as great as the rate constant for the hydrolysis of the protonated intermediate, IH_2^+. This result is not inherently unreasonable, and the mechanism of Chart II is therefore a possible explanation of the data as published. To emphasize the obvious, agreement between a kinetic equation and experiment in no way guarantees that the mechanism in question is correct. Our only contention is that the proposed scheme accounts for the data at present available.

(2) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, **83**, 2267 (1961).
(3) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272 (1959).
(4) H. A. Staab and K. Wendel, *Chem. Ber.*, **93**, 2903 (1960).
(5) H. Schaller, H. A. Staab and F. Cramer, *ibid.*, **94**, 1621 (1961); R. Blakeley and F. H. Westheimer, unpublished.

Appendix

Derivation of Equation 2.—Define $(IH'')/(ImH)(L) = K$ as the equilibrium constant for the formation of the intermediate IH″ which would obtain if the rate constant for the product-forming step, k_3, were zero (Chart I). Then at kinetic equilibrium

$$k_1(L)(ImH) = k_2(IH') \qquad (7)$$

Since $(IH') = (IH'')/K_3$

$$(IH'')/(L)(ImH) = k_1K_3/k_2 = K \qquad (8)$$

Similarly, for the pathway *via* k_4 and k_5

$$k_4(I^-) = k_5(L)(Im^-) \qquad (9)$$

Since $(Im^-) = K_2\,(ImH)/(H^+)$ and $(I^-) = K_4\,(IH'')/(H^+)$

$$(IH'')/(L)(ImH) = k_5K_2/k_4K_4 = K \qquad (10)$$

From 8 and 10

$$k_1k_4K_3K_4 = k_2k_5K_2 \qquad (2)$$

Derivation of Equation 6.—Assume that the various protonated forms of the intermediate, IH′, IH″ and IH_2^+ maintain steady states with respect to reactants during most of the reaction (Chart II). Then

$$\frac{d[(IH') + (IH'') + (IH_2^+)]}{dt} = k_1(ImH)(L) - k_2(IH') - k_6(IH_2^+) = 0 \qquad (11)$$

Since $(IH'')/(IH') = K_3$ and $(H^+)\,(IH'')/(IH_2^+) = K_5$

$$(IH_2^+) = \frac{k_1(ImH)(L)}{\frac{k_2K_5}{K_3(H^+)} + k_6} = \frac{k_1(B)(L)}{\left[\frac{k_2K_5}{K_3(H^+)} + k_6\right]\left[\frac{(H^+)}{K_1} + 1\right]} \qquad (12)$$

where (B) is the sum of the concentrations of imidazole and imidazolium ion. Let

$$-d(L)/dt = k_{obs}(L)(B) = k_6(IH_2^+) \qquad (13)$$

Then from eq. 12 and 13

$$k_{obs} = \frac{k_1}{\left[\frac{k_2K_5}{k_5K_3(H^+)} + 1\right]\left[\frac{(H^+)}{K_1} + 1\right]} \qquad (6)$$